ANAESTHESIOLOGY

NOTES FOR PREGRADUATE STUDENTS, INTERNS, AND COMMUNITY SERVICE DOCTORS

COMPILED BY

DR FJ SMITH
DEPARTMENT OF ANAESTHESIOLOGY

ANATOMICAL SKETCHES BY MARINDA PRETORIUS
DEPARTMENT OF ANATOMY

SCHOOL OF MEDICINE
FACULTY OF HEALTH SCIENCES
UNIVERSITY OF PRETORIA
PRETORIA
SOUTH AFRICA

PREFACE

The aim of these notes is not primarily to burden the student with stacks of facts, but rather to inculcate an integrated way of thought; integrating knowledge acquired from the preclinical and clinical disciplines. The intension was not to write a comprehensive guide to anaesthesiology, but to present some basis, which can be applied when practising anaesthesiology during the periods of internship and community service. Remember, knowledge does not only give the doctor the insight what to do, and how to do it, but also what he/she cannot do. Students are invited to criticise the notes: correctness, contradictions, lack of clarity, layout, etc.

FJ Smith MD
Department of Anaesthesiology
University of Pretoria

January 2013

CONTENT

CHAPTER 1

INTRODUCTION

"For some must watch while some must sleep" - *Hamlet act III, scene 2.*

Key points

- *The task of the anaesthesiologist* focuses on the manipulation of consciousness, nociception, muscle tone, and homeostasis
- *The anaesthetic state*
- *Components of general anaesthesia*: Sensory blockade, motor blockade, loss of reflexes, loss of consciousness
- *The process of anaesthesia*: Preparation, premedication, induction, airway management, maintenance of anaesthesia, recovery phase, choice of anaesthetic technique
- *Requirement during all procedures*:

- The presence of an *anaesthesiologist*.
- The anaesthesiologist must be a *competent clinician*.
- A broad knowledge of *anatomy*
- A sound knowledge of *physiology*
- A sound knowledge of clinical *pharmacology*
- Knowledge regarding the *monitoring of body functions* (homeostasis).
- *Skills to perform particular procedures*, e.g. airway management, vascular access, and regional anaesthesia.

In clinical medicine and research, the expertise of the anaesthesiologist is often called on to enable procedures, which would otherwise not have been possible. These procedures are therapeutic and/or diagnostic.

The task of the anaesthesiologist focuses on the manipulation of the following body functions:

1. **Consciousness:** anxiolysis, amnesia, sedation, hypnosis, anaesthesia
2. **Nociception:** analgesia
3. **Muscle tone:** muscle relaxation
4. **Homeostasis:** maintenance and monitoring of cell function during diagnostic and therapeutic procedures. Anaesthetists ensure the adequate supply of substrate (water, oxygen, nutrients, electrolytes), which is necessary for organ function and the elimination of the metabolic end-products of cell metabolism (CO_2, H^+, NH_3, sulphates, phosphates, etc). They also take note of the intake and excretion of toxic therapeutic and diagnostic substances, e.g. antibiotics and radio-contrast agents.

These functions of the anaesthetist describe ***the scope of anaesthesiology***: all these facets may be involved simultaneously or in different combinations. However, the homeostasis component is always involved; in fact, *any doctor who does not take cognisance of homeostasis during patient care might as well leave clinical medicine altogether*.

During procedures that are not painful, ***sedation*** only may suffice, e.g. angiography and patients in intensive care. Some procedures require ***analgesia*** only, e.g. labour, and caesarean section. Analgesia is either *systemic*, e.g. using opioids, or *regional* using local anaesthetics to block nerve conduction, e.g. a brachial plexus block. The anaesthesiologist is often involved in the rendering of a *postoperative pain service*, treatment of *chronic pain*, and the *palliative care* of cancer patients. Often, the anaesthesiologist must monitor and care for a patient during unpleasant and potentially painful interventions, e.g. enteroscopies. During these procedures, ***both sedation and analgesia*** are required. This is a potentially dangerous technique and requires *monitored anaesthetic care* (MAC). ***Muscle relaxants*** are not often used in the awake patient but usually form *part of a general anaesthetic* (hypnosis + analgesia + muscle relaxation + maintenance of homeostasis) or *intensive care* (sedation + muscle relaxation + maintenance of homeostasis). They are sometimes used alone, e.g. *emergency airway management*, *relaxation and ventilation* of comatose *patients*, or the management of brain-dead organ donors.

Regarding homeostasis; anaesthesiologists are often involved in *intensive care*, i.e. the management of patients whose vital functions have deteriorated to such an extent that management in the general ward is not possible.

The anaesthetic state
- Anaesthesia is defined as the absence of all responses to sensory stimuli due to the suppression of the central nervous system by anaesthetic agents.
- Certain drugs have the ability to bind to neuroreceptors and thereby alter (potentiate or attenuate) the effect of neurotransmitters. By injecting these drugs, the anaesthetist induces a "pharmacological" state of unconsciousness, unresponsiveness, or loss of sensation. It is the task of the anaesthesiologist care for the patient until consciousness or sensation has been regained.

The anaesthetic state is the result of suppression of the central nervous system (brain and spinal cord). This suppression of the central nervous system is characterized by the inhibition of some tracts or facilitation of others. This does **not** occur progressively from top to bottom, but in the following order:
1. Cortex (movement, sensation, higher brain function, including psyche)
2. Basal ganglia and cerebellum (movement, sensation)
3. Spinal cord (movement, sensation)
4. Medulla oblongata (vital centres). When this level is suppressed, the anaesthetic plain is to deep and causes failure of the cardiovascular and respiratory centres.

Components of general anaesthesia
1. **Sensory blockade**
Conduction of **s**timuli from the peripheral nervous system is blocked in the central nervous system.
2. **Motor blockade**
General anaesthesia decreases muscle tone.
3. **Reflexes**
General anaesthesia decreases reflex activity, mainly by inhibiting the reflex integration centres in the central nervous system. These include:
- **airway reflexes** (decreased mucus production, decreased laryngeal muscle tone, and decreased bronchial muscle tone).
- **circulatory** (decreased effect of the response of the autonomic nervous system which is responsible for cardiovascular homeostasis, namely vasoconstriction, tachycardia, and the stress response)
- **gastro-intestinal** (Decreased saliva production, vomiting, gastrointestinal motility)
4. **Loss of consciousness**
- Calmness
- Sedation and sleepiness
- Light sleep and hypnosis
- Loss of consciousness
- Deep sleep and anaesthesia (surgical anaesthesia)
- Complete anaesthesia
- Medullar suppression

THE PROCESS OF ANAESTHESIA

The process of anaesthesia is divided into the following phases.
1. **Preparation**
A complete history and focussed clinical examination is warranted pre-operatively. The disease necessitating the procedure, as well as co-existing diseases must be evaluated and optimized, e.g.

diabetes mellitus, anaemia etc.

2. **Premedication**
- The **pre-operative visit** is more important than medication.
- The patient should be reassured, and if necessary, sedated to enable him/her to be relaxed and co-operative in theatre.
- Apart from a sedative (if necessary), the patient's therapy for co-existing disease is usually prescribed. It may be dangerous to stop these drugs.
- Pre-medication should not be prescribed telephonically, before the patient has been seen.

3. **Induction**
- The nature of this phase depends on the *anaesthetic technique*: sedation, general anaesthesia, or regional anaesthesia.
- This phase includes the performance of some *conduction block*, e.g. the spinal cord or brachial plexus, and or the smooth transition from the awake state to *sedation of a state of unconsciousness* allowing painful procedures to be performed (general anaesthesia).
- Induction of general anaesthesia or sedation can be done via *different routes*, namely by administering drugs orally, subcutaneously, intramuscularly, intravenously, rectally, or as a vapour that is inhaled.
- No anaesthetic (regional, sedation, or general anaesthesia) should be administered without prior *intravenous access*, except for paediatric patients who are induced with a volatile agent or oral, subcutaneous, or intramuscular agents.
- Induction of general anaesthesia is usually accompanied by loss of *airway tone, airway reflexes, and apnoea*. The patient is therefore at risk of *airway obstruction, aspiration, and hypoventilation*. Induction of anaesthesia is therefore absolutely contraindicated when the attending doctor is not *conversant in airway management*, airway protection (suction), and the maintenance of oxygenation and ventilation. The same may follow regional anaesthesia and sedation. *Before any anaesthetic is induced, the following facilities must be available*:
- Reliable *oxygen* supply (see Chapter 4)
- An anaesthetic *machine* (see Chapter 4)
- An anaesthetic *circuit* (system consisting of tubing, valves, and a reservoir bag) (see Chapter 4)
- An anaesthetic *mask* to enable spontaneous and assisted ventilation
- A *laryngoscope* (see Chapter 3)
- An *oral airway* to maintain patency of the upper airway once the patient has lost consciousness (see Chapter 3)
- A choice of *endotracheal tubes* (see Chapter 3)
- *Suctioning* to remove stomach content, secretions, and blood
- A *theatre table* that can be tilted into the Trendelenburg, anti-Trendelenburg, and lateral positions (see Chapter 3)
- Availability of *resuscitation drugs and defibrillator* (see Chapter 15)
- *Essential monitors* (see Chapter 4)

4. **Airway management**
- It is imperative that every doctor is able to perform this procedure.
- Endo-tracheal intubation is not necessary in all general anaesthetic cases. The anaesthetist must decide which patients need endotracheal intubation (see indications for intubation).
- An endotracheal tube is placed into the trachea either via the mouth or the nose.
- A neuromuscular blocking agent is usually indicated for endotracheal intubation. In the deeply anaesthetized patient, intubation may be possible without neuromuscular blockade.

5. **Maintenance of general anaesthesia**
- The level of unconsciousness (anaesthesia) and analgesia is maintained throughout the operation. Prevent intra-operative awareness.

- Maintenance of unconsciousness is achieved with a volatile anaesthetic or TIVA (total intravenous anaesthesia).
- The patient breathes spontaneously or may be ventilated with an anaesthetic ventilator.
- The anaesthetist is solely in charge during the period of anaesthesia and surgery and must observe the patient throughout. He/she ensures that homeostasis is disturbed as little as possible, including attenuation of the stress response associated with surgery appropriately. Treat any dangerous complications of surgery such as hypotension, arrhythmias, hypoxia, hypercarbia, bronchospasm, etc. immediately.

6. Recovery phase

Recovery from anaesthesia usually occurs in the postanaesthetic care unit. This area is part of the theatre complex where patients are monitored until they are awake, painfree, and physiologically stable enough to be transferred to the ward.

From the above, it should be clear that the following factors are imperative during all procedures:

- **The presence** of an anaesthesiologist.
- The anaesthesiologist must be a **competent clinician.** The surgical and co-existing disease profiles influence the management and the course of the anaesthetic.
- **A broad knowledge of anatomy** is essential in monitoring, for safe regional anaesthesia, for an appreciation of the impact of a procedure, and the requirements of doctors involved in the procedure (surgeon, radiologist, endoscopist, etc.).
- **A sound knowledge of physiology** is essential, especially of the nervous, respiratory, cardio-vascular, renal, hepatic, haemopoietic, and endocrine systems, as well as their interactions.
- The anaesthesiologist must have a sound knowledge of **clinical pharmacology** of anaesthetic drugs, drugs prescribed for co-existing disease, recreational drugs, and their interactions.
- Knowledge regarding the **monitoring** of body functions (homeostasis). The anaesthesiologist must keep a contemporaneous record of all the aspects of the procedure. This is not only important regarding patient care (to observe a trend and timely intervention), but also for academic (teaching and research) and medico-legal reasons. The anaesthesiologist should also have basic knowledge about the physics of the relevant **equipment.**
- In order to conduct a safe anaesthetic, it is essential that the anaesthesiologist does not only have adequate knowledge, but also the **skills** to perform particular procedures, e.g. airway management, vascular access, and regional anaesthesia.

7. The choice of anaesthetic technique depends on:

- The anaesthetist: His/her competence to perform a particular anaesthetic technique.
- The patient's condition: Ability to maintain and protect the airway (rather intubate than supraglottic airway), cardiac condition (failure, ischaemia, etc.), vascular (peripheral vascular disease), volume state (hypovolaemia), drug therapy (e.g. anticoagulants contra-indicate neuraxial blocks), the ability of the patient's organ reserve to tolerate the anaesthetic technique (e.g. the negative effects of anaesthetic vapours on the heart in a patient with cardiac failure), the organ reserve to survive the procedure (necessity of postoperative intensive care), etc.
- The procedure: certain techniques are preferred for particular procedures, e.g. spinal anaesthesia for caesarean section, limb surgery in patients with cardiovascular or respiratory disease, etc.
- Patient choice

CHAPTER 2

PREANAESTHETIC ASSESSMENT

Key points
- The purpose of the preoperative visit
- The aspects of the history important to the anaesthesiologist
- The systemic questioning
- The approach to the physical examination
- Evaluation of the airway: the history, clinical examination, and different tests
- The principles of requisition of special investigations: stratification (ASA) and optimisation
- Conditions and criteria that justify the cancellation of elective procedures
- What to suggest to surgeons to optimise the patient
- The drugs used for premedication, including the doses: anticholinergics, benzodiazepines, morphine and tilidine, and drugs used in patients at risk to aspirate
- *Medico-legal issues*: Accountability, responsibility, negligence, informed consent

Purpose of the preoperative evaluation

The purpose of the preoperative evaluation is the identification, stratification, and optimisation of the physiological effects of diseases and their treatment. The anaesthetic already begins at the preoperative visit. During this visit, the patient develops rapport with the anaesthetist and psychological support for the stressful time ahead is given. At this time, the anaesthetic technique is formulated based on the patient's condition, treatment, the proposed operation, and the abilities of the surgeon. The anaesthetic technique is discussed with the patient. You must take into account the Patient's preferences if possible and safe.

The importance of a preoperative visit can never be stressed enough. The preoperative status of the patient is determined by the illness that requires surgery, as well as other concurrent conditions. Both the surgical and concurrent disease impact on morbidity and mortality and must be considered and discussed with the patient.

DURING THE PREOPERATIVE ASSESSMENT, THE ANAESTHETIST MUST KEEP THE FOLLOWING ASPECTS <u>AND THEIR INTERACTIONS</u> IN MIND:
- **The anatomical defect (macroscopic, microscopic) and its effect on the physiology**
- **Organ function (physiology), its effect on the anatomy, and its treatment**
- **Management of the anatomical and physiological derangements (pharmacological, surgical), and the effect of management on the anatomy and physiology (side effects)**
- **Assessment of the anatomy, physiology, and management: chemical, haematological, imaging, pharmacological (drug levels), etc.**

THE CLINICAL ASSESSMENT

ALL findings must be documented on the anaesthetic record

History
An accurate history should be taken and the following aspects should be attended to:
- Previous anaesthetics and surgery
- Problems with previous anaesthetics
- Allergy or unusual reaction to medicines
- Current medication; both prescribed and self-medication
- Cortisone treatment in the past 12 months
- Previous or current oncotherapy (*multisystem side effects*)

Systemic questioning
Cardiovascular
Patients may present with a history of one or more of the following: dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea, chest pain, palpitations, dizziness, syncope, high blood pressure,

chest pain and variations thereof, heart attack, claudication, or rheumatic fever. Remember that patients with significant cardiac disease may still be asymptomatic. In these patients risk factors must be identified, cardiovascular disease suspected, and excluded before surgery.

The New York Heart Association **functional** classification refers to fatigue, dyspnoea, or angina:
Class 1: Symptoms occur on *extraordinary* exertion.
Class 2: Symptoms occur on *ordinary* exertion, e.g. climbing two flights of stairs.
Class 3: Symptoms occur on *less than ordinary* exertion, e.g. getting dressed.
Class 4: Symptoms occur *at rest.*

Respiratory
Patients may present with a history of smoking, dyspnoea, cough, sputum, haemoptysis, chest pain, wheezing, asthma, bronchitis, emphysema, recent cold, flu, pneumonia, or tuberculosis. Enquire about snoring and daytime somnolence (sleep apnoea). Enquire specifically about positional dyspnoea (mediastinal mass).

Endocrine
These include diabetes, hyper- or hypothyroidism, Cushing syndrome, etc. Patients may present with abnormal growth and development, abnormal external features (obesity, weight loss, short or tall stature, etc.), abnormal intermediary metabolism (glucose, fat, protein, water and electrolytes, temperature control, etc.) or infertility. **Is the patient pregnant? (If so, for how long?)**

Gastro-intestinal
Enquire about heartburn, reflux, nausea, vomiting, diarrhoea, bowel preparation, jaundice or hepatitis, and bowel preparation (dehydration). Remember, heartburn contraindicates insertion of a laryngeal mask since this airway device does not prevent aspiration of regurgitated matter.

Kidney disease
Is there a history of renal disease? Does the patient undergo dialysis (venous, peritoneal). Are there any arterio-venous fistulae for dialysis?

Neurological disease
Is there any history of dizziness, fainting, epilepsy, stroke, sensory disturbances (pain, paraesthesia, numbness), or muscle weakness or stroke?

Haemopoietic and immunological systems
Question the patient about a tendency to bleed or bruise, previous thrombosis/embolism (legs/lungs), recurrent infection, or night sweats.

Musculo-skeletal system
A history of neck of spinal injury or surgery is vital as it may involve the spinal cord and the airway. Several systemic diseases may involve the musculoskeletal system, e.g. rheumatoid arthritis, diabetes mellitus, acromegaly, cervical immobility, morbid obesity, and the different forms of dwarfism. Look for myopathies, either muscular dystrophy or secondary myopathies, e.g. toxic, inflammatory, endocrine, etc.).

Myopathies are often associated with proximal muscle weakness with intact reflexes and sensation and multisystem involvement, especially a cardiomyopathy. These patients may be very susceptible for the effects of muscle relaxants and negative inotropic anaesthetic drugs.

Family history of abnormal response to anaesthesia
Hereditary diseases like porphyria, malignant hyperthermia, or suxamethonium apnoea may complicate anaesthesia.

Social history

- Does the patient smoke? If so, how many cigarettes per day?
  Pack year = the number of cigarettes a person smoked over time.
  One pack year = 20 manufactured cigarettes (one pack) smoked per day for one year.
  Example: I smoked 1.5 packs per day for 26 years = $1.5 \times 26 = 39$ pack years
- How much *alcohol* does the patient consume?
- Does the patient take any other recreational drugs (neutriceuticals, anabolic steroids, homeopathic drugs, etc.)?
- Enquire about and look for signs of drug abuse, e.g. opioids, amphetamine derivatives, cannabis, etc.

Mass and height
Take note of weight loss or gain, and morbid obesity.

When did the patient last eat and drink? Is there anything else the anaesthetist should know about?

Physical examination
The preoperative physical examination is guided by the history. Guidelines regarding a full physical examination of such systems can be obtained from an appropriate textbook. The anaesthetist may concentrate on physiological systems of greatest relevance, i.e. cardiovascular and respiratory systems. Get a *general impression* of the patient. Pay attention to state of consciousness, cognitive function, signs of weight loss or gain, anaemia, polycytaemia, jaundice, cyanosis, oedema, dehydration and preferred position. Note the presence and function of venous, central venous, arterial, intercostal, nasogastric, and urinary catheters.

Nervous system
A detailed examination is usually time consuming and unnecessary. Assess consciousness, facial expression, speech, motor function, sensory function, and autonomic function. The neurological examination is extremely important as general and regional anaesthesia may (rarely) be complicated by neurological deficit. The anaesthetist must therefore note any preoperative abnormalities.

Cardiovascular system
The anaesthetist must take the blood pressure (BP) and heart rate (HR) him/herself. BP must be measured in both arms. Feel for the carotid, radial, ulnar, and dorsal pedal pulses. Listen to the heart. Examine the hands, arms, legs, and feet for arterial pulses, venous distension, and venous access. Assess the carotid pulses and jugular venous pressure. Patients with a tight aortic stenosis (present with a soft systolic ejection murmur) and patients in cardiac failure, including peripartum cardiomyopathy, are at a very high risk to develop complications perioperatively.

Are there any vascular catheters in situ (venous, central venous, arterial) and are they functional and clean? ***Stay away from a limb with arterio-venous fistulae for dialysis: do not apply a BP cuff and do not put an infusion on that limb.***

Respiratory system
Determine the respiratory rate and pattern and listen for hoarseness and stridor. Exclude pleural effusions, pneumothorax, pleural effusions, bronchospasm, pulmonary oedema, airway, and pulmonary infection.

Abdomen
Inspect, palpate, percuss, and auscultate. Note abdominal distension of scaphoid abdomen, striae, petechiae, abnormal discolouration, distended veins, and ascites.

Musculo-skeletal system
Take note of deformities of the limbs and spine (scoliosis, kyphosis, and previous spinal surgery),

atrophy, hypertrophy, arthritis, ankylosis, etc.

Evaluation of the airway (See Chapter 3)

Special investigations
After identification and stratification of the pathophysiological state, the anaesthetist must decide if the patient suffers from any condition, if it is optimally treated, and it if may complicate the perioperative course. He must then decide if further consultation or special investigations are justified to improve perioperative outcome. Before ordering extensive investigations, the anaesthetist should ask himself the following questions:
- Will this investigation yield information not revealed by physical examination?
- Will the results of the investigation alter the management of the patient?

It is generally accepted that the clinical history and physical examination represent the best method of screening for the presence of disease. Routine laboratory tests in patients who are apparently healthy on history and clinical examination are invariably of little use and a waste of resources. Discretion and common sense should prevent the anaesthetist requesting unnecessary expensive investigations or cancelling a case for slight unimportant deviations. Guidelines for special investigations in asymptomatic patients are summarized in Table 1.

CONDITIONS THAT JUSTIFY THE CANCELLATION OF ELECTIVE PROCEDURES

- Untreated *cardiac disease* (except for diagnostic or surgical cardiac procedures) and hypovolaemia
- A resting *systolic blood* pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg
- *Bronchospasm*, an *upper airway infection* within the previous 2 weeks of a productive *cough* or pneumonia within the previous 6 weeks
- *Anaemia and polycythaemia* are important. The following haematocrit guidelines apply to normovolaemic patients and surgery during which minimal blood loss or haemodilution is expected: Anaemia must be treated in patients with compromised blood flow to vital organs, e.g. any cardiac disease and cerebrovascular disease, and peripheral vascular disease. To adequately oxygenate these organs, oxygen content of the blood (dependent on the amount of haemoglobin) must be at an acceptable level. In these patients, the haematocrit (HCT) must be kept > 25%. Patients without cardiovascular and respiratory disease can tolerate a haematocrit of > 21%. Babies younger than 3 months have a high oxygen consumption and require a haematocrit > 30% and babies older than 3 months a haematocrit of > 27%. Patients with hypoxic hypoxia (lung disease) have a low PaO_2 and require a minimum haematocrit of 30%. Remember that intraoperative fluid administration causes haemodilution, which will further decrease an already low haematocrit. In life-threatening situations, blood has to be brought to theatre and the operation has to continue. Calculation of volume of blood (ml) required to raise the haematocrit makes use of the body mass (kg) and the change in haematocrit (%):

  Whole blood: 2.5 × kg (Desired haematocrit – Present haematocrit)
  Packed cells: 1.5 × kg (Desired haematocrit – Present haematocrit)
  (Remember, these formulae are only valid if the higher haematocrit is ≤ 40%. For the correct but more difficult formula, see Chapter 18)

  A *haematocrit of > 58%* is associated with an adverse outcome. A leukocyte count of $< 2\,400 \times 10^9$ L^{-1} or $> 16\,000 \times 10^9\,L^{-1}$ must be attended to.
- Abnormal clotting, which has not been attended to.
- Significant electrolyte imbalances: $Na^+ > 150$ mM or < 120 mM; $K^+ > 5.5$ mM or < 3.0 mM; $Ca^{2+} > 3.0$ mM or < 0.7 mM. Hypokalaemia is important, especially in patients taking digoxin and in the presence of ischaemic heart disease.
- Uncontrolled hyperthyroidism or diabetes mellitus.
- Ingestion of solid food less than 6 hours before the operation. Shorter fasting periods for breast milk (3 hours), formula (4 hours) and light meals (6 hours) are well documented. To prevent preoperative

dehydration, it is recommended that clear isotonic liquids (e.g. half-strength clear fruit juice) be allowed up to two hours preoperatively in otherwise healthy patients. A special preoperative nutritive formula (ProvideXtra) is on the market for this purpose.

- No informed consent
- When poor facilities, faulty or absent equipment, or inferior surgical capability put the patient at risk to develop complications
- When the anaesthetist does not feel confident to anaesthetize the patient

Table 1 Special investigation in *asymptomatic* patients

Preoperative condition	FBC	Clotting	UCE	BGA	Blood glucose	LFT	ECG	Chest X ray	Lung functions*	Blood typing
Major blood loss expected	X	X	X				X			X
Neonates	X		X							
40-49 years (males)							X			
50-64 years							X			
≥65 years	X		X		X		X	X		
Cardiovascular disease	X		X				X	X		
Lung disease,	X						X	X		
Bronchial hyperreactivity									X	
Smoking ≥ 20 pack years							X	X		
Lung resection	X		X	X			X	X	X	
Kidney disease, diuretics	X		X				X	X		
Hepatobiliary disease	X	X	X		X	X				
Diabetes mellitus	X		X		X		X	X		
Central nervous system disease	X		X							
Malignancy, oncotherapy	X		X			X	X	X		
Abnormal clotting	X	X								
Cardiovascular medication			X				X			
Corticosteroids			X		X					
Anticoagulants	X	X								
Induced hypotension planned	X		X			X				
Need for postoperative intensive care				X						

*Simple lung function tests can be done at the bedside. A patient must be able to hold their breath for at least 15 s (Sabrazes' test). This measures of the functional residual capacity. FBC, Full blood count; Clotting, APTT, PT, INR; UCE, Urea, creatinine, and electrolytes; BGA, Blood gas analysis; LFT, Liver function tests

After a patient has been evaluated, his pre-operative physical status can be stratified (classified) according to the American Society of Anaesthesiologists (ASA) classification (Table 2).

Table 2 The ASA stratification

STATUS	DESCRIPTION
I	Healthy patient.
II	Mild systemic disease, e.g. obesity or treated hypertension, controlled type II diabetic
III	Severe systemic disease, not incapacitating, e.g. mild cardiac failure, previous myocardial infarction.
IV	Severe systemic disease that is a constant threat to life, e.g. exsanguinated patient with ruptured ectopic pregnancy, or severe renal failure.
V	Moribund, not expected to survive 24 hours irrespective of the operation.
VI	Brain dead person presenting for organ donation.
E	Added as a suffix for emergency operation.

PREMEDICATION DRUGS

The goals of premedication are sedation, amnesia, analgesia, reduction of secretions and vagal activity, and increase of gastric pH and accelerated stomach emptying. A patient who has received sedative premedication will often enter the theatre complex relaxed, sedated, and cooperative. It is well recognized that a clear explanation of anticipated events and a rapport with the anaesthetic team provides more effective anxiolysis than drugs. Sedative should be avoided in patients in whom sedation may aggravate hypoxia (e.g. lung disease and cyanotic heart disease), any airway pathology (decreased muscle tone can cause obstruction), and increased sensitivity to sedative agents (sleep apnoea)

Patients usually receive *all their routine medication. β blockers and statins must however specifically be continued perioperatively.* The doses of glucocorticosteroids and insulin must often be adjusted.

Anticholinergic drugs
These drugs were used previously to dry up airway secretions and to suppress reflex activity. Modern anaesthetic drugs (except ketamine) do not increase secretions. Atropine or glycopyrrolate are usually given in situations where instrumentation of the airway is anticipated, e.g. awake fibreoptic intubation, intraoral surgery. When administered orally, subcutaneously or intramuscularly these drugs do not suppress vagal reflexes reliably.

Atropine is a tertiary amine that crosses the blood brain barrier and the placenta. It decreases the tone of the lower oesophageal sphincter and especially during caesarean sections, regurgitation may occur. Atropine is a potent antisialagogue. It also has antiemetic properties. *The dose is about 10 μg kg^{-1}* orally or subcutaneously one hour preoperatively.

Glycopyrrolate (Robinul) is a quaternary amine and therefore does not cross the blood-brain, -placenta, or -eye barrier. Therefore, glycopyrrolate is preferred to atropine in the elderly (atropine may cause confusion), pregnancy (atropine causes foetal tachycardia), and glaucoma (atropine causes cycloplegia). Glycopyrrolate causes less of a tachycardia. This is important in patients with ischaemic heart disease since a tachycardia disturbs myocardial oxygen balance. The onset of action of glycopyrrolate is longer than that of atropine. Therefore, atropine is preferred to glycopyrrolate if a vagolytic action is needed urgently, e.g. a severe reflex bradycardia. Absorption from the gastrointestinal tract is poor. Glycopyrrolate is a better antisialagogue than atropine. The *dose is about 5μg kg^{-1}* subcutaneously 2 hours preoperatively.

Sedatives
Sedatives are from different classes of drugs, namely benzodiazepines, antihistamines, and opioids. Nowadays, only the benzodiazepines and opioids are used. The advantages of the antihistamines include their antisialogue and antiemetic effects. These drugs may however have untoward effects, including extrapyramidal effects, prolonged sedation (trimeprazine) and hypotension due to an α-blocking effect (especially trimeprazine). Opioids and benzodiazepines cause hypoventilation. These patients must therefore not be left unattended; patients with cardiac or respiratory disease must

receive *supplemental oxygen*.

The benzodiazepines include midazolam (Dormicum 7.5 mg and 15 mg tablets), temazepam (Normison 10 mg and 20 mg capsules).Oxazepam (Serepax 10 mg, 15 mg and 30 mg tablets). These drugs are sedative, cause anterograde amnesia, and are administered orally 1 to 2 hours preoperatively.

The dose of **midazolam** is 0.1 mg kg^{-1} to 0.2 mg kg^{-1} in adults and about 0.5 mg kg^{-1} (to a maximum of 20 mg) in *children*. Midazolam syrup (1.5 mg ml^{-1}) can by prepared with midazolam injection 15 mg per 3 ml added to 7 ml of 50% dextrose injection. About 3% of children developed paradoxical excitation reactions to midazolam after midazolam premedication, which is treated with **ketamine** (about 5 mg kg^{-1} orally). The doses of **temazepam** and **oxazepam** are 0.1 mg kg^{-1} to 0.2 mg kg^{-1}.

Opioids
These drugs are useful as sedatives in patients that experience pain preoperatively. Preoperatively administered opioids may have pre-emptive analgesic effects. Opioid side effects include nausea, respiratory depression, hypotension, and increase in intracranial pressure (due to hypoventilation).
Morphine 0.1 mg/kg to 0.2 mg kg^{-1} is administered subcutaneously or intramuscularly 1 hour to 2 hours preoperatively.
Tilidine (Valoron 50 mg capsules and drops 2.5 mg per drop) is given orally about 1 hour preoperatively; the dose is 0.7 mg kg^{-1} to 1.0 mg kg^{-1}. In children, it is useful to administer tilidine drops paracetamol syrup (about 20 mg kg^{-1}). For example, a baby of 12 kg will receive tilidine about 10 mg in *paracetamol* syrup containing 240 mg of paracetamol. Each Valoron drop contains 2.5 mg of tilidine and 5 ml of paracetamol syrup contains 125 mg of paracetamol. Therefore, the baby may receive 3 drops to 4 drops of tilidine drops in 10 ml of paracetamol syrup.

Patients at risk to aspirate may receive *metoclopramide* about 0.15 mg kg^{-1}2 hours preoperatively. Metoclopramide accelerates stomach emptying, and increases lower oesophageal tone. It can cause extrapyramidal symptoms as it crosses the blood brain barrier. In addition to metoclopramide, patients receive *ranitidine* 2 mg/kg 12 hours and again 2 hours preoperatively, as well as 30 ml of a 0.3 M solution of *sodium citrate* (Pneucid) 30 minutes preoperatively.

As a rule, babies younger than 1 year of below 10 kg should not receive preoperative sedation, unless the patient is under constant observation. The same applies to patients with a history sleep apnoea. Deep preoperative sedation should be avoided.

Specific instructions
These include disease specific monitoring and treatment, e.g. blood glucose monitoring and an insulin sliding scale (see Chapter 17), and intravenous hydration of a patient receiving bowel preparation

BEFORE GOING TO THEATRE

Dentures, glasses, contact lenses, jewellery (theft), etc. should be removed and dental caps, crowns, and bridgework should be noted. Jewellery in the airway (lips, tongue) must be removed since it interferes with laryngoscopy and can be aspirated or swallowed. Consent for procedure is sighted. The bladder must be emptied.

MEDICO-LEGAL ISSUES

You can learn to give anaesthesia only in the operating theatre. Try to perform as many procedures under supervision from different teachers. This will ensure conversance in the principles and practice of anaesthesia. It is also incumbent on you to maintain your knowledge and competency when you leave medical school. In that regard, you are welcome to spend short periods in a training department to refresh your skills.

It is not required from an anaesthesiologist to be omnipotent or omniscient, but he/she must always

know his/her limitations and request help. Gordon Ostlere gives the following good advice:

1. "Work within the limits of your ability - don't try any fancy tricks witnessed from the experts".
2. Keep your head in an all emergencies.
3. Remember - safety first. Anaesthetics are dangerous drugs and it is not at all difficult for carelessness to lead to death on the table. Even though you may not aspire to being an expert anaesthetist, you must at least become a safe one. So let us apply the following advice: If you cannot be good, be careful.

The physician who practices anaesthesia is being scrutinized much more closely not only due to the actual procedures that are being performed, but due to the fact that a patient who dies shortly after having received an anaesthetic, is not deemed to have died of natural causes. Therefore, such an incident is often referred to as an "anaesthetic death".

When a patient dies or retains some deficit after a procedure, the incident is always thoroughly investigated to *determine responsibility and negligence*. It is therefore imperative for the anaesthetist to keep record of all the aspects of the case, i.e. the anatomical, physiological, pharmacological, and monitoring (progress) aspects of the patients during the pre-, intra-, and postoperative phases. *A contemporaneous record of all anaesthetic procedures is therefore compulsory*.

Accountability, responsibility, and negligence

- The doctor is responsible for the patient's safety and is accountable for his/her actions regarding the management of the case. *Accountability* includes not only those actions that have been taken; but also the actions that have not been taken. ***Accountability*** confers guilt and guilt can be attributed to:
  - Active aim to damage or maim.
  - Negligence.
- To determine whether ***negligence*** has occurred the following factors are taken into account:
  - The insight and precautionary measures taken by the inexperienced doctor compared to a doctor who has more experience in a specific area.
  - Whether the reasonable doctor *could foresee* certain consequences and then applied reasonable measures to prevent the disaster from occurring.
  - Whether *care* was taken and maintained.
  - Whether an emergency situation was present that necessitated the physician to take an *immediate decision*. In this situation, the doctor did not have the opportunity to consider his decision at leisure and this is always taken into account in the ruling.
  - Whether the problem was caused due to an error of *judgement*.
  - Whether the management was performed in *ignorance*.
  - Whether the physician was *unobservant*. He can be blamed for this, but not if he was inexperienced or not competent to do the specific procedure.
  - *Risky experimentation* is not acceptable.
- ***Responsibility*** for complications can only be postulated if *cause and effect can be linked*.
- Because any allegations of negligence or even appearance in court can lead to huge expenses, it is prudent for any doctor to have the necessary ***insurance cover***.

CONSENT

- Every accountable patient has a free will to decide what will be done to his/her body. This consent has to be given in writing after the patient has been informed of *the procedure* and the complications thereof. Therefore, the doctor's management is dictated by what the patient has consented to.
- The patient must also *consent to the planned anaesthetic technique*, e.g. epidural anaesthesia or analgesia. In order to enable proper decision-making, the patient must be given sufficient details and information about the procedure regarding benefits, side effects, dangers, and alternatives.

Any procedure undertaken without the patient's consent may be considered an assault in a civil court and may be regarded as serious professional misconduct.

- ***<u>Consent must be given by a lucid person only. Once the patient has received sedatives, he/she is no more legally competent to give consent or to change consent.</u>***
- Permission only includes permissible risks and does not give the doctor the right to be negligent.
- The patient has the right to refuse all or part of the treatment.
- When an adult (person older than 12 years) is not *able to consent* to a procedure (unconsciousness, life-saving procedures), consent may be obtained from a husband, wife, relative, guardian, or superintendent.

Consent has to adhere to the following pre-requisites.

- It has to be given *voluntarily*.
- It must be given *before* the procedure; it cannot be given retrospectively.
- The person that gives permission must understand what the treatment entails and what all the possible risks could be. This is called *informed consent*.
- *Medical paternalism* is not acceptable. This implies that the doctor cannot make decisions on behalf of the patient. Patients have to make their own decisions (*autonomy model*).

If consent cannot be obtained from the patient or from the guardian, the following has to be taken into account:

- The procedure must be *urgent*.
- The treatment must be in the *patient's interest*.
- Only procedures that would be *covered by consent under normal circumstances* can be done.

CHAPTER 3

ESSENTIALS OF AIRWAY MANAGEMENT

This chapter deals with the essentials of airway management. This is not only important in anaesthesiology, but also in all the clinical disciplines of medicine. It is advisable that you print this Chapter 1nd take it with you to theatre during your anaesthetic rotation. You should familiarize yourself with all the equipment and techniques described and get hands-on experience.

Key points
- Anatomy of the airway
- Assessment of the airway
- Definitions of failed, difficult intubation and mask ventilation
- Endotracheal intubation
- Supraglottic airway devices
- Special intubation scenarios
- If there is a high likelihood that mask ventilation and/or direct laryngoscopy will be difficult, secure the airway awake, either with a blind nasal intubation or with a fibre-optic bronchoscope.
- Airway filters between the tube and the anaesthetic circuit and essential. They filter micro-organisms, humidify, and heat the anaesthetic gases. The capnograph fits onto the filter.
- ***If you are unsure that the tube is in the trachea, remove it. Do not waste valuable time if you cannot verify the correct position of the tube.***
- ALWAYS EXTUBATE PATIENTS AWAKE
- In a rapidly decompensating patient, a CRICOTHYRODOTOMY is the only option
- MANAGEMENT OF A FAILED INTUBATION IS A PASS/FAIL QUESTION.
- The position of the head is in full extension for the insertion of an LMA, but for the insertion of an endotracheal tube the head is placed in the sniffing position.

The airway is the passage that connects the mouth and nose to the bronchi. *Airway management* is the intervention whereby the airway is:
- opened (created),
- maintained (kept open),
- protected the lungs from contamination, and
- cleaned

All these functions of the airway allow ventilation – *spontaneous and assisted ventilation*.

Loss of any one of these functions can lead to obstruction, pneumonia, hypoventilation, and hypoxia. ***Therefore, airway management is indicated when***:
- The patient has an *airway obstruction*.
- The patient *cannot maintain* the airway due to anatomical abnormalities, loss of muscle tone (unconsciousness, peripheral causes).
- The patient *cannot protect* the airway. This refers to the inability to swallow or to cough following loss of airway sensation (reflexes). This happens in the unconscious patient and with topical or regional anaesthesia of the airway.
- The patient cannot *ventilate* effectively, e.g. unconsciousness and inability to perform adequate work of breathing (Chapter 13).

These indications for airway management can also be divided into anatomical, physiological, and pharmacological indications:
- *Anatomical and surgical factors*
   These indications usually also necessitate *tracheal intubation.*
   o To *overcome obstruction* due to any pathology that occludes the airway
   o *Maintain patency* of the airway that is jeopardized by anatomical factors, surgery involving the airway (from the face to the bronchi; outside the lumen, in the wall, in the lumen)
   o *Protect the airway* from above (bleeding, pus, saliva) or from below (regurgitation). In these cases, tracheal intubation is essential. A *rapid sequence induction* is performed to minimize the time from loss of consciousness until the tube is in the trachea.
   o If you cannot reach the airway during surgery
   o The non-supine position (lateral, prone, rotation of the head)

- *Physiological factors*
  - Central nervous system suppression (Glasgow coma scale ≤ 8/15)
  - Loss of muscle tone
  - Loss of reflexes (loss of airway sensation)
  - Ventilation – if intubation is not indicated
  - Prolonged procedures cause atelectasis and accumulation of secretions. These conditions often need lung recruitment and toilet and are actually indications for intubation.
  - Patients of the *extremes of age* have anatomical and physiological factors that make them more prone to loss of the airway, decreased muscle tone, and decreased airway reflexes.
- *Pharmacological factors*
  - Loss of airway sensation (topical anaesthesia)
  - Neuromuscular block
  - All central nervous system suppressants cause a dose-dependent loss of airway tone.

You may have noticed that unconsciousness is one of the main indications for airway management. All patients with a Glasgow Coma Scale of ≤ 8/15 must be intubated and ventilated. This forms part of neurological resuscitation and the prevention of secondary brain injury in the patients who have sustained brain injuries. Remember: the most common cause of coma is general anaesthesia. Therefore, general anaesthesia is the most common indication for airway management and ventilation.

While reading the rest of this chapter, you must constantly keep the following aspects of the airway in mind and integrate them:
- The *anatomy* of the airway
- The *physiology* of the airway
- The *pharmacology* of the airway
- *Monitoring* of the airway: are the indications and methods of airway management appropriate and safe? In this regard, pulse oximetry and capnography (see Chapter 4) is indispensible. Briefly, the *pulse oximeter* measures the oxygen saturation of arterial blood. There is a very good agreement between the saturation displayed by the pulse oximeter (SpO_2) and arterial oxygen saturation (SaO_2).

  The capnograph samples gas from the filter between the airway and the anaesthetic circuit (the tubing system connecting the patient airway to the anaesthetic machine). When the patient exhales, the gas contains CO_2, and when the patient inhales, the gas contains a little (rebreathing system or circuit) or no CO_2 (non-rebreathing or circle system). The CO_2 in the gas is analysed by the capnograph and displayed on a graph (*the capnogram*) with CO_2 on the y axis and time on the x axis. If the CO_2 does not increase during expiration, the patient is not breathing, there is an obstruction in the airway, the artificial airway is not functional (e.g. oesophageal intubation), disconnection between the airway and anaesthetic circuit, or a disconnection of the capnograph sampling cannula. For a discussion on capnography and oximetry, see Chapter 4.

ANATOMY

In this section, the anatomy that is pertinent to management of the airway is discussed. ***Please look at the relevant structures in your anatomy atlas***. The airway refers to the continuous tube and is divided into two parts:
- The upper airway stretches from the lips and nostrils to the vocal cords.
- The lower airway consists of the trachea and bronchi.
- The level of the sixth cervical vertebra is an important landmark as this is the junction between the larynx and trachea.

All the parts of the airway are composed of a *lumen, a wall, and structures outside the wall* (Figures 1 and 2). The wall consists of mucosa, muscle, skeleton (bony or cartilaginous). The airway is in

relation to structures along its path. *Structures in the wall* of the airway (may protrude into the lumen), include the teeth, tongue, palatine tonsils, pharyngeal tonsils, epiglottis, and vocal cords. *Structures outside the wall* of the airway include the cervical vertebrae, facial spaces in the neck, thyroid, blood vessels, mediastinal structures (oesophagus, lymph nodes), and lungs. Each of these components of the airway may be distorted or enlarged, which may compromise the patency of the airway.

The functions of the airway are mainly *airflow* (ventilation), *protection* (swallowing and coughing prevents soiling of the lungs), and *speech* (phonation and articulation). The motor functions of the airway differ from voluntary movement, e.g. movements of the limbs, in that they are controlled by accurately controlled muscle activity. The voluntary movements include phonation, articulation (speech), coughing, and swallowing. Although a person decides to do any of these activities, they involve very finely coordinated movements, which one does not control voluntarily. The swallow and cough reflexes are dependent on sensation of the upper and lower airway. Loss of motor or sensory function of the airway always jeopardises airway function: ventilation, protection (swallowing, coughing), and speech. Any factor that interferes with motor or sensory function of the airway can potentially cause obstruction and contamination of the airway.

The term "*airway management*" refers to interventions that ensure maintenance of ventilation and protection of the airway. In the anaesthetic and emergency medicine environment, *the approach to airway management* includes assessment of the three functions (speech, ventilation, and protection).

Airway patency involves anatomical and physiological factors. *Anatomical factors* include all the lesions that involve structures in the wall and outside the wall of the airway. These include congenital, infective, traumatic, neoplastic, metabolic, autoimmune, and degenerative lesions. Enlargement or distortion of any of these structures or their relative sizes, compromise the patency or the airway – from the teeth to the bronchi. *Physiological factors* include *sensory and motor* function of the airway. The upper airway requires *sensation* (it feels if it is open, if there is foreign matter that causes irritation, or obstruction), and *muscle tone* of the muscular structures in the wall (tongue, pharynx, laryngeal muscles).

The mouth

The *muscle tone of the muscles forming the floor of the mouth and the bony structures they are attached to, are pivotal in airway management. The muscles* include the tongue and the diaphragm of the mouth. The *bony structures* include the mandible and the hyoid bone. The tongue consists of *intrinsic and extrinsic muscles*. The *extrinsic muscles* anchor the tongue to the styloid process at the base the skull (*styloglossus*), to the inside of the mandible anteriorly (*genioglossus*), and the hyoid bone laterally (*hyoglossus*). The extrinsic muscles of the tongue and those in the floor of the mouth pull the tongue upwardly and anteriorly out of the pharynx.

The *diaphragm of the mouth* mainly consists of the hammock-like muscle (*mylohyoid*). This flat muscle (left and right) stretches between the mylohyoid line on the medial aspect of the mandibular arch, and the anterior arch of the hyoid. The left and right muscles meet in a median raphe. This raphe is covered on the superior surface of the mylohyoid by the *geniohyoid*. The anterior and posterior bellies of the *digastric muscle* is also supported the hyoid bone. The mylohyoid supports the structures in the floor of the mouth, namely the tongue and the salivary glands.

Nerve supply of the nasal cavity and mouth
Motor supply
All the intrinsic and extrinsic muscles of the tongue are innervated by the hypoglossal nerve (N XII). The mimic muscles of the mouth and cheek (buccinators) receive their nerves from the facial nerve (N VII). The muscles of the floor are supplied as follows:
Digastricus posterior belly: N VII
Digastricus anterior belly: N V3
Mylohyoid: N V2
Other muscles in the floor of the mouth: C1 to C3
Muscles of mastication: N V3

Sensory supply
The tongue: General sensation to the anterior two thirds: lingual nerve (N V3); taste to the anterior two thirds: chorda tympani (N VII); taste and general sensation to the posterior third: glossopharyngeus; base of the tongue: superior laryngeal nerve (N X).
The rest of the inside of the mouth: N V2 and V3

The roof, and upper parts of the septal and lateral parts are of the nasal cavity is innervated by the olfactory nerve for smell. General sensation: N V1 and V2

The pharynx

The pharynx consists of the upper, middle, and lower constrictors. These fanlike muscles are prevertebral. The superior constrictor arises from the pterigo-mandibular ligament in the cheek (actually continuous with the buccinator). The middle constrictor arises from the hyoid bone and stylohyoid ligament, which anchors the hyoid to the base of the skull. The inferior constrictor arises from the thyroid and cricoid cartilages.

The pharyngeal constrictors as well as the tongue are involved in swallowing. The pharynx is surrounded by deep facial spaces, which extends posteriorly (retropharyngeal space) and downward into the mediastinum. The cervical vertebrae are posterior to the pharynx. The pharynx may be narrowed by deep neck sepsis (Ludwig angina) and a prevertebral haematoma following a neck injury.

Nerve supply to the pharynx

The pharyngeal constrictors and palatine muscles, except stylopharyngeus (N IX) and tensor palati (N V3), receive their motor innervation from the spinal accessory nerve (N XI) via vagus pharyngeal plexus. The pharynx, soft palate, and tonsils receive their sensory nerve supply from glossopharyngeus, with contributions from N V2 to the roof, and the internal laryngeal nerve (from superior laryngeal branch of vagus) around the inlet to the larynx.

Loss of sensation (e.g. *topical anaesthetic* applied to the mouth and pharynx) causes loss of pharyngeal reflexes (tone, cough, swallow), while loss of motor function (general anaesthesia, muscle relaxants) causes collapse of the airway and inability to swallow. The muscles of the airway are particularly sensitive to the *non-depolarising muscle relaxants*. *Therefore, both sensory and motor dysfunction causes airway obstruction and pulmonary aspiration.* ***Unconsciousness (general anaesthesia, head injury) is a very common cause of loss of all the functions of the airway, and therefore, obstruction and contamination.***

The larynx

The *larynx* is a collection of cartilaginous structures to which extrinsic and intrinsic muscles are attached. The larynx consists of an *external and internal* framework. The *external* framework consists of the *thyroid* and *cricoid* cartilages, while the *internal* framework includes the *arytenoid* and *epiglottis c*artilages. The thyroid cartilage is connected to the hyoid bone superiorly with the thyrohyoid ligaments and muscles, and inferiorly to the cricoid ring and sternum with the cricothyroid membrane/ligament and muscles, and the sternothyroid muscles, respectively   inferiorly. The *cricoid* is the point where the developing upper and lower airways meet. *In babies, the cricoid ring is the narrowest part from the mouth to the trachea*.

The *stalk of the epiglottis* is attached to the posterior surface of the thyroid cartilage above the attachment of the vocal ligaments (chords) in the angle between the thyroid cartilage laminae. The supporting membrane between the anterior surface of the epiglottis and the hyoid ring (*hyoepiglottic ligament*) pulls the epiglottis anteriorly and thereby prevents it from falling backwards over the glottic opening.

The *arytenoid cartilages* are triangular. The arytenoid cartilage has *three angles* (processes) and *three borders*. The *arytenoid processes* are apical (superior), muscular (posterior), and vocal (anterior):
- The *apex* carries the corniculate cartilage.
- The *muscular process* is posterior and four muscles are attached to it, namely the *arytenoideus, posterior cricoarytenoid, lateral cricoarytenoid,* and
- The *vocal ligaments* and vocales muscles are attached to the vocal processes of the arytenoids posterior and the angle between the thyroid laminae anterior.

The *borders of the arytenoids* and their attachments:
- The *bases* of the arytenoids articulate with the arytenoid facets on the superior aspect of the lamina of the cricoid ring.
- The *lateral* borders of the arytenoids are attached to the *posterior borders of the quadrangular membrane* (aryepiglottic membranes and muscles). The free *superior borders* of quadrangular membranes are the aryepiglottic ligaments and muscles. The *anterior borders* of the quadrangular membranes and muscles are attached to the border of the epiglottis, while the *inferior free borders* are the *ventricular ligaments* (false vocal cords). The lateral borders also attach the *thyroarytenoid muscles.* The free medial borders of these muscles are the vocalis muscle adjacent to the vocal ligaments.
- The *posterior borders* attach the transverse arytenoideus muscle between the two arytenoids.

The *cricothyroid membranes* (*triangular membrane or conus elasticus*), median cricothyroid ligament, and the *cricothyroid muscles* bridge the gap between the thyroid and cricoid cartilages. The *vocal ligaments* form the free superior border or the triangular cricothyroid membrane. ***The cricothyroid muscles, membrane, and ligament are subcutaneous structures and is the site where a median needle crico-thyroidotomy is done in the "cannot-intubate-cannot-ventilate" scenario.***

The *ventricular ligaments* (free inferior borders of the quadrangular aryepiglottic membranes) and the *vocal ligaments* (in the free borders of the triangular cricothyroid membranes) are covered by mucosal folds. These folds are called the *vestibular and vocal folds*, respectively. The mucosa-lined pouches between these folds are called the *ventricle*. Therefore, the *laryngeal cavity* can be divided into three parts from superior to inferior, namely the *vestibule, ventricle, and infraglottic* cavity.

Function of the muscles of the larynx:

- *Opening the rima glottidis during breathing by abduction of the vocal cords* (rotating the vocal processes of the arytenoids laterally): the posterior cricoarytenoids only.
- *Closure of the rima glottidis during swallowing by adduction of the vocal cords* (rotating the vocal processes of the arytenoids medially): the lateral cricoarytenoids, thyroarytenoids, and the arytenoideus.
- *Closure of the rima glottidis during swallowing by closing the vestibule from superior*: the thyroarytenoids tilt the arytenoids forward and constrict the vestibule, while the aryepiglottics and thyroepiglottics tilt the epiglottis backward over the rima glottidis.
- *Regulating the tension of the vocal cords for phonation*: during adduction of the cords, their tension is increased when the *cricothyroids* (tensor of the vocal cords) contract and tilt the thyroid cartilage forward and away from the arytenoid cartilages. All the muscles between the arytenoids and thyroid laminae as well as between the epiglottis and the thyroid laminae are stretched. The posterior cricoarytenoids stabilize the arytenoids on the cricoid facets. Therefore, during speech, the tension in the vocal cords increases, while the epiglottis is removed from the inlet to the vestibule. The *vocalis* do fine adjustments to the tension in the vocal cords.

Nerve supply to the larynx

The larynx receives its their motor, sensory, and autonomic innervation from the superior laryngeal and recurrent laryngeal branches of the vagus nerve:

- *Motor* to all the intrinsic muscles: *the recurrent laryngeal nerve. This nerve is sometimes injured during neck surgery, especially thyroidectomy.* If the *nerve is severed*, both the adductors and abductors are paralysed and the vocal cords are in a neutral position (*the rima glottidis is open*). If the *nerve is only injured*, the phylogenetically older muscles, the adductors, are spared and they contract (*rima glottidis closes*). If *both nerves are injured*, the adductors from both sides contract, and the rima glottidis closes and the *patient has stridor and can suffocate*. If only one nerve us severed or injured, the adductors from that side will relax or contract, respectively. The *patient will be hoarse*.
- *Motor* to the cricothyroids: the *external branch* of the superior laryngeal nerve.
- *Sensory* to the larynx *above the vocal cords*: the *internal branch* of the superior laryngeal nerve.
- *Sensory* to the larynx *below the vocal cords*: *the recurrent laryngeal nerve.*
- *Autonomic*: The vagus nerve carries *sympathetic (vasomotor) fibres* and is responsible for the haemodynamic response to airway management (hypertension and tachycardia).

Laryngospasm refers to prolonged intense glottic closure due to adduction, constriction and backward movement of the epiglottis. ***(Laryngospasm must be distinguished from bronchospasm; see Chapter 13.)*** Laryngospasm occurs in response (reflex) to direct glottic or supraglottic stimulation by inhaled irritants, secretions, foreign bodies, or mechanical stimulation (suctioning, laryngoscopy during shallow levels of anaesthesia. Stimulation
from the periosteum, celiac plexus, or dilatation of the rectum or cervix can also precipitate this reflex. This reflex tends to persist even after the stimulus has been removed.

Laryngospasm must be *distinguished from loss of muscle tone of the upper airway*. All the muscles of the upper airway are striated and very sensitive to the action of *non-depolarising muscle relaxants*. This obstruction is characterized by inspiratory stridor in the supine position, which improves when the patient leans forward. This position moves the tongue and epiglottis out of the airway. These muscles also lose their tone when the *mucosa is anaesthetized* with topical or regional anaesthesia. ***Therefore, it is dangerous to apply topical anaesthesia to a threatened airway. If you would do it, be sure that someone can perform a crico-thyroidotomy or a tracheostomy if the airway would become obstructed.***

The trachea

The trachea and oesophagus start where the pharynx and larynx end at the cricoid cartilage. In adults, the trachea starts in front of C6, about 150 mm from the incisor teeth, about 50 mm above the suprajugular notch of the manubrium, which is about 50 mm from the carina at the level of the sternal angle. The trachea ends at the carina where it bifurcates to form left and right main bronchi. In supine adults, the carina is about 100 mm to up to 150 mm from the cricoid. Therefore, about half of the trachea lies outside the thorax, and the other half in the superior mediastinum. The transverse diameter of the trachea is larger than the sagittal diameter. The diameter varies between 17 and 25 mm and is larger in men. There is no significant correlation between tracheal calibre and body mass or height.

The carina is at the plain between the superior and inferior mediastinum at the horizontal level between the sternal angle (Louis) and vertebrae T4/5 (in babies at T3/4). In the head-up position the carina moves down to the level of about T6, while it moves more cephalic in the head-down position. Therefore, a tracheal tube that is fixed to the mouth easily slips out of the trachea when the patient is put in the head-up position, while it moves endobronchially (usually to the right) with the patient in the head-down position.

The right main bronchus is shorter (about 30 mm) and more vertical than the left (about 50 mm). The angle between the

main bronchi is < 70°. The more vertical slope and shorter length of the right main bronchus are the reasons why endobronchial intubation (the endotracheal tube has been inserted too deep) occurs more commonly and why a right endobronchial tube occludes the upper lobe bronchus.

The trachea consists of about 20 C-shaped cartilages rings with a membranous part posterior. The membranous part contains smooth muscle. The trachea is lined by a mucosa of pseudo-stratified ciliated columnar epithelium. Throughout its length, the trachea lies in front of the oesophagus with the left recurrent laryngeal nerve in the angle between them. Above the manubrium, the trachea is in contact with a lobe of the thyroid gland on each side and the isthmus in front of the upper 2 or 3 tracheal rings. The thyroid also expands downward on the side of the trachea and upward on the larynx and pharynx. Each lobe is attached to the cricotracheal ligament with a dense ligament. Therefore, enlargement of the thyroid can displace and obstruct the trachea from the pharynx to the trachea.

Behind the manubrium, the anterior and left lateral aspect is in contact with the aortic arch. Behind the upper part of the manubrium, the brachiocephalic, left common carotid, and left subclavian arteries lie from right lateral to left lateral anterior to the trachea. The tracheobronchial lymph nodes occupy the angles between the trachea and bronchi. These lymph nodes can enlarge, forming large mediastinal masses, which can narrow the trachea.

The trachea, like the pharynx, larynx, and other body openings, is ***abundantly innervated***. The trachea receives its motor (smooth muscle) and sensory (mechano- en irritant receptors) fibres from the vagus nerve. Stimulation of mechano- and irritant receptors causes constriction of the membranous part and coughing. The *carina is particularly richly innervated* with these sensory fibres. Irritation of these receptors by a tracheal tube or irritating fluid can provoke reflex laryngo-and bronchospasm. *Reflex coughing, laryngo-, and bronchospasm* are not only provoked by local irritation, but also by stimulation of structures that are *richly innervated with parasympathetic fibres*, particularly in the *lightly anaesthetized* patient. This is observed in, e.g. laryngoscopy, tracheal intubation, and procedures on the neck, rectum, cervix, urethra, and bladder. Therefore, if patients receive only a supraglottic airway (see next section) for these highly stimulating and painful procedures, a deep plain of anaesthesia is required. This makes anaesthetizing patients for these seemingly minor procedures an art; they require a deep plain of anaesthesia for procedures lasting only a few minutes.

The ***trachea is perfused*** from the inferior thyroid arteries and the tracheobronchial arteries in the thorax. The *blood pressure in the submucosal capillaries* is probably in the region of 20 mm Hg. This pressure is important since it varies with systemic blood pressure and is compromised by pressure on the mucosa by a tracheal tube. If the *systemic blood pressure would decrease*, the mucosa is more vulnerable to pressure and may become *ischaemic and necrotic*. This leads to *fibrosis and stenosis*. ***This is a very important aspect of airway management***.

To summarise: Any anatomical abnormality of the skeletal elements to which the airway muscles are attached (congenital, sepsis, malignancy, fractures), enlargement of structures related to these muscles (vertebral, mandibular, hyoid, salivary glands), and loss of motor tone in these muscles may interfere with the patency of the airway and with swallowing, i.e. cause airway obstruction and contamination.

Exercise: Starting with the lips and ending with the bronchi, name lesions that may cause airway obstruction and soiling. Hint: look at all the structures named in Figures 1 and 2. Give special attention to the muscles of the mouth floor and their attachments.

You must know the differences between the adult and infant airway (Chapter 22) and the airway changes during pregnancy (Chapter 21).
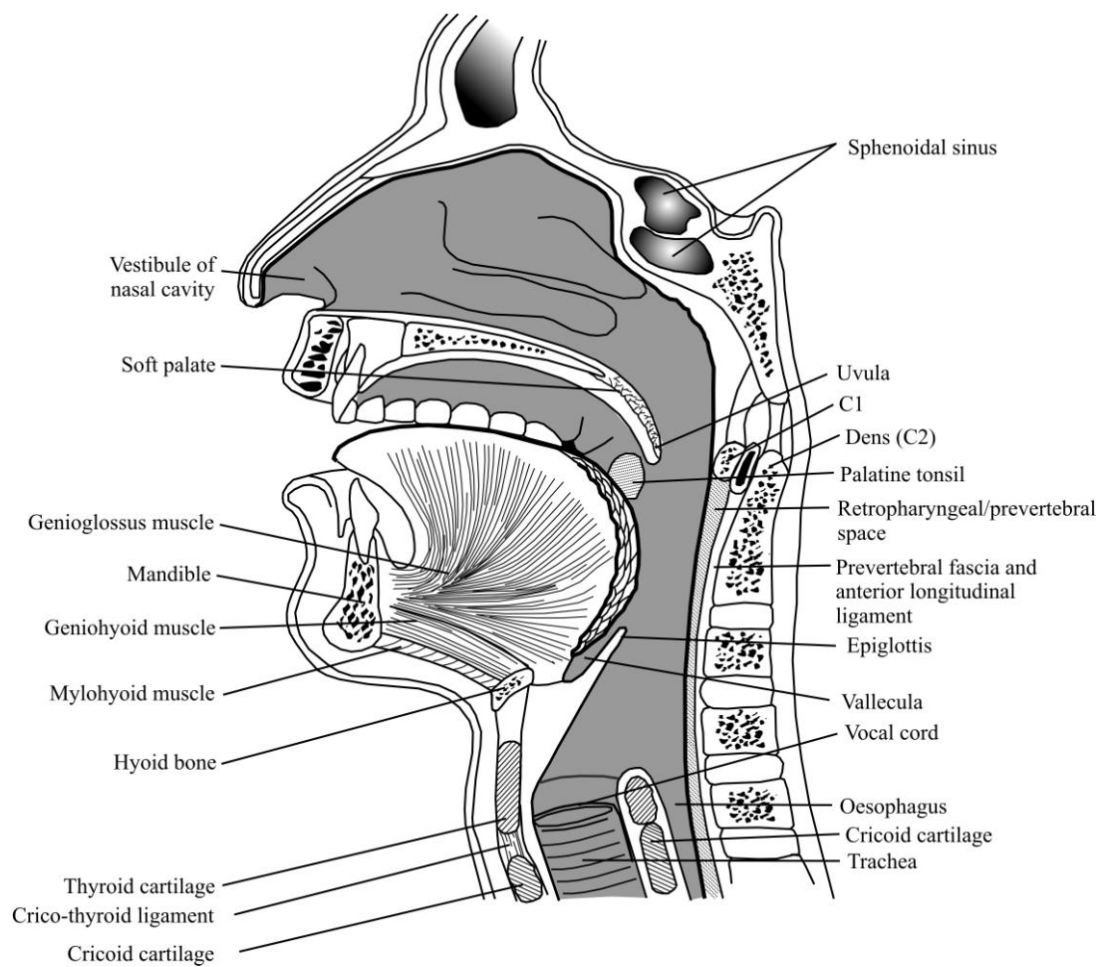
Figure 1 Midsagittal section of the upper airway and related structures.
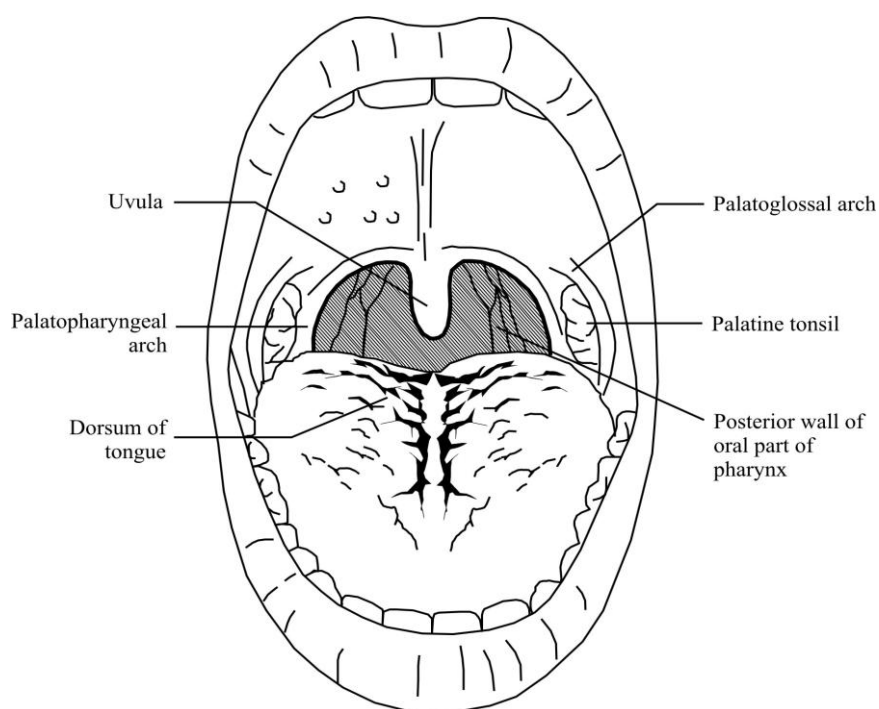RP and PV spaces = Retropharyngeal and prevertebral spaces

Figure 2 Mouth and pharyngeal structures

METHODS OF AIRWAY MANAGEMENT

Regarding acute airway management, the priorities are patency and protection of the airway.

Pre-induction equipment check
Before you embark on airway management, the equipment necessary to create, maintain, and secure the airway must be immediately available:

- An assistant. ***Do not do airway management on your own***.
- The anaesthetic machine must have been checked.
- Suction.
- The theatre table must be in working order.
- An intubation pillow (about 10 cm thick for adults and 5 cm for children)
- Laryngoscope with a choice of blade sizes
- Stylet and Magill forceps
- An oral airway and laryngeal mask airway (LMA) (see Table 1)
- An endotracheal tube of which the cuff has been tested for a leak must be on the anaesthetic machine. A tube of one size smaller must also be available.

The indication for airway management determines *the method or route (Tables 1 to 3)*. These methods are supraglottic, translaryngeal, and transtracheal.

- *Supraglottic* (Table 1): These open the airway up to *the hypopharynx*. Supraglottic airways are inserted with the knowledge what path they follow, but usually not under direct vision; they are *inserted blindly* and may be used when inspection of the airway (pharynx and vocal cords) is not possible. Therefore, supraglottic airways are often used *when laryngoscopy has failed* and/or as emergency airways. They do not ensure patency of the rima glottides, such as anatomical lesions and laryngospasm. All the transoral supraglottic airways keep the upper and lower jaws apart and therefore prevent swallowing. They can also, irritate the pharynx, cause coughing, vomiting, and laryngospasm and therefore promotes aspiration – especially in the lightly anaesthetized patient. Therefore, *they create and maintain the upper airway but do not protect the airway*. They do not protect the airway from aspiration. They are often used to create and maintain an airway *in an emergency, e.g. cannot intubate cannot ventilate (CICV)*. The supraglottic airways are contraindicated in *elective (planned) surgery if the patient*:
  - If the patient runs the risk to *regurgitate and aspirate*;
  - If the patient is operated in any *other position than the position*;
  - If the patient runs must be *ventilated* during the procedure.
  - When the airway is shared with the surgeon or when you will be *unable to reach the airway* during surgery (head and neck surgery)

- *Translaryngeal* (Table 2): "Endotracheal tubes" (ETT) is the collective term for tubes that are inserted via the mouth or nose into the trachea. These tubes remain the safest and most predictable airways. Insertion of translaryngeal airways *requires direct or indirect (fibreoptic) laryngoscopy.* If one knows how, or is lucky, an ETT can be inserted *blindly*. Translaryngeal airways create, maintain, and protect the airway, and allow ventilation. Bronchoscopy and bronchial toilet can be done through the straight tubes but not through RAE tubes. The number of the tube refers to the inner diameter in mm. The size inserted is determined by the size and age of the patient. Men are usually intubated with Nr 8 to Nr 9, and women with Nr 7 to Nr 8. For paediatric sizes, see Chapter 22.

- *Infraglottic* (Table 3): These airways are obtained electively or in the CICV scenario. These are surgical airways where an airway is passed into the trachea under vision.

Table 1 Supraglottic airways (See airway equipment at end of chapter)

The facemask O + N→P	Allows oxygenation and ventilation before insertion of an airway or laryngoscopy. Gas flows through the nose and mouth to the pharynx.
Guedel oral* airway O→P	This curved airway pushes the tongue and mouth floor inferiorly and anteriorly and opens the airway from the lips to above the hypopharynx. It is used after induction of anaesthesia to allow mask ventilation.*
Nasopharyngeal airway N→P	This soft tube is inserted through the nose into the hypopharynx. An ordinary endotracheal tube can also be used. It is useful in patients with a threatened airway with any pathology that prevents O→P access, e.g. trauma, sepsis (Ludwig angina), tumour.
Laryngeal mask airway (LMA). O→P The variations are available: Classic Supreme Intubating LMA (FasTrach)	The **ordinary ("Classic") LMA** consists of a tube connected to an inflatable cuff in the form of a pear cut in half in the longitudinal axis. The tube opens at the flat side. The mask pushes the epiglottis anteriorly to open the ventricle of the larynx, while the narrow tip fits into the opening of the oesophagus. The cuff is inflated with a volume of air indicated on the mask or until no air leak is heard with gentle manual ventilation. The patient can still regurgitate and aspirate since there is still communication between the upper and lower airway. Fluid from above the mask can also tract past the mask to the trachea. The **"Supreme"** has an additional tube that stretches from proximal to the tip of the LMA. A tube can be passed through it to remove fluid from the ventricle and stomach. LMAs can either be *reinforced or not*. The **"FastTrach"** is an emergency airway device. It is a LMA with a metal curved (about 90°) tube, which allows blind intubation. This tube (usually) enters the trachea. The mask is removed and the tube remains in the trachea. It is not advisable to use a device for the first time in an emergency situation.
I-gel O→P	This device is similar to the LMA but has a non-inflatable distal part.

O→P Oropharyngeal; O + N→P Oro- and nasopharyngeal.

*__Regarding the Guedel airway, it is important to note that it should not be used to prevent the patient from biting the ET tube since the masseter muscles can exert as much as 1200 N. This can cause fracture of the incisors. Before waking up a patient, it is better to insert a role of gauze (not hard objects) between the molar teeth. Remember, the gauze must be visible all the time so that you do not forget to remove it after extubation__.

Table 2 Translaryngeal airways

"Straight" endotracheal tube (ETT). N→T or O→T	These tubes are cuffed or uncuffed (usually for babies and small children < 8 years). They may be reinforced with metal wiring to assume different curves without kinking. Reinforced tubes are inserted when the patient is operated on in the non-supine position or when pressure from tumours may compress the tube, e.g. a large thyroid or mediastinal masses.
RAE N→T or O→T	These ETTs are preformed to keep the tube out of the surgical field, e.g. oral RAE for nasal or eye surgery and nasal RAE for oral surgery.
Combitube O→T and O→P	This is an emergency airway and consists of a short and a long lumen, each with a cuff. In the CICV situation the tube can be inserted into the pharynx and the cuffs are inflated. The proximal tube is perforated distal to the cuff. If the long tube enters the oesophagus, the patient can be ventilated via the perforations distal to the pharyngeal cuff. If the long tube enters the trachea it is treated as a normal ETT. It is not advisable to use for the first time in an emergency.

O→P Oropharyngeal; O→T orotracheal; CICV cannot intubate cannot ventilate.

Table 3 Infraglottic airways

Crico-thyroidotomy with cannula S→T	This is an *emergence airway* in the CICV. A *intravenous cannula* is connected to a water-filled *5 ml syringe*, feel the CTM and plunge the needle through the membrane while aspirating. The appearance of *air bubbles* in the syringe indicates that the tip of the cannula stylet is in the trachea. Advance the needle slightly more to ensure that the *cannula is in the trachea*. Detach the syringe and advance the cannula into the trachea. *Remove the plunger* of the syringe and insert a cuffed endotracheal tube or only the tube connection into the cylinder.* Connect the syringe to the cannula and connect a *Jackson Rees anaesthetic system* with capnograph to the cannula. Ventilate at low pressures with *100% oxygen*.
Cricothyroidotomy with tube S→T	Ready-made products are available consisting of a CT cannula, guide wire to put through the cannula into the trachea, and a tube over a dilator to put over the guide wire into the trachea.
Tracheotomy S→T	The tubes are uncuffed or cuffed. The cuffs can be inflated with air or are self-inflating (foam cuff tube). The tracheotomy tube is inserted through an incision in the skin, subcutus, and trachea. A tracheotomy can be done electively or emergently. Whenever there is a possibility that irreversible airway obstruction may occur, it may be decided to perform a tracheotomy under local anaesthesia. Or the anaesthetist may decide to attempt endotracheal intubation but have a surgeon in theatre should an emergency tracheotomy be indicated.

S→T Skin to trachea; CICV scenario cannot-intubate-cannot ventilate; CTM cricothyroid membrane; *This device must be in your bag or on the anaesthetic machine.

A basic but essential aspect of supraglottic airway management is the facemask

The facemask is used to:

- *Oxygenate* the hypoxic patient;
- *Preoxygenate* before induction of anaesthesia (the patient that may become hypoxic during induction or anaesthesia and subsequent insertion of a supra- or infraglottic airway);
- *Assisted (manual) ventilation* during induction of anaesthesia;
- *Spontaneous or assisted ventilation* for short procedures, e.g. dilatation and curettage and C, insertion of myringotomy tubes.

Mask ventilation (spontaneous and assisted) is an essential skill in the management of any airway. It must be performed appropriately and correctly to prevent complications, namely inability to ventilate, inflation of the stomach, regurgitation and aspiration.

Mask ventilation consists of three steps:

- *The first step in mask ventilation is correct positioning.* This creates a continuous column of air/gas between the mouth or nostrils and the trachea. This positioning of the head and mandible moves the floor of the mouth and the tongue anteriorly and inferiorly, *similar to the line of vision (see LOV under the next section: Laryngoscopy and endotracheal intubation).* This is essential since mask ventilation is very often followed by laryngoscopy – which requires the LOV (Figures 4a and 4b).
- *The second step is the **jaw thrust**.* The fingers of one or both hands are placed at the angle of the jaw and the jaw lifted up. This manoeuvre moves of the tongue and mouth floor out of the way of the LOV (pharynx) (see the anatomy of the mouth floor). An ***appropriately*** sized oropharyngeal airway may also allow improved airflow (Figure 3).
- *The third step is to place a facemask over the mouth and nose.* Attach the mask to the anaesthetic machine (or to an ambu bag in the wards) and manually ventilate the patient. *You must see* the chest (not the stomach) moving, a capnogram on the monitor must indicate ventilation, and pulse oximeter must indicate adequate oxygenation. If you do not see these signs, mask ventilation is ineffective and the patient position, jaw thrust and airway must be reassessed. *If you are struggling*, request assistance. Ask your assistant to squeeze the bag while you hold the mask with both hands. If properly done, this technique is effective in 98% of patients. In the 2% that you cannot ventilate, you have 2 choices:
  - When the anaesthetic is deep enough (to prevent laryngospasm), a quick laryngoscopy may

be attempted to see if you can intubate the trachea
- o Or a laryngeal mask airway (LMA) may be inserted. You may decide to leave the LMA as the airway conduit for the rest of the operation or you may call for help to exchange this for an endotracheal tube.

Figure 3a The jaw thrust and mask ventilation

LARYNGOSCOPY AND ENDOTRACHEAL INTUBATION

The device most commonly used to create and open, maintain, and protect an open airway is the *tracheal tube*. The tracheal tube may be inserted through the mouth (*orotracheal*) or nose (*nasotracheal*) or per cutaneously (through an incision in the skin) directly into the trachea (*crico-thyroidotomy or tracheotomy*), or less commonly, submento-tracheal (through the floor of the mouth). Oro- and nasotracheal tubes are collectively called *endotracheal tubes* (ETTs). In order to pass an ETT, one must be able to see the vocal cords (*laryngoscopy*). The vocal cords can be inspected directly using a laryngoscope (*direct laryngoscopy*) or indirectly using optical instruments (reflective or, more commonly, *fibre optic laryngoscopy*).

During *direct laryngoscopy*, the intubator looks directly at the vocal cords and the path between the vocal cords and the eyes of the intubator is a straight line (Figure 4). This line is called the *line of vision (LOV)*. The LOV stretches from the tips of the upper incisors to the tips of the arytenoid cartilages (corniculate cartilages) posterior to the vocal cords (please see a sketch of the skeleton of the larynx from superior in your anatomy atlas).

The line of vision must be uninterrupted to see the vocal cords. If the line of vision is interrupted but the intubator decides to insert the ETT by steering it in the direction he/she thinks the glottic opening is, it is called a *blind intubation*. A blind nasal intubation is regularly performed. If a fibre optic laryngoscope or bronchoscope is used to insert an ETT, it is called a *fibre optic intubation*. A fibre optic intubation is the method of choice and safest to intubate the trachea when direct laryngoscopy has failed. If one cannot insert an ETT, it is called a *failed intubation*.

During direct laryngoscopy the head and neck is *positioned* in such a way that the relative positions of the components of the airway change in such a way that the LOV reveals the vocal cords, namely the sniffing position. The *sniffing position* is obtained by elevating the occiput 10 cm, flexing the neck, and extending the atlanto-occipital joint. Now look at figures 4a and 4b.
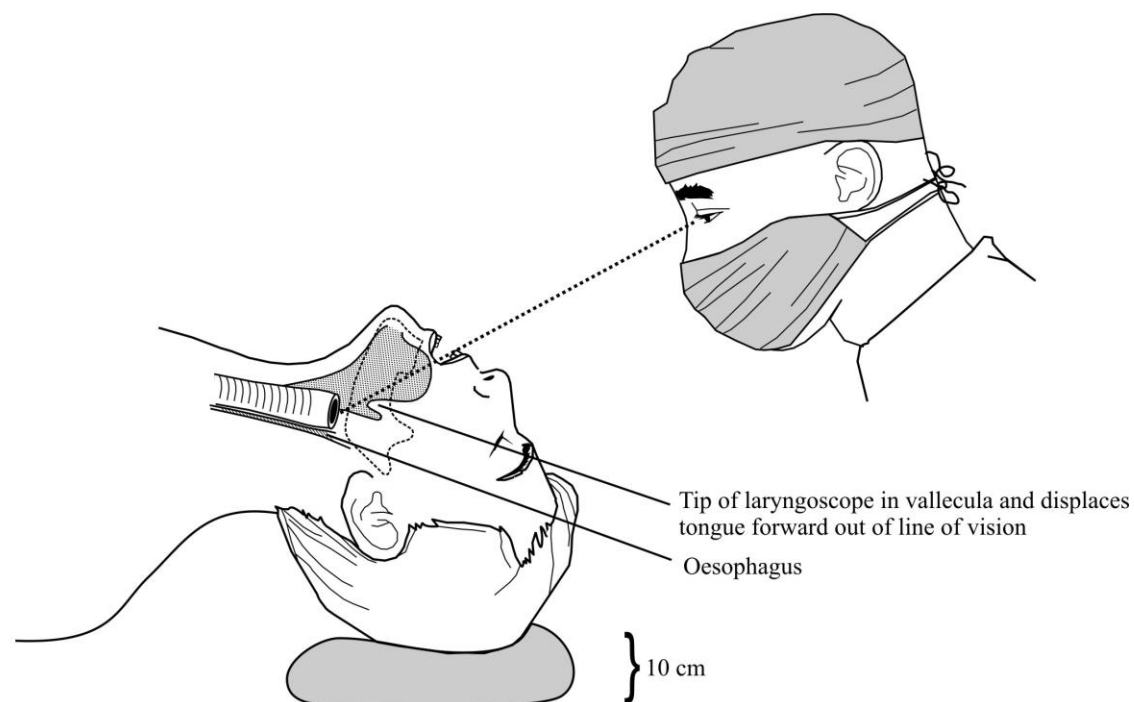
Figure 4a The line of vision with the head in the sniffing position

Tip of laryngoscope in vallecula and displaces tongue forward out of line of vision

Oesophagus

10 cm
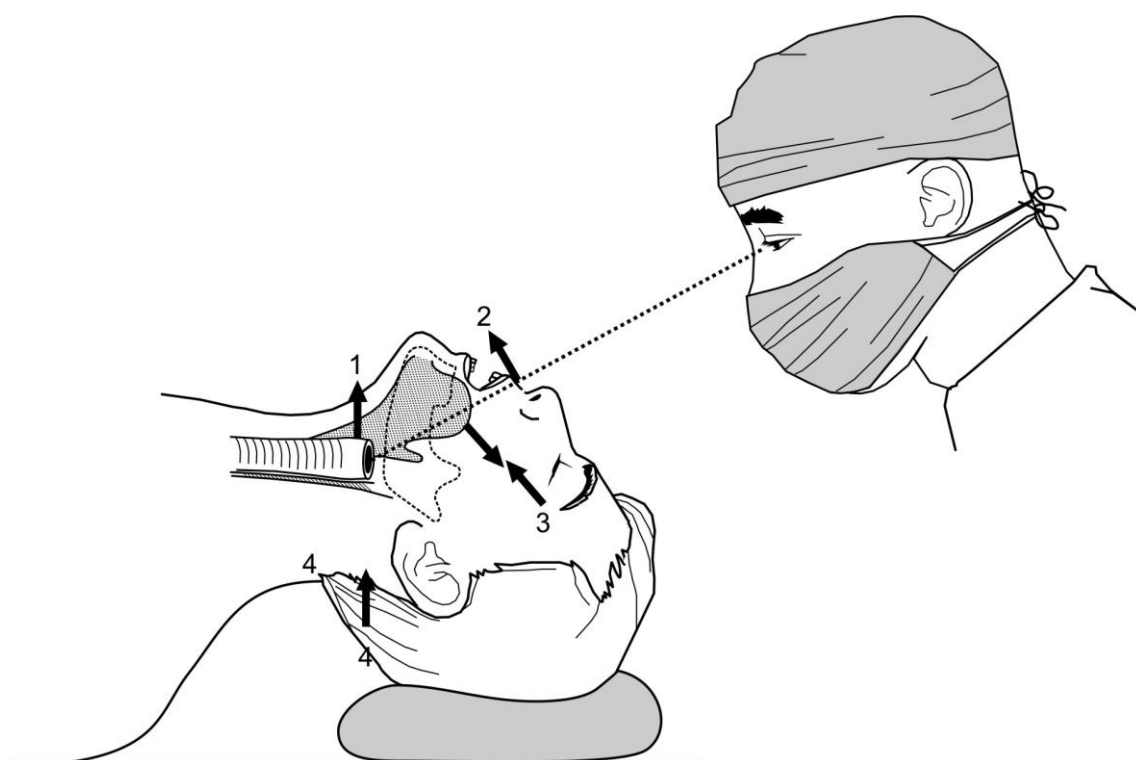
Figure 4b Interruption of the LOV by:
1. An anterior larynx
2. Inability to open the mouth; prominent teeth which shifts the line upwards
3. A large tongue, tongue tumours, supra- and inframylohyoide tumours or infection (Ludwig angina) immobile tongue, or small mandible (protruding tongue); palatal tumours
4. Retropharyngeal lesions (retropharyngeal haematoma, sepsis, Ludwig angina), prevertabral haematoma, sepsis)

1 to 4. Poor positioning; inability to open the mouth, flex the neck or to extend the atlanto-occipital joints (sniffing position)

Direct laryngoscopy and endotracheal intubation consists of the following steps:
- *Pre-induction equipment check* forms part of airway
- Put the head in the *sniffing position*.
- Before you attempt an elective laryngoscopy and intubation, *the patient must be well preoxygenated*, since a (hopefully short) period of apnoea occurs during laryngoscopy and intubation. Preoxygenation consists of mask ventilation with at least 80% of oxygen for at least 3 minutes to fill the functional residual capacity (FRC) with oxygen. This will sustain oxygenation during the subsequent period of apnoea. This is especially important in patients with as small FRC (pregnancy, obesity), and when a difficult intubation is anticipated.
- Hold the laryngoscope in the left hand and *open the mouth* with the right hand. Opening of the mouth gives access to the laryngoscope and moves the floor of the mouth and with it, the tongue away from the LOV.
- Insert the laryngoscope from the RIGHT side of the mouth and push the tongue to the LEFT.
- *Slide the laryngoscope blade over the tongue* while following the movement of the tip of the blade as it is entering the oropharynx and the hypopharynx.
- The *tip of the epiglottis* becomes visible. When using a *curved blade* (Macintosh) the tip of the blade is advanced into the *vallecula* (in front of the epiglottis). When one uses a *straight blade* (Magill, Miller, Jackson-Wisconsin), the tip of the blade is positioned posterior to the epiglottis.
- With the tip of the blade in position, *the whole blade is lifted up parallel to the LOV (45º to the floor) to move the tongue out the way of the LOV. Do not use the upper incisors as a fulcrum!*
- Now the *vocal cords should be visible*. **Please note: one does not visualize (imagines, envisages) the cord – one sees (observes, notices) the cords.**
- Insert the ETT into the trachea ***under vision***.
- Often, the vocal cords are visible, but the tip of the ETT keeps on slipping into the oesophagus (look at Figures 4a and 4b). This problem is overcome by inserting a malleable metal or plastic *stylet* into the ETT. The distal, say 5 cm, is curved upwards so that the tip of the ETT can be steered into the glottic opening. Therefore, before you embark on *orotracheal intubation, be sure there is a stylet on the anaesthetic machine*.
- Once the tube in place, *attach it to the breathing circuit and ventilate* manually or switch on the ventilator.
- *Check correct placement* of the ET tube by looking for moisture in the tube, equal chest movement, auscultation of the epigastrium and axillae, appearance of a capnogram and sustained good oxygenation (pulse oximeter).
- Gently *inflate the cuff* until the air leak disappears at normal peak inspiratory pressures.

One of the most common mistakes all of us make, is to insert the laryngoscope blade overzealously and without following the tip as it enters the hypopharynx. Then you fail to see the epiglottis and put the tip of the blade into the oesophageal opening. Simply withdraw the blade until you see the vocal cords. Ask the anaesthetist to demonstrate this mistake to you. Study Figures 4a and 4b attentively again.

Nasotracheal intubation
- *Nasal intubation* is indicated to allow *surgical access,* e.g. oral surgery and when *long-term intubation is expected (controversial). During nasotracheal intubation*, the steps up to visibility of the vocal cords are the same. There are some special considerations when performing a nasotracheal intubation:
  - You must ask the patient which nasal cavity is the largest; left or right. Does he/she experience obstruction to airflow through either when breathing through the nose? If nasal breathing is difficult through both nasal cavities, it may be that both cavities are narrowed or that there is an obstruction in the nasopharynx, e.g. retropharyngeal/prevertebral lesions (haematoma, abscess, tumour) that bulge into the pharynx. If uncertain about the cause of the obstruction, avoid nasotracheal intubation.
  - Enquire about previous nasal surgery (reconstructions). Do not destroy the good results! It may cost you a few Rand.

- o Does the patient have any bleeding diathesis: hereditary, anticoagulants, thrombo-cytopaenia, anti-platelet agents, DIC, etc. If so, avoid nasotracheal intubation.
- o The nose is a vascular *area*. Therefore, extreme care must be taken during nasal intubation to adequately soften the tube in hot water, lubricate it, and possibly apply a vasoconstrictor into the nose before placement of the tube into the nose.
- o Perform the laryngoscopy and be *confident that the vocal cords are visible before the ETT* is passed through the nose into the nasopharynx, oropharynx and then into the hypopharynx. If the laryngoscopy is difficult and you have caused an epistaxis, you make a difficult situation worse.
- o Once you can see the vocal cords, carefully advance the ETT directly posterior along the floor of the nose until the tip becomes visible in the oropharynx behind the uvula. Advance the tube into the trachea. Often, the curvature of the tube is such that the tip of the tube gets stuck on the anterior wall of the trachea. The tube is carefully rotated (screwed) into the trachea.
- o The analogue of the stylet for nasotracheal intubation is the *Magill forceps*. This is an angulated forceps. It is inserted through the mouth into the hypopharynx. The tip (not the cuff) of the ETT is grabbed with the tip of the forceps and steered into the glottic opening. Therefore, before you embark on a *naso- or orotracheal intubation, be sure there is a Magill forceps on the anaesthetic machine*.
- o A nasal intubation is relatively *contraindicated* in the presence of *fractures of the base of the skull* (raccoon eyes), since the tube may be inserted into the cranium or cause *meningitis*.
- ***Omission or inability to perform any one of the above steps may make laryngoscopy difficult or impossible.***
- ***If you cannot see the vocal cords, try to rectify the position, allow yourself another attempt, and simultaneously call for help. Do not injure the airway (swelling, oedema) any further.***
- ***Any difficult laryngoscopy is potentially lethal.***
- ***IF YOU ARE NOT SURE THAT THE TUBE IS IN THE TRACHEA, REMOVE IT. DO NOT WASTE VALUABLE TIME IF YOU CANNOT CLINICALLY VERIFY (as described above) CORRECT POSITION OF THE TUBE***

Complications of airway management
Anatomical
- *Inability* to place the airway is complicated by trauma, aspiration, and/or hypoxia (see discussion later under "Difficult and failed airway management").
- *Misplacement of the airway can have fatal consequences* since the airway loses the indication for its insertion. A malpositioned airway may cause or *aggravate airway obstruction, predispose to aspiration, and prevent adequate ventilation and oxygenation*. This applies to supraglottic, translaryngeal, as well as transtracheal airways. E.g., an *LMA* can cause total airway obstruction; an *endotracheal tube* may be in the oesophagus or too deep; a *nasotracheal tube* may tear the posterior mucosa of the nasopharynx forming a false tract in the retropharyngeal space; and a *tracheotomy tube* may be inserted into a false subcutaneous tract. Misplacement of the tube into a false tract often gives rise to surgical emphysema in the neck, which can tract upward to the face and downward to the thoracic wall and mediastinum. ***Therefore, if in doubt, take it out!!!***
- Some degree of *trauma* always occurs during airway management. *Sore throat* is very common after airway management. However, the degree of sore throat does not correlate with the amount of trauma caused during airway management, e.g. a difficult or traumatic laryngoscopy. *Repeated attempts* to insert an airway, particularly laryngoscopy and endotracheal intubation, cause *oedema and bleeding* which often hamper subsequent attempts and compromise the airway further. *Therefore, call for help early*. Stop trying to insert an airway – especially an endotracheal tube before the patient looses the little airway he/she has.

  Trauma may occur from the entrance (mouth or nose) to the distal end of the airway, and may be caused by laryngoscopy and pressure effects of the airway itself. The airway may be injured during laryngoscopy by pinching the lip between the blade and the teeth. The incisors are injured when you use the teeth as a fulcrum for the blade. All airways, including a mask, can cause ischaemia if pressure is exerted on the skin, mucosa, or submucosal structures, especially nerves. Therefore,

when you secure the airway to the skin, ensure that the lips, nasal septum, nasal alae, or tongue are not compressed by the airway (mask, tube, etc.). Submucosal structures are very vulnerable to pressure, especially in hypotensive patients.

Neuropraxia of the lingual, hypoglossal, and laryngeal nerves as well as *vocal cord palsy* have occurred with the use of the LMA. This may be explained by malpositioning of the airway with subsequent pressure on the vocal cords, dislocation of the arytenoids, stretching of the laryngeal nerves due to hyperextension of the neck, and local toxicity of the lignocaine gel applied to the cuff. *Over-inflation of the cuff* is probably the most important mechanism.

The larynx can be injured if a too large tube is forced through the rima glottidis or cricoid ring. An endotracheal tube or tracheostomy can injure the trachea if the tip presses on the mucosa, or when the cuff is over-inflated.

- *Obstruction of the airway* occurs when secretions accumulate in the lumen of the airway. This is particularly true for endotracheal and tracheotomy tubes. Therefore, suctioning of these tubes is indicated, especially in patients that are intubated for several hours, and in patients with underlying lung pathology, e.g. pneumonia, secretions, after aspiration of foreign matter, etc. *Herniation of a tube cuff* can occur when nitrous oxide is used. The gas diffuses into the cuff at a higher rate than nitrogen with which the cuff has been inflated diffuses out. Remember, 79% of air consists of nitrogen. Therefore, the cuff expands and may herniate over the distal opening. Cuff pressures of all cuffed airways must be checked when using nitrous oxide. All airways, except the Magill, FasTrach LMA (metal), I-gel (bite block), and tracheotomy tube (no extratracheal part) *can kink* – especially when they get warm or are curved beyond their limits of pliability.

Physiological

The airway is richly innervated and airway management, including laryngoscopy and insertion of an airway, evokes reflexes, including hypertension, tachycardia, bradycardia, secretions, laryngospasm, coughing, vomiting, and bronchospasm. These reflexes are particularly lively during light anaesthesia. Therefore, if a difficult airway is anticipated, the following precautions can be taken:

- *Before induction or airway manipulation*: An *antisialogogue*, e.g. intravenous glycopyrrolate 5 μg kg^{-1} to 10 μg kg^{-1} or atropine 10 μg kg^{-1}. Parasympatholytics decrease subcutaneous blood flow. *Airway oedema* can be attenuated with a glucocorticosteroid, e.g. intravenous methylprednisolone about 0.5 mg kg^{-1} or dexamethasone about 0.05 mg kg^{-1}.
- *The sympathetic response to laryngoscopy and intubation* (the main culprit) can be attenuated by an opioid. The most predictable method (in my hands) is alfentanil 15 μg kg^{-1} to 20 μg kg^{-1} 120 s to 150 s before laryngoscopy. Therefore, inject the alfentanil, followed by the induction agent and muscle relaxant, deepen the anaesthetic during the next 150 seconds and then intubate. In this regard a fast-acting relaxant such as rocuronium comes in handy. The sympathetic response can also be suppressed with a *β blocker*, such as esmolol 0.5 mg kg^{-1} to 1.0 mg kg^{-1}.

Contamination of the airway

The upper and lower airway, including the lungs may be contaminated. The contamination may come from outside or from inside the body:

- *From the outside*
  Contamination from outside is always iatrogenic and includes the use of contaminated equipment. This happens when secretion or blood from one patient is passed from one patient to the next by contaminated equipment, i.e. *laryngoscopes, Magill forceps, and suction tubes*. The *laryngoscope blade* must not be detached from *the handle* after intubation since the tip of the blade touches the handle when it is "closed". Therefore, the closed laryngoscope is placed into a container and *not on the working area* of the anaesthetic machine. After the patient has been extubated, the laryngoscope (blade and handle) is disinfected. The same applies to any equipment that was in contact with the patient; put it into the contaminated container and disinfect or discard it after the procedure.

Another source of contamination is *the anaesthetic circuit*. If the circuit is not replaced with a clean one after each case, a *microbial filter* must be placed between the airway (mask, LM, ET tube) and the anaesthetic circuit. Anaesthetic circuits filter out about 99.99% of all microorganisms, including viruses. They also contribute to humidification and warming of the anaesthetic gasses.

Remember, that *the filter increases the apparatus dead space* (see Chapter 4) and must be as small as possible. The range of tidal volumes allowed is indicated on the filter, e.g. 50 ml to 250 ml. For babies, specially designed small filters are used. They are a combination of the filter and the male connection on the ET tube. All airway filters are equipped with a capnography port on the circuit side of the filter.

- *From inside*
  Secretions, blood, puss, bowel content, etc. can be aspirated during airway management. Remember that all anaesthetised patients lose the ability to protect the airway (coughing, swallowing, and patency). Therefore, the anaesthetist must be vigilant during airway management. He/she must always be prepared to prevent soiling of the lungs. The ***anaesthetist must always have an assistant during airway management*** to apply cricoid pressure, turn the patient on the side, hand the suction to the anaesthetist, etc. The prevalence of aspiration is high during *difficult airway management* since the time that the airway is unprotected is prolonged.

Mechanical
- The airway may be removed inadvertently.
- The airway may get disconnected from the anaesthetic circuit.

Now that you appreciate the principles of airway management, you will be able to detect factors that may predict a difficult laryngoscopy: *that is the assessment of the airway*.

ASSESSMENT OF THE AIRWAY

Careful assessment of the airway is an essential component of every preoperative visit. Difficulty in airway management is the single most important cause of anaesthesia-related morbidity and mortality. It may be obvious that a patient's airway will be difficult (e.g. masses, abscesses, anatomical abnormalities, etc.), but most catastrophes happen when unexpected difficulty occurs. Assessment of the airway involves the history, examination, the use of bedside tests, and special investigations.

Airway assessment should not only focus on predicting the ability to see the vocal cords during laryngoscopy, but also the ability to *apply mask ventilation, to insert an LM*, and *access to the cricothyroid membrane and trachea* for a surgical airway, which are all interventions to oxygenate the patient should laryngoscopy or intubation fail.

History of the airway
Listen to the patient:
- Consciousness: unconsciousness may be due to a head injury, which may be accompanied by a neck and face skeletal injury; both can involve the airway, e.g. facial fractures and prevertebral haematoma.
- Hoarseness and dysphonia (laryngeal pathology, including infiltrates, tumours, paralysis),
- Nasal speech, blocked nasal passages
- Stridor (turbulent air flow due to upper or lower airway obstruction *may be a sign of threatening total airway obstruction*), dysartria (distortion, infiltration, paralysis of speech organs including the tongue, soft palate, uvula, pharynx, and larynx).

Smell the patient: Halitosis is indicative of poor mouth hygiene, sepsis (tooth abscess, Ludwig angina, malignancy)

Enquire about previous anaesthetics, systemic disease, and pathology involving the airway
- Scrutinize previous anaesthetic records. Check for previous airway problems. If the patient was intubated, look for comments about findings during previous attempts or methods of intubation. When airway or intubation problems have been recorded, were they related to an acute event (e.g. trauma, airway disease process, pregnancy) or is the underlying problem still present?
- Ascertain whether the patient has had previous head, maxillo-facial (including the mandibular and tempero-mandibular joint, nasal, pharyngeal, laryngeal, and neck surgery, or radiotherapy involving the airway region.
- Several multisystem conditions may involve the airway that may predispose to difficult tracheal intubation, namely pregnancy, obesity, diabetes mellitus (prayer sign, Figure 5), acromegaly, rheumatoid arthritis, juvenile rheumatoid arthritis, cervical spine immobility, dwarfism, and obesity. Patients with Down's syndrome or degenerative cervical spine disease are at increased risk of atlanto-axial instability.
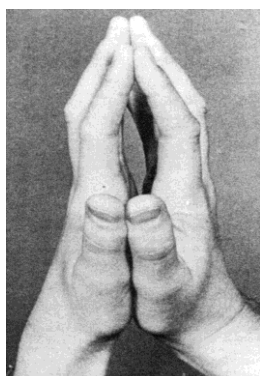
Figure 5 The prayer sign of the stiff joint syndrome of diabetes mellitus in a diabetic patient. The patient is unable to approximate the palms. This stiffening of the joints may involve the atlanto-occipital and laryngeal joints.

Inspection of the airway and related structures
Any deviation (congenital, traumatic, neoplastic, infective, inflammatory, or surgical) that involves the airway, or occupies it must be noted! Look at the head, mouth, and neck. The following features must be noted:

Relationship between the head, neck and trunk: ancylosing spondylitis and rheumatoid arthritis
Devices that impede accessibility to the airway, including halo traction for neck injuries, surgical collar, neurosurgical stereotactic frame around the head.

The face
- Puffy face, facial congestion (pre-eclampsia, superior vena cava syndrome), scleroderma
- Blocked nose, rhinorrhoea (secretions, exudates, CSF). Which nostril is more patent.
- A beard, which may hide abnormal anatomical features.
- Genetic defects, e.g. Down syndrome patients have atlanto-axial instability.
- Small mouth: tumours, previous surgery, trauma, burns, scleroderma
- Jewellery in the lips or tongue
- Inability to swallow (drooling)

The mouth, tongue, and oropharynx
- Large protruding tongue: infection, Ludwig angina, malignancy, Pierre Robin syndrome, Treacher Collins syndrome
- Tumours of the pharynx
- Jewellery in the tongue

Skeleton of the face and mouth:
- Trauma, discolouration of the eyes, bruising, asymmetry
- Receding mandible (shin), protruding maxilla, high arched palate (Marfan), cleft palate
- Abnormal teeth (buck teeth), mouth hygiene, loose teeth, absence of some (passion gap) or all

teeth, upper and lower teeth that are wired together, crowns, dentures
- Complex of receding mandible with protruding tongue and cleft lip and palate (Pierre Robin, Treacher Collins, Goldenhar)

The neck
- Thick neck: obesity, infection (Ludwig angina, deep neck space infection), venous congestion (superior vena cava syndrome), malignancy
- Masses, thyroid, scars of previous head and neck surgery, skin changes associated with radiotherapy
- Injury or burns
- Deformity of the neck due to, for example trauma, ancylosing spondylitis. Lesions involving vertebrae C1 and C2 are more predictive of difficult airway management than lower lesions.

To summarize, the following features occur commonly and may predict a difficult laryngoscopy:
- Pregnancy
- Morbid obesity
- Thick neck (circumference of > 44 cm)
- Large breasts.
- Any condition (congenital, traumatic, neoplastic, infective, surgical) that involves the head, neck, face, and airway
- Small mouth
- Receding chin (small mandible/micrognatia)
- Abnormal teeth (buck teeth), absent teeth, crowns, bridges
- Jewellery in the lips, or tongue
- Large tongue
- High arched palate
- Large hair pieces

*The following features are associated with difficult mask ventilation (**BONES**):*
Beard, **O**besity, **N**o teeth, the **E**lderly, and **S**leep apnoea or snoring, **S**evere prognathia, receding mandible, or other facial deformities.
The following features are associated with difficult insertion of an LM:
- Limited access to the mouth (an inter-incisor distance < 2.5 cm)
- Intraoral tumours e.g. tongue tumours
The following features are associated with a difficult crico-thyroidotomy and tracheostomy:
- Fixed flexion of the neck, e.g. ancylosing spondylitis, scaring (radiotherapy, burns)
- Deviation of the larynx and trachea
- Tissue overlying the cricothyroid membrane and trachea, e.g. fat, goitre, sepsis
- Devices overlying the trachea, e.g. surgical collar

An entity that may involve several of the above airway features is obstructive sleep apnoea (OSA).
OSA occurs commonly and affects about 15% of the population. About 85% of patients are not diagnosed. OSA is defined as five or more apnoeic events (no airflow ≥ 10 s despite respiratory effort) per hour, or fifteen or more hypopnoeic events (airflow decrease > 50% for ≥ 10 s) during a study period of seven hours. OSA occurs during REM sleep (decreased muscle tone) causing hypoxaemia and arousal. Patients suffer from day time somnolence since sleep is fragmented and REM sleep is not sustained.

Complications of OSA:
Very sensitive to the effects of sedatives (including opioids)
- Control of breathing
- Decreased muscle tone – especially the airway.
Airway management
- Difficult mask ventilation
- Difficult laryngoscopy
Cardiovascular
- Sympathetic activation: Systemic hypertension, myocardial ischaemia, left heart failure, dysrhythmias, stroke

- Chronic hypoxia and hypercapnia: Pulmonary hypertension, right heart failure, polycythaemia
Cognitive
- Hypersomnolence
- Personality changes
- Cognitive deficits
- Accident prone

Some obese patients develop the obesity hypoventilation syndrome (OHS), consisting of a body mass index (BMI) > 40 kg m^{-2}, chronic daytime hypoxaemia, hypercapnia, and day time somnolence (Pickwickian syndrome). Hypercapnia in the absence of significant obstructive pulmonary disease in an obese patient is diagnostic of OHS.

The definitive diagnosis of OSA is made with polysomnography in the sleep laboratory. The test is cumbersome and can be predicted using the ***STOP BANG questionnaire.*** A count of $\geq$ 3/8 indicates a high risk of OSA:[1]

Do you **SNORE** loud enough to be heard through closed doors?

Do you often feel **TIRED**, fatigued, or sleepy during daytime?

Has anybody **OBSERVED** you stop breathing during your sleep?

Do you have or are you being treated for high blood **PRESSURE**?

BMI > 35 kg m^{-2}?

AGE > 50 years?

NECK circumference at cricoid > 40 cm?

GENDER male?

Clinical tests to predict the ease of laryngoscopy

Several clinical predictors of a difficult laryngoscopy have been described. However, the following factors confound their utility.

- On its own, each predictor has poor sensitivity and specificity.
- The tests are very subjective (large inter-observer variability).
- All anaesthetists do not define the "difficult airway" the same.

The *sensitivity and specificity of these tests improve when they are combined into a core*, e.g. the *Wilson score.*[2] The Wilson score takes into account five variables. They are graded subjectively (*!*) from 0 to 2 where 0 is normal and 2 abnormal. A count of $\geq$ 2 has a true positive value of 75% and a false positive predictive value of 12% (Table 4).

Table 4 The Wilson score2

Risk factor	Level	Criteria
Body mass	0	< 90 kg
	1	90 kg to 110 kg
	2	> 110 kg
Head and neck movement	0	> 90°
	1	About 90° (± 10°)
	2	< 90°
Jaw movement	0	IG $\geq$ 5 cm* or SL > 0
	1	IG < 5 cm and SL = 0
	2	IG < 5 cm and SL < 0
Receding mandible	0	Normal
	1	Moderate
	2	Severe
Buck teeth	0	Normal
	1	Moderate
	2	Severe

IG, inter-incisor gap; SL subluxation of the temperomandibular joint; *5 cm $\approx$ 3 fingers

If possible, the following clinical tests to predict the ability to do a successful laryngoscopy should be performed in all patients preoperatively:

1. Inter-incisor gap

Ask the patient to open their mouth as wide as possible. A distance of less than two fingers breadths (3cm) between the upper and lower incisors or alveolar ridges is associated with difficult laryngoscopy.

2. Protrusion of the mandible

Ask the patient to protrude their mandible. Inability to protrude the lower incisors in front of the upper incisors predicts a difficult laryngoscopy. This is called prognathia.

3. Mallampati score

The Mallampati score is done in an *awake*. The patient is asked to open the mouth and protrude the tongue. The patient must *not phonate* or extend the head. The *view of the uvula* is recorded (Figure 6). This score evaluates the ability to open the mouth, the size and mobility of the tongue, and any mass in the passage between the mouth and fauces:

- Class I: Faucial[i] pillars (palatoglossal and palatopharyngeal folds), soft palate, and uvula are visible.
- Class II: Faucial pillars and soft palate are visible, but the base of tongue masks the tip of the uvula.
- Class III: Only the soft palate and base of the uvula are visible.
- Class IV: Only the hard palate is visible.
- Grade I and II predict easy intubations, III and IV predict potentially difficult intubations

Mallampati test correctly identifies about 50% of difficult intubations. With the head in a neutral position, the patient must open the mouth maximally and protrude their tongue without phonating. Note which of the structures are visible (Figure 6).
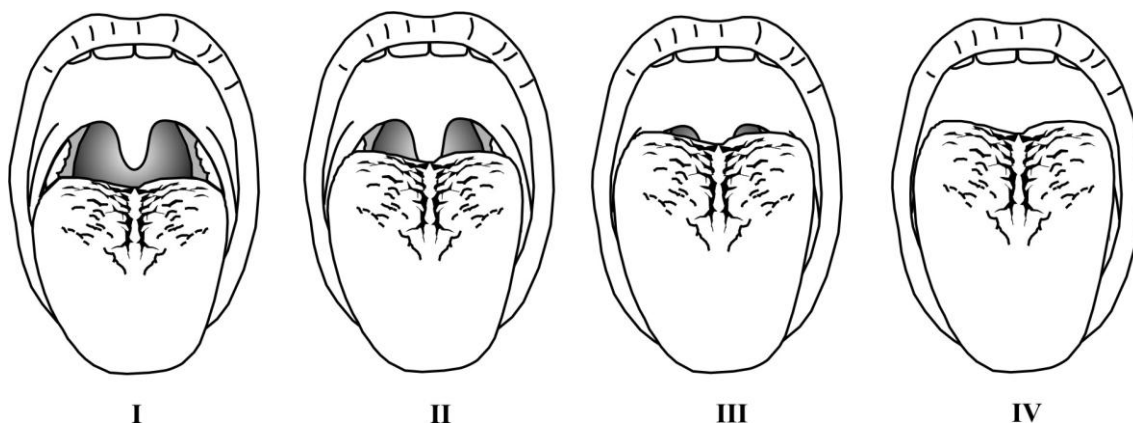
Figure 6 Mallampati score

4. Flexion and extension at the craniocervical junction
A pen can be held between the teeth whilst maximally flexing and extending the neck. Movement of > 90° should be possible.
5. Thyromental distance (Patil's test)
The distance from the tubercle of the thyroid cartilage to the tip of the mandible, with the neck fully extended should be > 6.5 cm (three finger breadths). This distance estimates the potential space into which the tongue can be displaced on laryngoscopy. A distance < 6 cm is associated with difficult laryngoscopy and has a 75% predictive value in adults.
6. Sternomental distance (Savva's test)
This is the distance from the upper border of the manubrium to the mental protuberance of the mandible with the neck fully extended. A distance < 12.5 cm is associated with difficult intubation in adults.
7. The mandibular space
Ask the patient to place four fingers under the chin and over the neck. Four fingers in both the sites indicate adequate anatomy.
8. The **neck circumference-thyromental distance (Patil) ratio (NC/TM ratio)**[3]

In obese patients a NC/TM ratio > 5 has a sensitivity and specificity of about 90%

If there is a high likelihood that mask ventilation and/or direct laryngoscopy will be difficult, consideration should be given to *awake fibreoptic intubation*.

Airway evaluation during laryngoscopy
An attempted look at the vocal cords may be made in the awake patient after applying local anaesthetic to the mouth and throat using a lignocaine 2% gargle. This can be done preoperatively

---

[i] *The fauces* is the door between the mouth and the pharynx. It consists of the tonsillar pillars laterally, the uvula and soft palate superiorly, and the tongue inferiorly.

using a mirror or a fibreoptic instrument. ENT surgeons often do this. This can also be done before induction of anaesthesia in theatre; using a laryngoscope, the anaesthetist may get an idea of the visibility of the vocal cords.

What the anaesthetist observes during laryngoscopy after induction of anaesthesia is often predictable from the preoperative airway evaluation. However, in about 2% of laryngoscopies this can be an unpleasant surprise.

The direct laryngoscopic view of the vocal cords in the anaesthetized patient is graded using the Cormack and Lehane Classification (Table 5 and Figure 7). The laryngoscopic view should be documented on the anaesthetic record. The anaesthetist must review previous anaesthetic records during the preoperative assessment. If a high Cormack and Lehane grade has been documented, steps can be taken to facilitate airway management during subsequent anaesthetics.
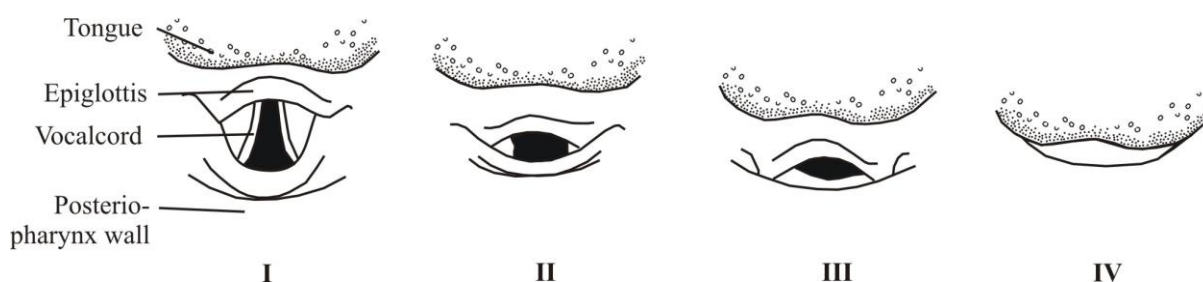
Figure 7 Cormack and Lehane vocal cord visualization grading

Table 5 Cormac Lehane grading of direct laryngoscopic view

Grade	Vocal cords	Epiglottis	Base of tongue	Posterior pharynx wall	Oesophageal inlet	Remark
I	Whole	Whole	Yes	Hypopharynx	Yes	
II	Partially	Whole	Yes	Hypopharynx	Yes	
III	No	Tip only	Yes	Hypopharynx	Yes	Cannot get round the corner; the cords are high up behind the base of the tongue. These views improve with better positioning of the head and neck (sniffing position). The McCoy laryngoscope blade may be helpful. You will need a 'hockey stick" stylet inside the endotracheal tube to insert the tube. Intubation is difficult, blind, or may be impossible.
IV	No	No	No	Oropharynx only	No	

DIFFICULT AND FAILED AIRWAY MANAGEMENT

The aim of airway management is to fulfil the indication of the airway management in the particular case, namely creation, maintenance, protection, and ventilation. If one of these is not possible, there is failure of airway management.

Airway management can fail due to inability to insert the supraglottic, translaryngeal, or transtracheal airway device and/or failed laryngoscopy. These can result from anatomical factors (outside the wall, in the wall, in the lumen) from the nose or mouth to the trachea.

"Failed insertion and/or laryngoscopy" refers to, e.g. the situation where laryngoscopy is easy but one cannot insert an ETT. This occurs typically with infraglottic lesions such as tracheal stenosis or compression by a mediastinal mass, or when insertion of an ETT is temporarily contraindicated, e.g. in the presence of foreign body in the airway. If one cannot insert a supraglottic airway, e.g. an LMA, airway management has also failed.

Failure of airway management with a supraglottic, translaryngeal, or transtracheal airway device often necessitates an attempt to insert an *airway of another class*, e.g. if the LMA does not "sit" properly in the hypopharynx or is complicated by laryngospasm, endotracheal intubation (translaryngeal airway) becomes necessary. Visa versa, if laryngoscopy has failed, an LMA or oropharyngeal airway (Guedel) may come in handy. *Since difficult airway management often occur unexpectedly, airways of a class other than the intended class must always be available in the theatre – not elsewhere in the hospital. E.g. if you plan to insert an LMA, there must be a laryngoscope and ETT on your anaesthetic machine, and vice versa.*

Unanticipated difficult laryngoscopy
This complication is feared by all doctors. ***The moment you realize that you cannot see the vocal cords or incompletely, immediately call for help.*** While an assistant is on his/her way, watch the oxygen saturation and ***ventilate with 100% oxygen*** before the patient becomes hypoxic. In this situation doctors *tend to become anxious* and attempt repeatedly and with *much force* to find the vocal cords. This causes airway *oedema and bleeding*, which *jeopardizes further attempts* and lead to *airway obstruction*. Therefore:
- Immediately *call for help*.
- You are allowed two additional* careful attempts (*a total of three attempts*).
- *Oxygenate* the patient between attempts.
- Get a *supraglottic airway device*, typically an oropharyngeal airway and LMA. Insert the Guedel airway and ventilate with 100% oxygen.
- Before attempting each of the next two* laryngoscopies, *the situation has to be improved* e.g. changing the *position of the head*, e.g. the sniffing position.
- One assistant must keep the *lip out of the LOV*.
- The person performing the laryngoscopy must handle the laryngoscope with the left hand, while the *larynx is manipulated with the right hand* in order to bring the vocal cords into the LOV.
- If the vocal cords become visible in this way, this position is maintained while a *second assistant does the intubation* – often with a *stylet* in the ETT.

Failed laryngoscopy and intubation
The doctor has been unsuccessful in laryngoscopy and tracheal intubation. Maintain ventilation with 100% oxygen. A laryngeal mask airway may allow ventilation of the lungs as an interim measure or the anaesthetist may decide to use this as the conduit for ventilation of the patient.

The cannot intubate, cannot ventilate scenario (CICV)
This mandates an immediate surgical airway if the patient is going to survive the episode unscathed. A infraglottic airway is recommended, namely a crico-thyroidotomy (Figure 8) ***In a rapidly decompensating patient a CRICOTHYROIDOTOMY is the only option. A tracheotomy takes longer to perform.***

```
                    IS OPERATION URGENT AND MUST CONTINUE?
                    ↓                                    ↓
                   YES                                   NO
                    ↓                                    ↓
               IS ETT ESSENTIAL?                   WAKE UP PATIENT
              ↓              ↓                            ↓
            YES             NO                   Local, neuraxis block
              ↓              ↓                   More proficient anaesthetist
  LMA + cricoid pressure   Mask                  Fibreoptic laryngoscope
  Intubation through       Guedel
  intubating LMA           LMA
              ↓
     TRACHEOSTOMY
```
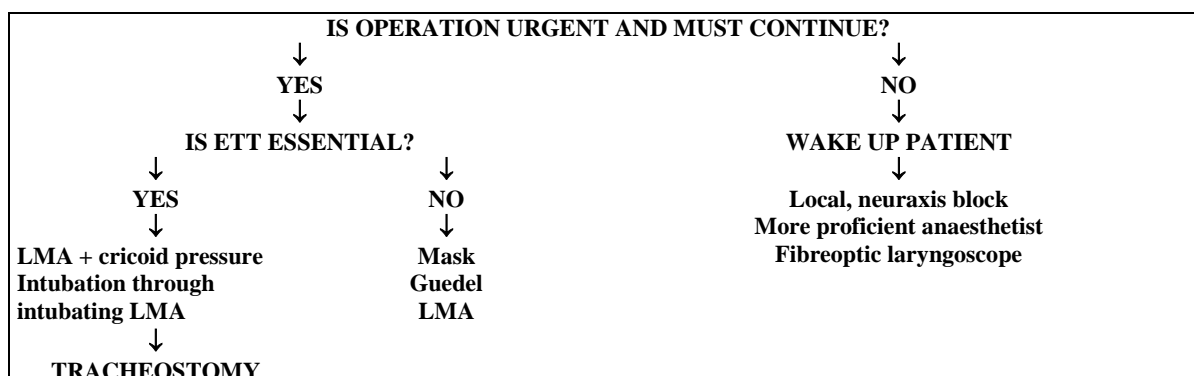**Figure 8**: Algorithm for failed intubation

Special intubation scenarios
Full stomach
In patients who run the risk to regurgitate and aspirate once they have lost consciousness, the time between induction and intubation must be kept as short as possible. This is done with the *rapid sequence induction*. The indications for a rapid sequence induction are:
Emergency operation, unfasted patient
Delayed stomach emptying: Acute abdomen, pyloric stenosis, hiatus hernia, and trauma
Pregnancy
Autonomic neuropathy: Renal failure, diabetes mellitus, etc.

The rapid sequence induction consists of the following steps:
- Precautions as for any airway management must be taken, i.e. apparatus (**_suction_**, laryngoscopes, Magill forceps, and stylet) and assistance. **_NB: no induction before suction_**!
- Preoxygenation with a mask and 100% oxygen for 3 minutes
- Intravenous induction is done with a drug with as fast onset of action, e.g. sodium thiopental, propofol, or ketamine.
- As soon the patient loses consciousness, cricoid pressure is applied. Cricoid pressure consists of firm pressure on the cricoid ring (not the thyroid cartilage or above the thyroid cartilage) to occlude the oesophagus posterior to it.
- This is followed by a fast acting muscle relaxant is administered, namely either suxamethonium 1.0 mg kg^{-1} to 1.5 mg kg^{-1} or rocuronium 0.6 mg kg^{-1} to 1.0 mg kg^{-1}. With suxamethonium complete muscle relaxation occurs within about 30 s, while it takes about 60 s with rocuronium.
- As soon as the patient is relaxed, laryngoscopy is performed, the trachea is intubated, and the cuff of the ETT is inflated.
- Thereafter, the correct position of the ETT is verified after which cricoid pressure is stopped. and.

Adverse effects of cricoid pressure
- May complicate intubation
- Distortion of the line of vision
- Stimulates a swallow reflex and lower the tone of the oesophageal sphincters
- Rupture of the oesophagus if the patient would vomit
- Pressure on other structures e.g. the carotid artery
- It is contraindicated in neck trauma. Therefore, *bimanual cricoid pressure* must be done.

Anticipated difficult intubation
- In a setting where no experienced help is available, transfer the patient to another institution.
- An awake laryngoscopy can be done. If the laryngoscopy confirms your expectation of a difficult airway, prepare for a difficult intubation. First, do no harm.
- A vapour induction rather than intravenous induction is safer. If the airway obstruction occurs, the anaesthesia will wear off. Once intravenous agents are administered, the drug cannot be removed and one has to wait for the drug to be metabolized or redistributed before the patient will wake up
- Have a scrubbed surgeon in theatre with a tracheostomy set open and ready to create an emergency airway.

REMOVAL OF THE AIRWAY

The airway may only be removed once the indication for its insertion does not exist anymore. This applies to all the routs of airway management: supraglottic, translaryngeal, and transtracheal. Remember, the more difficult it was to create an open airway, e.g. difficult intubation, the more difficult it may be to remove the airway. In such cases, the anaesthetist must be prepared to re-insert the airway, e.g. re-intubate. All devices that were present for the difficult airway management must be available. You must have an assistant. Re-intubation, even of a normal airway, is often complicated by airway swelling (tongue and epiglottis). Re-intubation is often attempted using a bougie (long stiff plastic probe). The bougie must be stiff (a soft nasogastric tube does not work) and must be at least

three times the length of the ETT. Special tube exchanger bougies are available. They are hollow and allows connection of the anaesthetic circuit to administer oxygen.

Therefore, the prerequisites are as follows:
- The patient must be *awake*.
- All foreign matter must have been removed (suctioned) from the airway (trachea, pharynx, and mouth).
- The patient must have a *patent airway* (from the mouth to the carina).
- The patient must be able to *maintain the airway*: muscle tone and sensation, absence of any obstruction.
- The patient must be able to *protect the airway*: muscle tone, *airway reflexes* (swallowing, coughing).
- The patient must be able to *remove secretions* from the lungs (coughing).
- The indications for *ventilation* must not exist anymore.

The following patients may be difficult extubate, and may require re-intubation:[4]
- Patient factors: ASA status $\geq$ III, age < 1 year, chronic pulmonary disease, preoperative hypoalbuminaemia, renal insufficiency
- Anaesthetic factors: use of muscle relaxants
- Procedure factors: Emergency cases, head and neck surgery, cardiothoracic surgery, airway surgery, surgery time > 3 hours

AIRWAY EQUIPMENT
(Please have a look at all the different devices in theatre and in the difficult-airway trolley)

Supraglottic airways
- *Oropharyngeal (Guedel) airway*

- *Nasopharyngeal airway*

- *Laryngeal mask*

- *I-gel*

- *FasTrach intubating laryngeal mask*
The ET is passed blindly through the mask into the trachea.

Transglottic (translaryngeal) airway (endotracheal tubes)
- *Straight endotracheal tube:*
These tubes are *cuffed (a) or uncuffed (b)* and are used for most cases where the patient is supine and the head in the neutral position. Traditionally uncuffed tubes are used in children below the age of 8

years to 10 years; it is not wrong to insert a cuffed tube in children and babies, but remember that the tube will have to be at least 0.5 mm smaller. A *microlaryngeal tube (MLT)* is as long as adult tubes but have the diameter of paediatric tubes (c). They are used in adults with tracheal stenoses where one needs a long but thin tube.

Reinforced tubes are pliable but do not kink (d). They are used in patients in any non-supine position or with extreme head rotation. Remember to insert a bite block (or rolled gauze between the teeth) to prevent the patient from biting the tube since the metal wire in the wall of the tube will not open up once it has been occluded.

a

c

b

d
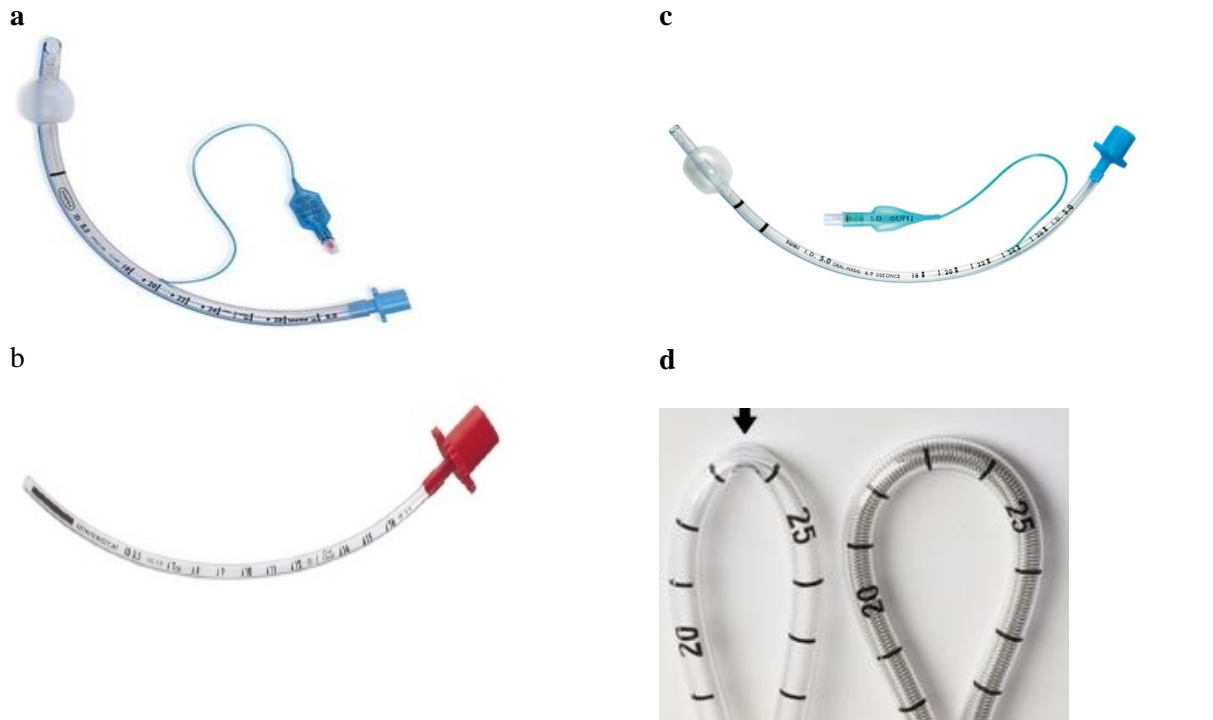
- *Preformed tube (RAE): oral and nasal*
These tubes are used when the airway is involved, e.g. oral and nasal surgery.

- *Combitube*
This tube consists two lumens. It can be regarded as a combination of a distal part resembling an ETT and a proximal part resembling an LMA. Each part has its own cuff. It is inserted blindly into the airway and both cuffs are inflated. The anaesthetic circuit is connected to the distal connection (ETT

part). If the ETT part has entered the trachea, a sustained capnogram will appear on the monitor and the lungs will be ventilated. If the ETT-like part would enter the oesophagus, it will occlude the oesophagus and oxygen will be delivered through the holes distal to the big cuff into the hypopharynx and from there to the trachea, provided the vocal cords are open. The anaesthetic circuit is connected to the proximal part and ventilation is verified by the capnogram and auscultation of the lungs.

Infraglottic airway (tracheostomy tube)
The example shows the introducer inside the tube and the cuff inflated

Laryngoscopes

- *The curved (Mackintosh) blade*

- *The straight (Miller) blade*

- *The McCoy blade with the flexible tip*

- **Magill forceps**

- **Pliable Intubation stylet**

The stylet is passed into the ET tube to increase the curvature. Remember, the tip of the stylet must not pass beyond the distal end of the ET tube since it may injure the trachea.

- **Airway filters**

Airway filters fit between the tube and the anaesthetic circuit and are *essential*. They filter bacteria, viruses, and TB and also are moisture and heat exchangers. The capnograph fits onto the filter.

- **Catheter mounts and angled connections**

The catheter mount connects the airway (LMA, ET, or tracheostomy tube) to the airway filter, which is connected to the anaesthetic circuit.

- **Fibreoptic (indirect) intubation devices**

Several fibreoptic (indirect) intubation devices are on the market, e.g. the GlideScope video laryngoscope, Airtraq, Pentax, etc. The following photo illustrates the Airtraq with small screen displaying the vocal cords

CHAPTER 4

ANAESTHETIC EQUIPMENT AND MONITORS

Key points:
- Understand the basic architecture of the anaesthesia machine
- Be able to test the machines in use in the institutions where they work
- Familiarise yourself with the breathing systems, CO_2-absorbers and ventilators used in their theatres
- Prepare theatres properly

- Have back-up plans if things go wrong, as mishaps still occur
- Monitors are there to improve patient safety
- You should know and understand what information can be attained from the different monitors
- If systems fail, an ambu bag and sets of face masks and tracheal tubes should be readily available

Anaesthetic complications still occur. Complications can be attributed to the anaesthetist, patient factors, or anaesthetic equipment. The equipment includes airway equipment, the anaesthetic machine and its accessories, physiological monitors, infusion pumps, imaging apparatus (ultrasound), nerve stimulators, etc. Proper functioning of equipment is crucial for patient safety. In this chapter, the principles of the anaesthetic machine and physiological monitors are addressed.

The most important component of anaesthetic equipment will not be addressed in this chapter or elsewhere in this book. It is very expensive, relies on very complicated, and often ill-defined and understood circuitry and programme software. The equipment may be fickle, get tired, get angry, can be caring, and even rude. It is required that all models are programmed with a conscience and ethical values. This equipment is indispensable and must always be present and functional whenever involved in patient care. It takes about nine months to collect the basic components for the monitor. Thereafter the monitor is assembled over a period of about thirty years. The monitor is very robust but requires regular maintenance. ***This is the anaesthesiologist.***

Before discussing the anaesthetic machine, monitors that reflect CO_2 excretion by the lungs and oxygenation of blood by the lungs will be discussed. Understanding these monitors is essential for understanding the performance of several components of equipment, including the anaesthetic machine, the anaesthetic circuit, the airway, and ventilation (spontaneous or assisted with a ventilator). It also monitors the interaction of lung ventilation and lung perfusion.

Capnography
The analysis of the excretion of CO_2 by the lungs is called *capnometry*. The capnometry (the digital value of exhaled CO_2) over time (s) is displayed on a *capnograph*. Nowadays, most capnographs are side-stream capnographs: a plastic cannula connects the airway filter to the capnograph. The capnograph extracts gas from the airway continuously (about 200 ml min^{-1}) and analyses the gas using infrared spectrophotometry. The number of molecules (partial pressure as mm Hg or kPa) or concentration (percentage in gas) of CO_2 in the in- and expiratory gas is displayed continuously on a graph with CO_2 on the y axis and time on the x axis, and is called a *capnogram* (Figure 1).

Three processes are required to reflect CO_2 on the capnogram:
- *Any substrate that fuels the Krebs cycle* (substances that can enter the Krebs cycle) increases CO_2 production in the presence of oxidative phosphorylation (with end products ATP + H_2O). This happens during:
  - *Aerobic cellular metabolism* (increased metabolic rate increases CO_2 production)
  - *Buffering of H^+ by HCO_3^-* ($H^+ + HCO_3^- \leftrightarrow H^+$ by $H_2CO_3 \leftrightarrow H_2O + \mathbf{CO_2}$) during treatment of a metabolic acidosis with $NaHCO_3$.
  - *Clearance of organic acids* via the Krebs cycle. These substances included lactate via pyruvate, which enters the Krebs cycle and citrate (the anticoagulant in blood products), which enters the Krebs cycle (lactate $\rightarrow$ pyruvate $\rightarrow$ AcCoA; AcCoA + oxalic acetate $\rightarrow$ citrate $\rightarrow \rightarrow CO_2$). This mechanism is observed during transfusion of blood products and clearance of accumulated lactate and CO_2, e.g. reperfusion during successful resuscitation of circulatory shock and after release of a tourniquet from a leg, release of an aortic clamp, and rapid decrease in elevated

intra-abdominal pressure.
- *Transport of CO_2* to the lung (cardiac output, i.e. *lung perfusion*)
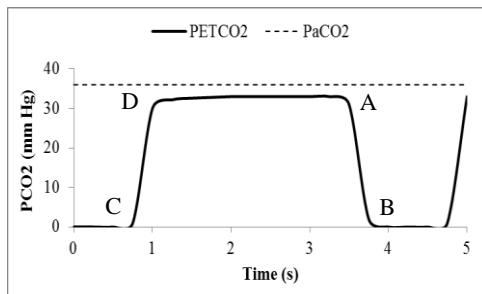- *Gas exchange* in the lung (removal of CO_2 from the lungs, i.e. *ventilation*)

Figure 1 The normal capnogram

The capnogram consists of four phases:
- The end of expiration and beginning of inspiration (AB)
- Inspiration of CO_2-free gas (BC)
- The end of inspiration (C)
- Beginning of expiration of gas from Vdanat containing some CO_2; the nearer the Vdanat to perfused and ventilated alveoli, the more CO_2 it contains (CD) [Remember, dead space is the volume of a tidal volume (Vt) that has not been exposed to gas exchange in the alveoli. Dead space consists of gas from unperfused alveoli (alveolar dead space), anatomical dead space (the airways) and apparatus dead space. The sum of the alveolar (Vdalv) and anatomical dead space (Vdanat) is the physiological dead space (Vdphys)]
- The alveolar plateau (DA), which contains most of the CO_2 of the expired Vt. When there is no delay in expiration and little mixing of alveolar volume and Vdanat, the alveolar plateau is horizontal. However, the normal alveolar plateau often slants a little to the right to end in A, which is slightly higher than D. A is called the end-tidal PCO_2 ($PETCO_2$). During general anaesthesia, normal fresh gas flows and normal dead space volumes, arterial PCO_2 ($PaCO_2$) ≈ $PETCO_2$, but $PaCO_2$ may be up to about 10 mm Hg higher than $PETCO_2$, especially in the elderly.

The following aspects of the capnogram are always evaluated:
- *Is it present? If not,*
  - The patient is not ventilating.
  - Oesophageal intubation may initially show a capnogram due to some CO_2 from the stomach reaching the endotracheal tube (ETT), but as the CO_2 escapes from the stomach, the capnogram rapidly fades to a $PETCO_2$ of zero. Apart from seeing the tip of the ETT entering the trachea through the vocal cords, the capnogram is the most reliable monitor to identify oesophageal intubation (Figure 1(a))
  - There is a total obstruction of flow between the patient (airway) and the capnogram sampling line.
  - There is a disconnection between the patient and airway (e.g. extubation) or a disconnection between the airway and the anaesthetic circuit (the piece of equipment between the airway and the anaesthetic machine), or a disconnection of the capnograph sampling line and the airway filter (Figure 1(b)).
- *Is the baseline (BC) zero?* If not, *but PETCO₂ is not increasing*, there is *rebreathing* of CO_2 due to
  - It is normal in rebreathing circuits/systems, i.e. the Mapleson circuits. (If the baseline reaches zero with these circuits, the fresh gas flows may be too high). This is also seen when the expiratory valve of the circle system is stuck. In the latter case the ventilator pressures will increase. See Figure 1(c).
  - Interruption of expiration (DA) by inspiration before expiration is complete and of inspiration (AB) by expiration before inspiration is complete. Therefore, the zero is not reached during inspiration and the alveolar plateau (DA) during expiration. Therefore, the $PETCO_2$ is lower

than expected. Since expiration is incomplete and rebreathing may occur, the CO_2 accumulates resulting in an increased difference between $PaCO_2$ and $PETCO_2$ $PaCO_2 >> PETCO_2$). This happens with tachypnoea. (Figure 1(d))

- *Is the alveolar plateau flat?* If not
  o There may be delayed expiration, e.g. bronchospasm. The slower expiration, the higher the gradient of the alveolar plateau will be; in severe cases the dead space portion of the capnogram (CD) may blend with the alveolar plateau (DA) and expiration becomes incomplete. Therefore, $PETCO_2 << PaCO_2$ (Figure 1(e)).
  o Ventilated patients may try to inhale while the ventilator is in its expiratory phase (CD or DA). If the inspiration attempts occur during the alveolar plateau, the plateau is interrupted by a cleft. The cleft may be an indication of a light level of anaesthesia, or it may be a sign that the muscle relaxant is wearing off, in which case it is called the *curare cleft* (Figure 1(f)).
  o A hump is sometimes observed at the end of the alveolar plateau. This usually seen in pregnant patients, the elderly, obese patients, and patients with COPD. It is ascribed to late (sequential) emptying of some under-ventilated (with high PCO_2) lung regions (Figure 1(u)). Sometimes, the PCO_2 of the hump may exceed $PaCO_2$.
- *Is the $PETCO_2$ rising over time while the baseline remains zero?*
  o This occurs commonly and is a sign of hypoventilation with a gradual increase of $PaCO_2$ and consequently of $PECO_2$ (Figure 1(g)).
  o There is an increase in CO_2 production following the administration of $NaHCO_3$ to treat metabolic acidosis, blood products containing citrate as anticoagulant, and clearance of lactate. The increase following administration of $NaHCO_3$ is usually short-lived (Figure 1(j)), while the other two mechanisms are usually more persistent until the acids have been cleared (Figure 1(h)).
  o There is an increased metabolic rate, e.g. thyroid storm (see Chapter 17) and malignant hyperthermia (see Chapter 11). See Figure 1(i).
  o Sudden wash out of accumulated CO_2 increases $PaCO_2$ and $PETCO_2$, e.g. release of a tourniquet from a leg, unclamping of a large artery such as the aorta, and resumption of cardiac output after a period of hypoperfusion (decreased dead space ventilation). See Figure 1(j)
  o CO_2 gas is used to inflate body cavities during endoscopic procedures, e.g. laparoscopy and thoracoscopy. The CO_2 is absorbed rapidly and increases the $PaCO_2$ followed by an increase in $PETCO_2$ (Figure 1(k). It is often necessary to increase ventilation to eliminate the increased $PaCO_2$.
  o This may occur with successful treatment of bronchospasm. Alveolar emptying is better resulting in flattening of the alveolar plateau, increase in $PETCO_2$ and a decrease in the $PaCO_2$-$PETCO_2$ difference (Figure 1(l)).
- *Is both the baseline and $ETCO_2$ rising?* The soda lime is exhausted (Figure 1(m)).
- Is the $PETCO_2$ decreasing over time? This happens with
  o Hyperventilation *gradually* decreases $PETCO_2$. Both $PaCO_2$ and $PETCO_2$ decrease and the difference is usually normal (Figure 1(n)) – unless the hyperventilation decreases cardiac output, in which case the difference between $PaCO_2$ and $PETCO_2$ will increase.
  o A sudden decrease in cardiac output due to embolism of any substance in amounts that can obstruct right ventricular outflow (massive dead space ventilation) causes an abrupt decrease in $PETCO_2$, e.g. massive thromboembolism, gas (air, CO_2) embolism, amniotic fluid embolism, and tumour embolism. Large solid emboli may be fatal and the $PETCO_2$ will remain low while the $PaCO_2$ will increase. During a *sudden decrease* in cardiac output, the $PETCO_2$ decreases abruptly while there is a concomitant sharp rise in $PaCO_2$. A decreased cardiac output resulting in a $PETCO_2 < 18$ mm Hg is regarded as a cardiac arrest, or put another way, if the $PETCO_2$ does not increase to levels > 18 mm Hg during CPR, the prognosis is poor. Both these instances (gradual or abrupt) is usually accompanied by anaerobic metabolism with the appearance of a lactic acidosis. If a patient survives the incident (resumption of cardiac output), the $PETCO_2$ will increase while the $PaCO_2$ will decrease again (Figure 1(o)).
  o A gradual decrease in cardiac output causes a gradual increase in dead space ventilation resulting in an increased $PaCO_2$ and a decreased $PETCO_2$. See Figure 1(p)

- A gradual decrease in metabolic rate occurs during hypothermia, resulting in a decline in both $PaCO_2$ and $PETCO_2$. During rewarming, the metabolic rate increases and both $PaCO_2$ and $PETCO_2$ increase. See Figure 1(q)

- A leak in the system that allows aspiration of the capnograph sampling line to draw gas from outside the closed patient-circuit system causes a flattened expiratory limb (CD) and shortened alveolar plateau (DA). This happens when gas leaks past a too small ET tube, partial disconnection, cracked connection, etc. See Figure 1(r)

- In small patients, cardiac contraction may influence gas flows in the lungs. These are often observed during the late alveolar plateau and end of expiration (AB) and is characterised by a saw tooth appearance of that part of the capnogram. Close inspection of these oscillations shows that their frequency corresponds to the heart rate (Figure 1(s).
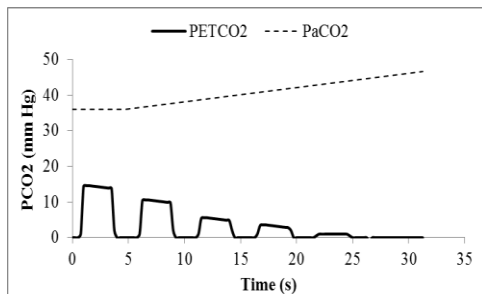
Figure 1(a) Oesophageal intubation
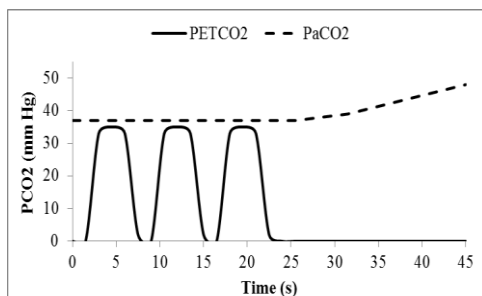
Figure 1(b) No capnogram,
 e.g. disconnection, extubation

Figure 1(c) Rebreathing circuits/systems, e.g. the Mapleson circuits.

Figure 1(d) Tachypnoea

Figure 1(e) Bronchospasm. $PaCO_2 - PETCO_2$ is increased.
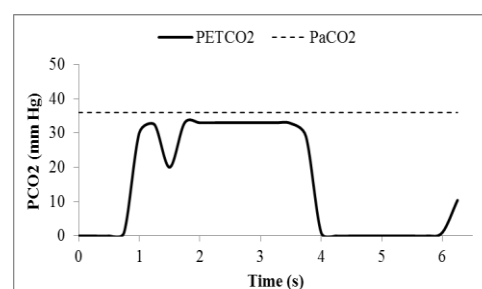
Figure 1(f) Curare cleft (anywhere in plateau).
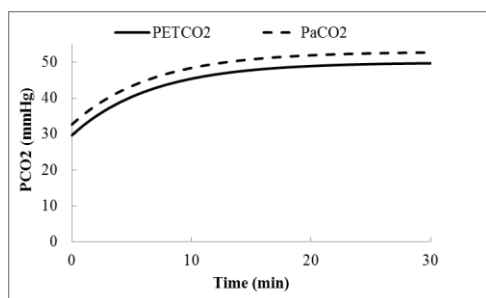
Figure 1(g) Hypoventilation (trend)
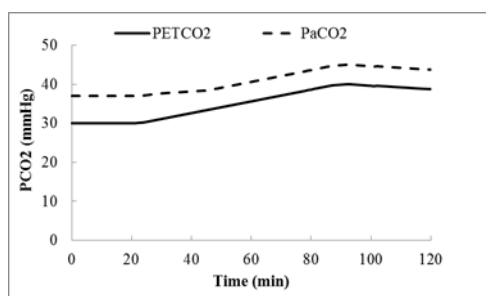
Figure 1(h) Increased CO_2 production (trend)
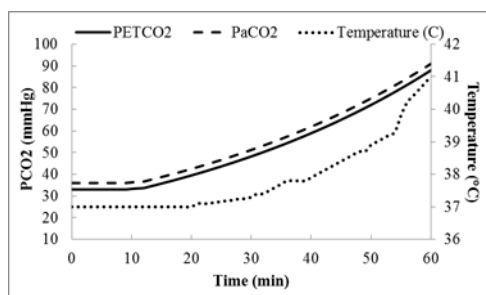
Figure 1(i) Hypermetabolism: malignant hyperthermia (trend)
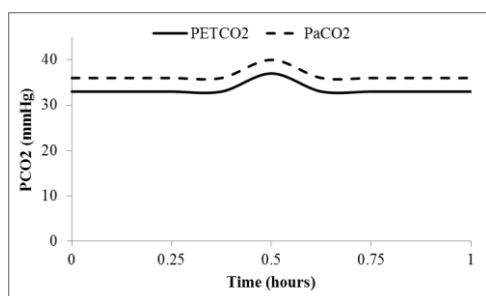
Figure 1(j) Sudden wash out of accumulated CO_2 (trend)
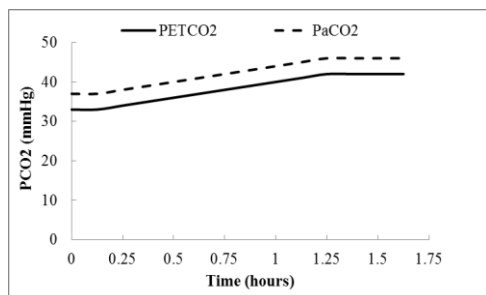
Figure 1(k) Inflation of body cavity with CO_2 (trend)
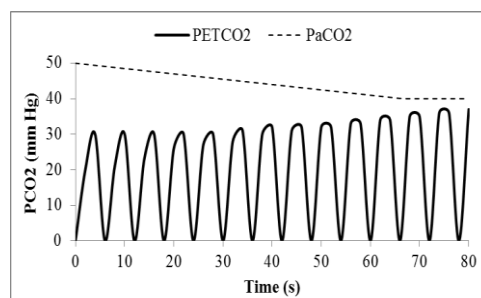
Figure 1(l) Treatment of bronchospasm. Note the flattening of the alveolar plateau
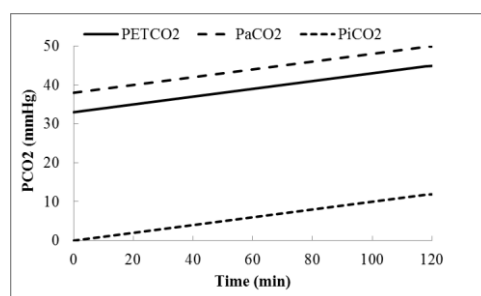
Figure 1(m) Soda lime is exhausted (trend) $PiCO_2$ = Inspiratory PCO_2
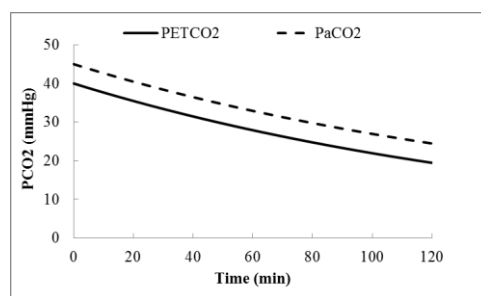
Figure 1(n) Hyperventilation (trend)
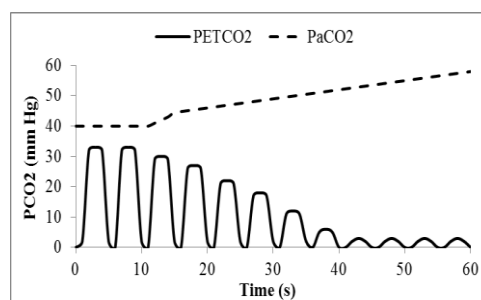
Figure 1(o) Sudden decreasing cardiac output, e.g. embolism and cardiac arrest
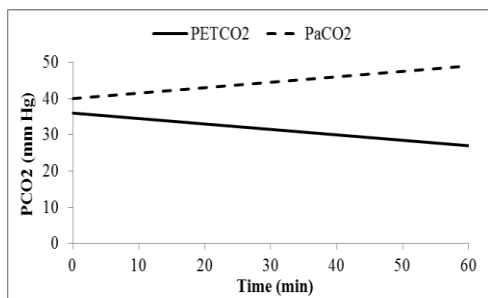
Figure 1(p) Gradual decrease in cardiac output (trend)
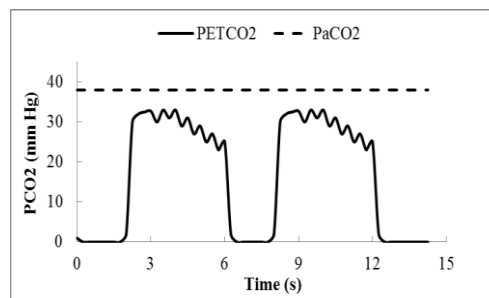
Figure 1(s) Cardiogenic oscillations
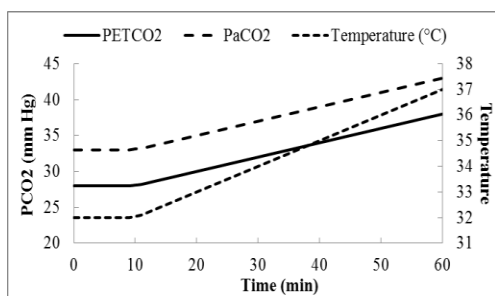
Figure 1(q) Hypothermia and rewarming (trend)
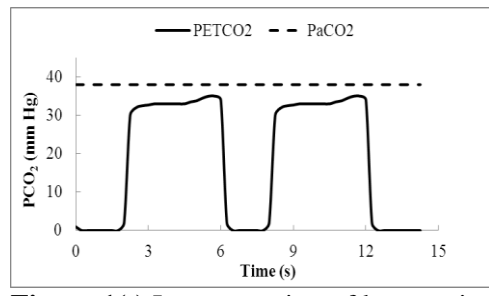
Figure 1(t) Late emptying of lung regions
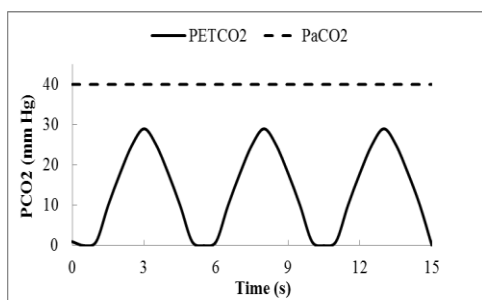
Figure 1(r) Leak in system

Pulse oximetry

The pulse oximeter is an *essential anaesthetic monitor*. It consists of a spectrophotometric device that emits light and measures the absorption of red (660 nm) and infrared light (940 nm) by a photo detector. Oxygenated haemoglobin (HbO_2) in arterial blood and deoxygenated (reduced) haemoglobin (HHb) in venous blood and of tissue have different absorption spectra. HbO_2 absorbs less red light and more infrared light and appears red, while HHb absorbs more light of 660 nm and less infrared light and is less red. The oximeter probe is attached to a body part, e.g. a finger or toe, to allow transillumination of the tissue. The ratio of the absorbance of the pulsatile matter (arterial blood) to the absorbance of non-pulsatile matter (venous blood and tissue) is analysed by the oximeter and displayed as a plethysmogram (pulse) and as the percentage saturation of arterial haemoglobin (SpO_2) (oximetry).

$$SpO_2 = 100 \times HbO_2/(HbO_2 + HHb)$$

When interpreting pulse oximeter displays, the following aspects should be attended to:

- The size is influenced by perfusion of the body part. The *plethysmogram is large* and the dicrotic notch displaced to the lower end of the catacrotic limb of the plethysmogram in vasodilated patients, e.g. sepsis, hyperthermia, fever, use of anaesthetic vapours (the ether group), etc. The *plethysmogram is small* and may disappear in severe vasoconstriction, a low cardiac output, and hypothermia. Pulse oximetry is unreliable in vasoconstricted patients.
- The ventilation-induced *undulation of the plethysmogram* disappears in hypovolaemic patients. This characteristic has been included in the algorithm of monitors to display pulse pressure

variation (see Chapter 18)

- *Pulse oximeters are calibrated using healthy volunteers.* Since it is unethical to expose volunteers to severe hypoxaemia, most oximeters are calibrate to PaO_2s > about 70 mm Hg. If the SpO_2 is < 70 mm Hg, the reading becomes unreliable and the cause of the low SpO_2 must be investigated. The safest approach in those cases is to increase the oxygen concentration in the inspiratory gas (FiO_2) and ensure that the SpO_2 increases. If the SpO_2 improves, the reason for the low SpO_2 must be sought (see Chapter 14).
- Apart from the causes of hypoxaemia (low PaO_2), *several artifacts* may affect the accuracy of pulse oximetry, including:
  - Pulse oximeters only "see" HbO and HHb. Abnormal haemoglobin species, including *methaemoglobin (MetHb) and carboxyhaemoglobin (HbCO).* Both these substances have absorption spectra that differ from that of oxyhaemoglobin. MetHb is red-brown and causes a saturation reading of about 86%; at low PaO_2s the saturation is falsely high and at high PaO_2, the saturation is falsely low. Since this haemoglobin cannot bind oxygen normally, these patients are cyanotic but the PaO_2 is disproportionately high. In CO poisoning, the oxygen is displaced from haemoglobin to form HbCO. HbCO has an absorbance similar to that of HbO and is also bright red. High CO levels give a SpO_2 of 96%. In these cases the SpO_2 is disproportionately high relative to the PaO_2. In both methaemoglobinaemia and carboxyhaemoglobinaemia, in vitro co-oximetry will reveal the high abnormal haemoglobin and a low HbO concentration. The PaO_2 is, depending on the underlying cause, high. MetHb is formed by oxidizing substances (e.g. sulphas, and nitrites) in patients with reduced reductase enzymes, e.g. glucose-6-phosphate dehydrogenase. HbCO levels may be high in burns and suicide with CO.
  - *Intravenous dyes* such as methylene blue absorbs light at 660 nm and decreases SpO_2
  - *Nail polish* interferes with accuracy and should be removed.
  - *Dark skin pigmentation* may cause overestimation of PaO_2. Therefore SpO_2 is slightly lower in Caucasians than in Blacks.
  - *Electromagnetic and electrocautery* interference may give spurious readings.
  - *Ambient light* and when light passes directly from the light-emitting diode to the photo detector without passing through tissue (*optical shunt*), interferes with the ratios of pulsatile and non-pulsatile absorbance (the ration approaches zero) and typically give a saturation of about 86%. The same happens when *arterial (oxygenated) blood appears in non-pulsatile (venous) blood*, e.g. in vasodilated patients or when the limb to which the probe is attached, is lower than the heart (this is called *penumbra of pulse oximetry*)
  - *Movement* interferes with oximeter function.

Since several factors may interfere with the accuracy of capnography and pulse oximetry, the anaesthetist must always correlate clinical signs with readings on these monitors. If in doubt, blood gas analysis is indicated (see Chapter 20)

The functions of the anaesthetic machine are to*:
- receive the anaesthetic gasses from the *high-pressure supply*,
- *reduce the pipeline pressures*,
- *regulate flow* to the anaesthetic vaporizer,
- and to serve as an *outlet of the anaesthetic gasses* to the ventilator, and finally, to the anaesthetic circuit.

*The **anaesthetic circuit is a conduit** between the anaesthetic machine and **the patient**.*

The anaesthetic monitors keep an eye on the:
- *gas* supplies,
- anaesthetic *machine*,
- anaesthetic *circuit* and ventilator,
- patient *physiology*, and the
- *interaction* between the patient and the extracorporeal components.

SUPPLY AND STORAGE OF ANAESTHETIC GASSES

Anaesthetic gasses are stored at high pressures in a *cylinder bank*, or in large *bulk containers* that supply several facilities with gas via a network of pipes. The cylinder bank usually supplies gasses to a small facility and is adjacent or near to the outlet. Despite these central gas sources, there must always be an emergency O_2-cylinder attached to the anaesthesia machine. Checking this cylinder forms part of the daily testing of the anaesthetic machine. It must be replaced immediately after it has been use. Small oxygen cylinders are also used during patient transport. *Colour coding* is essential for the identification of different *cylinders and pipes* containing that gas (Table 1)

Table 1 Anaesthetic inhalant colour codes

Gas	Colour code of cylinder	Pipe colour
Oxygen	Black cylinder with white shoulder	White
Carbon dioxide	Green cylinder with white shoulder	-
Nitrous oxide	Blue cylinder	Blue
Entonox (O_2 50% + N_2O 50%	White or blue with blue and white shoulder	
Air	Grey with black and white shoulder	Black
Suction	-	Yellow
Scavenger	-	White-blue-yellow

- All gas cylinders are fitted with a cylinder head. The cylinder head consists of a pressure gauge (and a flow regulator, depending on the purpose of the cylinder).
- Oxygen has a *critical temperature* (the temperature above which a substance in the gaseous phase cannot be liquefied however high the pressure) of -119°C. The vapour pressure of a substance at its critical temperature is the *critical pressure*. Therefore, oxygen cannot be liquefied at higher temperatures. Consequently, the pressure inside an oxygen cylinder is proportional to the amount of oxygen. Therefore, the pressure is an indication of the amount of oxygen present in the cylinder; the pressure in the cylinder will decrease as the amount of gas in the cylinder decreases. The volume of oxygen at ambient pressure that the cylinder will deliver, can be calculated according to Boyle's law ($P_1V_1 = P_2V_2$). With this volume known, and the flow from the cylinder, the time that the oxygen will last can be calculated.

  Example:
  The pressure inside a *"700 L"* oxygen cylinder is 5 000 kPa. When full, the pressure inside the cylinder is 15 000 kPa. The "700 L" means that the volume of oxygen in the cylinder (when full) will expands to 700 L at ambient pressure *at sea level* at room temperature (20°C).

  a. What is the volume of the cylinder (V_2)?
  $P_1V_1 = P_2V_2$. Therefore, 100 kPa × 700 L = 15 000 kPa × V_2 and V_2 = 4.67 L = volume of the cylinder
  b. How long will the cylinder last if you would set the flow at 5 L min^{-1} in Durban and in Pretoria? Remember, ambient pressure at sea level is about 100 kPa and 87 kPa in Pretoria.
  A full (15 000 kPa at 20°C) E type cylinder supplies 700 L of oxygen at sea level (100 kPa).
  Therefore, 5000 kPa will hold (5000 kPa/15000 kPa) × 700 L = 233 L.
  At a flow of 5 L min^{-1}, the cylinder will last 233 L/(5 L min^{-1}) = 46.7 min
  In Pretoria, the same pressure of oxygen in the cylinder will expand to a larger volume.
  Therefore, in Pretoria the oxygen will last (100 kPa/87 kPa) × 46.7 min = 53.6 min
  c. What must the minimum pressure in the cylinder be, to allow a transport time of 2 hours in Pretoria?
  2 hours = 120 minutes
  Volume of oxygen needed = 120 minutes × 5 L min^{-1} = 600 L
  The pressure in the cylinder must be ≥ (100/87) × (600/700) × 15 000 kPa = 14 778 kPa.

- *Nitrous oxide* has a *critical temperature* (the temperature above which a substance in the gaseous phase cannot be liquefied however high the pressure) of 36.5°C. At temperatures above 36.5°C, nitrous oxide will always exist as a gas.

The vapour pressure of nitrous oxide at 20°C is 52 bar (5 200 kPa). At this temperature and pressure, nitrous oxide in a cylinder will exist as a liquid and a gas. When gas is released from the cylinder, the liquid evaporates and the pressure returns to the vapour pressure at that temperature. The pressure will only decrease once no more liquid can evaporate. The pressure inside a nitrous oxide cylinder is therefore not an indication of the amount of gas available. The only way to know the amount of nitrous oxide in a cylinder is to weigh it.

If a nitrous oxide cylinder is completely filled at 20°C, it may explode when it is exposed to higher temperatures. Therefore, nitrous oxide cylinders are only filled to a maximum of 0.65 of the content of the cylinder. The cylinder is also fitted with a pressure relief valve that opens at a pressure well below the pressure at which the cylinder can withstand. A "full" E type nitrous oxide cylinder can deliver 1590 L of gas a sea level. When all the liquid has evaporated, about 400 L of nitrous oxide is left and the pressure in the cylinder will start to decrease with further release of gas.

- Entonox is a 50:50 mixture of oxygen and nitrous oxide, which is stored in white or blue cylinders with blue and white shoulders. Mixing of gasses change their physical characteristics. Pure nitrous oxide has a critical temperature of 36.5°C and oxygen of -119°C. Entonox is prepared by bubbling oxygen gas through liquid nitrous oxide. The liquid nitrous oxide is vaporized and forms a gas mixture containing 50% of oxygen and 50% of of nitrous oxide (the Poynting effect). Entonox has a critical temperature of -5.5°C (the pseudocritcal temperature). Below -5.5°C, nitrous oxide liquefies so that a gas mixture containing > 50% oxygen lies above the nitrous oxide liquid (this is called lamination). If this gas is released from the cylinder, the oxygen concentration will gradually decrease until the gas will contain only nitrous oxide. Therefore, a cylinder that has been exposed to temperatures < -5.5°C, should be warmed in a water bath at 37°C for 2 hours in a room of 15°C. Thereafter, the cylinder should be inverted several times before use. If gas has been released from a cylinder before warming, it should not be used. Piped nitrous oxide at 4.1 bar has a pseudocritical temperature of less than -30°C.[5]

Central oxygen bank
In large institutions, liquid oxygen is stored in large bulk vacuum-walled cylinders at a temperature of -183°C in vacuum.

PRESSURE REDUCING VALVES

The anaesthetic gasses are distributed to different facilities via a network of pipes. The pressures in the gas banks are reduced by pressure reducing valves so that the pressure of piped gas is about 400 kPa. This pressure is reduced in the anaesthetic machine to about 100 kPa at sea level.

Safety measures regarding gas supply
- Pipes connecting the high pressure (400 kPa) gas point in the theatre wall or pendant from the ceiling are colour-coded. The *socket union* between the gas pipe metal plug and the gas outlet socket is also gas-specific, which ensures connection of the particular pipes into the correct gas outlet.
- *Pin index system*: On the front of block of the cylinder head are holes, which correspond to pins on the anaesthetic machine. Each gas cylinder has its own pin shape that only fits its specific pin configuration.
- *International colour coding* of the supply pipes and cylinders (Table 1).
- *An oxygen alarm* that sounds when the pressure in the gas supply is disconnected or decreases to below about 175 kPa.

THE ANAESTHESIA MACHINE

The main components of the anaesthesia machine are:
- Gas inlet: piped gas and cylinders
- Pressure regulators and pressure reducing valves
- Flow meters with flow adjusters
- Vaporizers
- Fresh gas outlets for the anaesthesia circuit and ventilator
- Scavenging system

Pressure regulators and pressure reducing valves

The anaesthetic machine receives the gas at a pressure at a high and variable pressure of about 400 kPa. These pressure regulators ensure a constant pressure and reduce the high pressures to less than about 350 kPa. Whereas the pressure regulators for air and nitrous oxide are connected directly to the flow meters, the oxygen line is also connected to a fail-safe valve, oxygen flush, and ventilator outlet:

- The *fail-safe valve* closes the nitrous oxide and air inlets if the oxygen inlet pressure decreases to below about 200 kPa. This prevents the administration of gasses with a low oxygen concentration.
- The *oxygen flush valve* allows high pressure oxygen to bypass the flow meters and vaporizers to the common gas outlet and ventilator. It allows a flow of about 50 l min^{-1} at a pressure of about 350 kPa. It is only used when large leaks occur distal to the flow meters or anaesthetic circuit. It must be used with caution, as barotrauma to the lungs is a real possibility.
- The high pressure *ventilator power outlet* drives the ventilator.

The flow meters

The anaesthetic machine allows the anaesthetist to adjust the flow to the anaesthetic circuit. The flow is set and read directly on the mechanical flow meter (rotameter) or indirectly with an electronic adjustment knob and displayed digitally and/or graphically and in the particular gas colour. Some anaesthetic machines have a mechanical adjustment knob but display the flows electronically.

The flow meters have mainly *four functions*:

- They *reduce the pressure* to about ambient pressure (87 kPa in Pretoria).
- They supply gas to the *anaesthetic circuit* at the required flow.
- They supply gas to the anaesthetic *vaporizer*.
- The relative flows in the different rotameters determine the *gas composition*.
- If the oxygen concentration of the gas mixture to the anaesthetic circuits decreases to less than about 30% the other gasses will shut down immediately (*anti-hypoxia guard*).

Flow meters are *gas-specific* since the viscosity and density of gasses differ. The mechanical flow meter consists of a flow-control valve, a tapered glass tube (narrow at the bottom and widening to the top, *Thorpe tube*) containing a bobbin. The valve is opened using the adjustment knob. The valve allows gas to flow from the high pressure to the glass tube. If the valve is closed, the bobbin is at the bottom of the tube. Once the valve is opened, the pressure below the bobbin increases, lifting it up, until its weight is equal to the pressure below it. If the flow through the valve increases, the pressure below the bobbin increases, raising it in the tube. The suspended bobbin rotates in the glass tube (*rotameter*).

Since the diameter of the tube increases to the top, the space (*orifice*) around the bobbin increases and the amount of gas passing the bobbin increases. As the flow increases while the resistance between the bobbin and tube wall decreases, the pressure drop across the bobbin will not change, regardless of the flow (*constant-pressure variable-orifice flow meter*). *Flows are read off* the top of cylindrical bobbins but in the middle of spherical ones.

The vaporizer

This component of the anaesthetic machine adds anaesthetic vapour to the fresh gas. Remember that the high-pressure oxygen after it has passed the pressure reducing valve, supplies gas to the ventilator, oxygen flush, and rotameters. The gas leaves the rotameters to supply the fresh gas to the anaesthetic circuit. Between the rotameters and the outlet to the anaesthetic circuit anaesthetic vapour is added to the fresh gas. The vapour can be added to the fresh gas in two ways: the *volatile liquid is vaporized (vaporizer)* or *injected electronically (injector)* into the fresh gas.

The volatile agent vaporizer receives all the fresh gas flow. A fraction (*variable bypass*) of the gas can be directed into the vaporizer. This fraction passes over the volatile liquid where is saturated with anaesthetic vapour. The partial pressure of the anaesthetic in the vaporization chamber (*saturated vapour pressure*) of the vaporizer at a particular pressure depends on the *physical characteristics (boiling point)* and *temperature*. When a liquid evaporates, molecules with higher energy leave the liquid phase, leaving behind a liquid with less energy. This results in loss of heat from the liquid and cooling of the vaporizer. Therefore, the number of molecules that evaporate, decreases. These two aspects have *three important implications*:

- Vaporizers are *agent specific*. The bottles containing the volatile anaesthetic are fitted with adaptors that will only allow filling of its specific vaporizer and injector.
- Vaporizers are designed with several mechanisms to *compensate for changes in temperature*, which ensures a constant vapour pressure, which is added to the fresh gas. Therefore, these vaporizers are called *te*mperature *c*ompensated (TEC). The Datex Ohmeda and Dräger vaporizers work on these principles. At sea level, desflurane has a boiling point of

22.8°C. Temperatures exceeding this temperature occur commonly in operating theatres due to air conditioning or ambient temperature. The liquid may therefore evaporate at such a rate that the vaporizer cools. To offset the cooling a mechanism to heat the vaporization chamber is incorporated in the desflurane vaporizer.

- Vaporizers are *pressure compensated* (the *working pressure*) to accommodate the effect of fresh gas flow (proximal pressure) and pressure in the circuit (distal pressure)

Please note that saturated vapour pressure is independent of ambient pressure. The *partial pressure* (mm Hg or kPa) output of *modern* vaporizers at sea level and high altitude is the same. Older vaporizers deliver *the percentage* (ml of vapour per 100 ml of fresh gas flow) set on the vaporizer dial, but the partial pressure, which actually matters, is decreased and should actually be increased to deliver the correct dose (number of molecules = partial pressure) to the fresh gas. When the partial pressure of vapour in the fresh gas is increased, the percentage will also increase. For example, to deliver a fresh gas mixture containing 1% of isoflurane at sea level, the vaporizer will add vapour to the fresh gas to ensure a partial pressure of 1% of 760 mm Hg (101.3 kPa) = 7.6 mm Hg (1 kPa).

However, to ensure the real dose (partial pressure) of isoflurane in Pretoria (at altitude of 1400 the ambient pressure is about 650 mm Hg or 87 kPa), the dial must be set at
$$(7.6 \text{ mm Hg}/650 \text{ mm Hg}) \times 100 = 1.17\% \approx 1.2\%$$

The magnitude of variable bypass is determined by the dial setting of the vaporizer and will determine the concentration of the vapour in the fresh gas. For example, the saturated vapour pressure of isoflurane at 20°C is 238 mm Hg (32 kPa). In order to obtain a gas mixture containing 1% of isoflurane at sea level, how much vapour (dial setting) must be added to every 100 ml of fresh gas?

If a gas mixture must contain 1% isoflurane vapour at sea level (1 kPa or about 100 kPa), how much is the vapour flow rate at 20°C if the fresh gas flow is 1 L min^{-1}?
$$P_1V_1 = P_2V_2. \text{ Therefore, } V_1 = (1 \text{ kPa} \times 1000 \text{ mL min}^{-1})/32 \text{ kPa} = 3.1 \text{ mL min}^{-1}$$

The student must not confuse the *dial setting* and the *concentration (%)* of vapour reflected on the *gas analyser monitor* and *the actual partial pressure* (mm Hg or kPa, the real dose) of the vapour in the fresh gas mixture (Fi) and in the gas mixture from the patient (Fe). When these monitors are available, anaesthetists adjust the dial on the vaporizer according to the concentration in the patient (represented by Fe). However, the vapour analyser gives the concentration of vapour as a percentage of volume of gas mixture at ambient pressure. Therefore, 1% of a vapour at sea level is (1/100)100 kPa vapour = 1 kPa. But in Pretoria, 1% of vapour is (1/100)87 kPa vapour = 0.87 kPa

Although vapour analysers determine the number of molecules (partial pressure), manufacturers persist in displaying percentage instead of partial pressure. The same applies to the oxygen and nitrous oxide. This is clearly misleading and clinically wrong!

The anaesthetic breathing circuit (system)

The anaesthetic breathing circuit is a *conduit* between the *anaesthetic machine fresh gas outlet* and the *patient*. It consists of an arrangement of corrugated plastic tubing whereby *fresh gas* (oxygen, air or N$_2$O, and volatile anaesthetic) is *delivered* to the patient, and **removes CO$_2$** from the patient. Remember, the amount of CO$_2$ removed from the lungs is dependent on pulmonary ventilation. The amount of CO$_2$ that is removed from the lungs is determined by the amount of gas going into and leaves the lung per time. The amount of gas moving in and out of the lung per minute is called the *minute ventilation or minute volume (Vm)*. Vm is the tidal volume (Vt) times the respiratory rate (RR): Vm = Vt × RR; Vt = 6 ml kg^{-1} to 8 ml kg^{-1}

Previously the circuits were classified as closed, semi-closed (*Mapleson classification*), semi-open, and open. This nomenclature is confusing and many of these circuits have become obsolete.

Currently, only the semi-closed and closed circuits are used. They are now called *rebreathing* and *non-rebreathing* circuits, respectively. The term "rebreathing" refers to gas that has been in the alveoli, particularly CO$_2$. *It is important that the patient and the circuit be regarded as one system, i.e. from O$_2$ supply to CO$_2$ elimination*. Depending on the configuration of the different components, the *rebreathing circuits* are classified as *Mapleson A to F* (Table 1, Figure 1).

An anaesthetic circuit consists of:
- a 1.1 m long *efferent* limb (to the patient, supplying *fresh gas*, i.e. gas that has not left the anaesthetic circuit),
- an *afferent* (from the patient) limb,

- a *Y-piece* between the efferent and afferent limbs,
- a volume of *dead space* (a volume that does not take part in CO_2 elimination)
- an adjustable *valve(s)*: *Heidbrink* pressure release valve (in the rebreathing systems), airway pressure-limiting (*APL*) valve, or *unidirectional ventilator* valves. The valve(s) allows *venting* of gas during spontaneous ventilation, and determines gas *flow direction* during controlled ventilation.
- a mechanism to *eliminate CO_2* from the afferent limb (flow- or chemical-dependent), and
- a *reservoir bag (1 L or 2 L) or ventilator*. The *functions of the reservoir bag* are to allow for peak inspiratory flows during inspiration (up to 50 L min^{-1} in adults), allows assisted ventilation when the valve is partially closed, and gives an indication *that* the patient is breathing (but *not* an indication of adequate breathing). When anaesthetising paediatric patients, the reservoir bag should be changed to a smaller one litre bag to enable the anaesthetist to deliver small tidal volumes manually.

The performance of an anaesthetic circuit (the ability to remove CO_2) is determined by the:
- FGF,
- minute ventilation,
- minute ventilation relative to FGF,
- mode of ventilation (spontaneous or controlled)
- tidal volume,
- respiratory rate,
- inspiratory:expiratory ratio (The longer the expiratory phase, the more efficient the FGF to wash out alveolar gas),
- peak inspiratory flow rate,
- volume of expiratory (efferent limb) and reservoir bag,
- apparatus dead space (amount of rebreathing relative to the fresh gas flow, FGF). [The higher the dead space (the amount of rebreathing), the higher the FGF needed to eliminate (wash out) the CO_2 from the system, and therefore, the less efficient (economical) the circuit.)],
- position of the valve(s) and reservoir bag (near to or away from the patient), and
- mechanism of CO_2 elimination (absorbing or washing out the CO_2 using higher FGFs).

Remember, FGF is calculated according to *obese dose-determining mass (ODDM)* (see Chapter 17).

Breathing circuits
The *term rebreathing* referrers to the *rebreathing of anatomical dead space*, i.e. gas from the lungs that did not take part in gas exchange. This gas does not differ from fresh gas, except that dead space gas contains water vapour and no CO_2. The performance of rebreathing circuits differs during spontaneous and controlled ventilation. You must know when a rebreathing circuit is more efficient, i.e. for spontaneous or controlled ventilation. If the circuit is used during the non-efficient breathing method, the FGF must usually at least be doubled. For example, the Magill circuit is ideal (more efficient) for spontaneous ventilation at a FGF of about 70 mL kg^{-1} min^{-1} to 100 mL kg^{-1} min^{-1}; during controlled ventilation, the valve is partially closed, gas flow directions and dead space change, which increase the FGF needs to about 140 mL kg^{-1} min^{-1} to 200 mL kg^{-1} min^{-1}.

Mapleson A (Magill)
This circuit is most efficient during *spontaneous* ventilation wherefore the FGF is equal to alveolar ventilation (Alveolar ventilation = Minute ventilation – Dead space ventilation) namely *70 ml kg^{-1} min^{-1} to 100 ml kg^{-1} min^{-1}*. During *spontaneous breathing* the Heidbrink valve must be open. Expired gas from the anatomic dead space (does not contain CO_2) moves past the valve, back to the corrugated tubing, while the FGF is diverted to the reservoir bag. As the pressure in the system increases, the bag fills, the valve opens, alveolar gas (contains CO_2) is vented out of the system, the pressure decreases, and the valve closes. During the next inspiration, the initial gas inhaled is the dead space gas from the previous breath (which has to some extent, been warmed and humidified), some mixed gas consisting of dead space and alveolar gas (rebreathing) and fresh gas from the reservoir bag (Figure 1).

The Magill circuit is *inefficient during manual or controlled ventilation*. During controlled ventilation, the Heidbrink valve is partially closed (increased resistance). During inspiration, part of

the alveolar gas is vented by the valve, while the rest is returned (rebreathing) to the patient (depending on the extent to which the valve is closed). Since more alveolar gas is prevented from being vented through the partially closed valve, more rebreathing occurs. Therefore, a higher FGF (140 ml kg^{-1} min^{-1} to 200 ml kg^{-1} min^{-1}) is needed to push the mixed and alveolar gas through the valve (Figure 1).

Mapleson B
This system is not used in South Africa. It requires a FGF of about 200 ml kg^{-1} min^{-1}.

Mapleson C and the ambu bag
The Mapleson C system is not used in anaesthesia but is similar to the Ambu bag (Figure 20). You must know how the Ambu bag works since it is used in situations where an anaesthetic machine, mechanical ventilator, or piped gas is not available, e.g. when transporting patients and for out-of-theatre ventilation. The ambu bag is not suitable for spontaneous ventilation. The FGF is oxygen and must be at least equal to the minute ventilation, i.e. 70 mL kg^{-1} min^{-1} 100 mL kg^{-1} min^{-1}.

During inspiration, the self-inflating bag (SIB) is filled from the reservoir bag, atmosphere, and oxygen. When the self-inflating bag is compressed, the outlet valves at the patient and at the inlet valve from the reservoir bag at the back of the SIB close and gas is forced into the patient. During compression of the SIB, oxygen cannot flow into the SIB and is directed into the reservoir bag.

During expiration, the valve to the SIB closes and expiratory gas escapes through the gas outlet at the mouth piece the atmosphere. Therefore, neither alveolar nor dead space gas flows back into the SIB (there is no re-breathing). The valve at the patient may be fitted with an adjustable resistance to allow positive end expiratory pressure (PEEP). This is often essential when transporting patients between theatre and the intensive care unit.

Mapleson D circuit
The co-axial Mapleson D is called the Bain circuit. The efferent limb (from the fresh gas outlet) is inside the afferent limb (from the patient). Both the Heidbrink valve and the reservoir bag are at the fresh gas inlet end of the circuit, i.e. away from the patient. This circuit is more efficient during *controlled* ventilation.

During *spontaneous breathing,* the Heidbrink valve must be open. Expired gas from the anatomic dead space flows into the afferent limb followed by alveolar gas (containing CO_2). Both these portions of exhaled gas mix with fresh gas. The fresh gas enters the circuit at the patient end of the circuit, and pushes the mixture into the afferent limb to the reservoir bag. At the end of expiration, the gas in the afferent limb close to the patient consists mainly of fresh gas. Since fresh gas continues to flow during and after expiration (significance of the expiratory phase), the pressure in the circuit increases. This increased pressure *opens the valve*, from where alveolar gas escapes. Remember that before the valve opens, gas from the anatomical dead space and alveolar gas have moved into the reservoir bag. Therefore, the reservoir bag is filled with a mixture of anatomical dead space (contains no CO_2), alveolar gas [contains CO_2 of 30 mm Hg to 40 mm Hg (4 kPa to 5 kPa)], and fresh gas (contains no CO_2).

During *spontaneous inspiration* the pressure in the afferent limb decreases, the *valve closes* and gas moves into the patient: first CO_2-free gas from the afferent limb closer to the patient and fresh gas, then a mixture of alveolar gas and fresh gas, followed by a mixture of all three gas portions. To prevent excessive rebreathing (hypercapnia) during spontaneous ventilation, the FGF must be high (140 ml kg^{-1} min^{-1} to 200 ml kg^{-1} min^{-1}, i.e. 2 times to 3 times the minute ventilation) to push the alveolar gas far back into the afferent limb and out at the valve.

During *controlled ventilation*, the Bain circuit is (a little) more economical. *During expiration*, the valve is open and the reservoir (ventilator bellows) is filled by dead space gas, alveolar gas and fresh gas, and alveolar gas is vented through the valve. During *positive pressure (controlled)* inspiration,

the valve closes and the pressure in the circuit increases. The pressure in the afferent limb (peak pressure of about 20 cm H_2O) exceeds the pressure in the efferent limb (pressure just above ambient pressure), and forces fresh gas into the patient, mixed with gas from the afferent limb. Therefore, mixing of fresh gas and alveolar gas will always occur. If minute ventilation is high, the end-tidal CO_2 depends on the FGF (the amount of rebreathing alveolar gas). Conversely, if FGF is very high, the end-tidal CO_2 is determined by ventilation.

It has been suggested that to maintain normocapnia (*PaCO$_2$ at sea level of about 40 mmHg or 5.3 kPa and a CO$_2$ production of about 2.2 ml kg^{-1} min^{-1}*), a *safe FGF/ventilation combination is 100/120 ml kg^{-1} min^{-1}*. Remember, that $PaCO_2$ is lower in Pretoria (we hyperventilate due to an altitude of about 1400 m). Therefore, the FGF and/or minute volume must be higher.

Mapleson E system (Ayre's T-piece)
This is a T-piece without bag or valve. It allows spontaneous breathing with the addition of oxygen. The degree of rebreathing is determined by the volume of the expiratory limb and FGF. Peak flow is drawn from the open limb; if the volume of this limb is not too large, CO_2 will not accumulate.

Mapleson F circuit (Jackson Rees circuit)
A small reservoir bag with a hole in the tail end is attached to the expiratory limb of the Mapleson E system. It also allows for spontaneous ventilation, but controlled ventilation is made possible by creating a valve action with the index finger and thumb while the bag is compressed between the other three fingers and palm of the hand. It functions like the D circuit, needs a FGF of about 2 times the minute volume, but a minimum of 4 l min^{-1}. The circuit has many advantages as it has a very low resistance, and small dead space. The reservoir bag is a one litre bag to enable the anaesthetist to deliver small tidal volumes during manual ventilation.

The ADE system (Humphrey)
The ADE circuit is a combination of the Mapleson A and D. The circuit can be switched from a Mapleson A to a D. The A mode is used during spontaneous ventilation and the D mode during controlled ventilation. The FGFs for both are about 70 ml kg^{-1} min^{-1}.

FGFs used in rebreathing circuits
FGFs used in rebreathing circuits are somewhat confusing. The student must read this paragraph attentively and repeatedly to grasp the underlying principle. *The problem of FGFs using rebreathing circuits may be overcome by using the capnogram.* Due to rebreathing the capnogram will not reach quite zero during inspiration *unless the FGF > minute volume or expiratory time > inspiratory time.*

With an adequate FGF, end-tidal CO$_2$ will be determined by minute volume. However, at very low minute volumes with adequate tidal volumes, very high FGFs will be needed to maintain normocapnia. With very low tidal volumes, even high minute volumes will be accompanied by low end-tidal CO$_2$s (increased anatomical dead space ventilation) but high PaCO$_2$s. Therefore, ventilate the patient with an appropriate tidal volume (6 ml kg^{-1} to 8 ml kg^{-1}) at a frequency of about 12 min^{-1}; that means a minute volume of about 70 ml kg^{-1} min^{-1}to 100 ml kg^{-1} min^{-1}, and adjust the FGF according to the end-tidal CO$_2$. In patients with a high CO$_2$ production (pregnancy, fever), higher FGFs and minute ventilations may be needed to maintain normocapnia.

Older machines, especially in rural areas, still use the rebreathing circuits; the Mapleson A for spontaneous ventilation and the Mapleson D for controlled ventilation. The Mapleson F is widely used in paediatric anaesthesia. *The student must know and get accustomed to the use of the latter three rebreathing circuits as well as the non-rebreathing circuit.*

Modern anaesthetic machines, e.g. the ADU (GE Healthcare), have a *single fresh gas outlet* to which a non-rebreathing or rebreathing circuit can be connected. Other machines, e.g. the Avance machine (GE Healthcare), have an *additional fresh gas outlet*, which allows the use of a rebreathing system.

Table 2 Classification of rebreathing anaesthetic circuits

Class	Name	FGI near bag / patient	Valve at / away from patient	Bag at / away from patient	Comment: uses, FGF
A	Magill	Bag	At	Away	Spontaneous breathing: FGF 70 ml kg^{-1} min^{-1} ≈ 1× MV
B		Patient	At	Away	Not used in SA. FGF 200 ml kg^{-1} min^{-1}
	Ambu bag	Bag	Both	Both	Resuscitation, transport. FGF 70 ml kg^{-1} min^{-1}
D	Bain	Patient	Away	Away	Controlled ventilation: FGF 100 ml kg^{-1} min^{-1} ≈ 1 MV with minute volume of 120 ml kg^{-1} min^{-1} Spontaneous ventilations: FGF = 200 ml kg^{-1} min^{-1} ≈ 3 × MV
E	Ayre's T-piece	Patient	Absent	Absent	Not used in anaesthesia. Used for spontaneous ventilation only. FGF 200 ml kg^{-1} min^{-1}
ADE	Humphrey	A: bag DE: patient	A: At DE: away	Away	Switches between A for spontaneous and D for controlled ventilation. FGF for both modes is 70 ml kg^{-1} min^{-1} ≈ 1 × MV
F	Jackson Rees	Patient	Away	Away	Children < 30 kg. Spontaneous/manual ventilation. Minimum FGF 4 l min^{-1}.

FGI, fresh gas inlet; FGF, fresh gas flow; MV, minute volume

Spontaneous ventilation

Controlled ventilation

■ Fresh gas
▨ Dead space gas
■ Alveolar gas
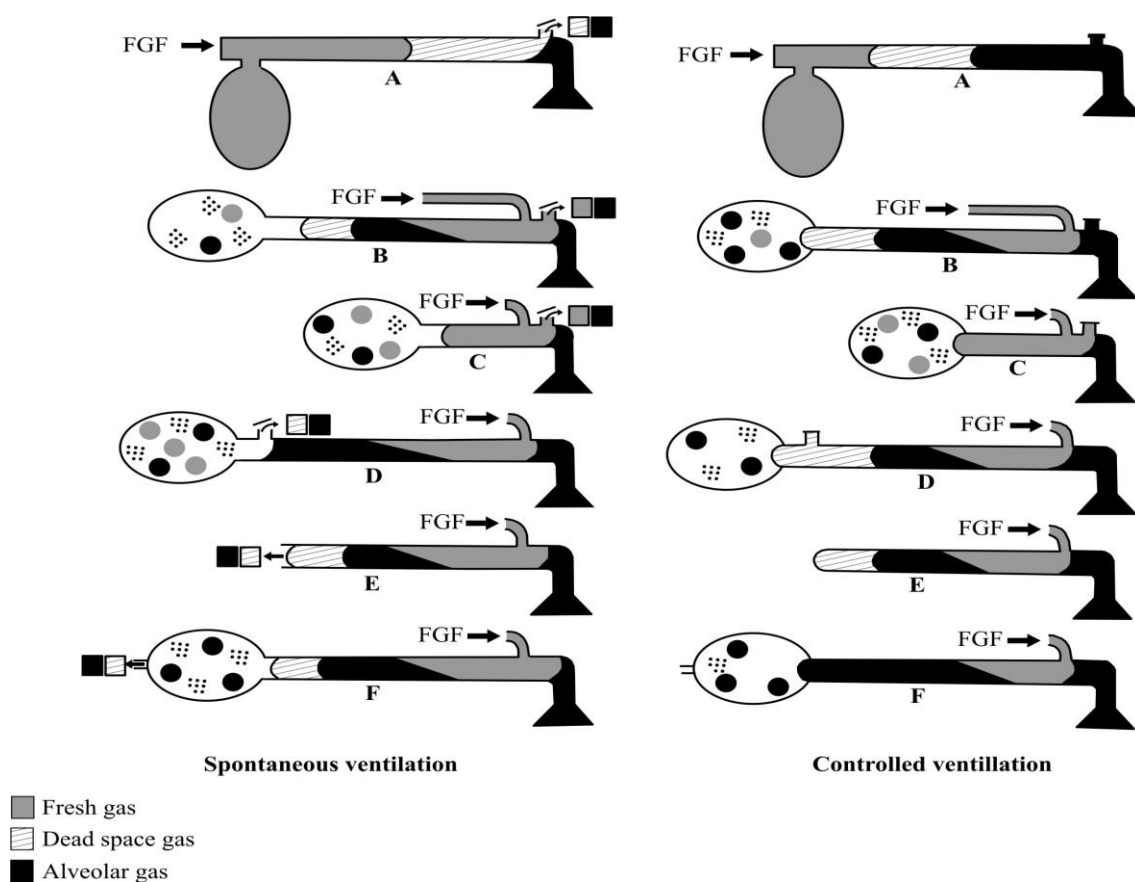
Figure 1 The rebreathing anaesthetic circuits *during expiration* of spontaneous and controlled ventilation. Note that the Mapleson E (T-piece) is used for spontaneous ventilation only.

Ambu bag during expiration

Bag inflates and draws gas from reservoir bag and outside

Air from outside is sucked into self-inflating bag

Reservoir bag sucked empty by self-inflating bag

Valve to bag opens

Valve to bag closes

Valve closes

O_2 flows to self-inflating bag

Gas from patient

Gas escapes through open valve
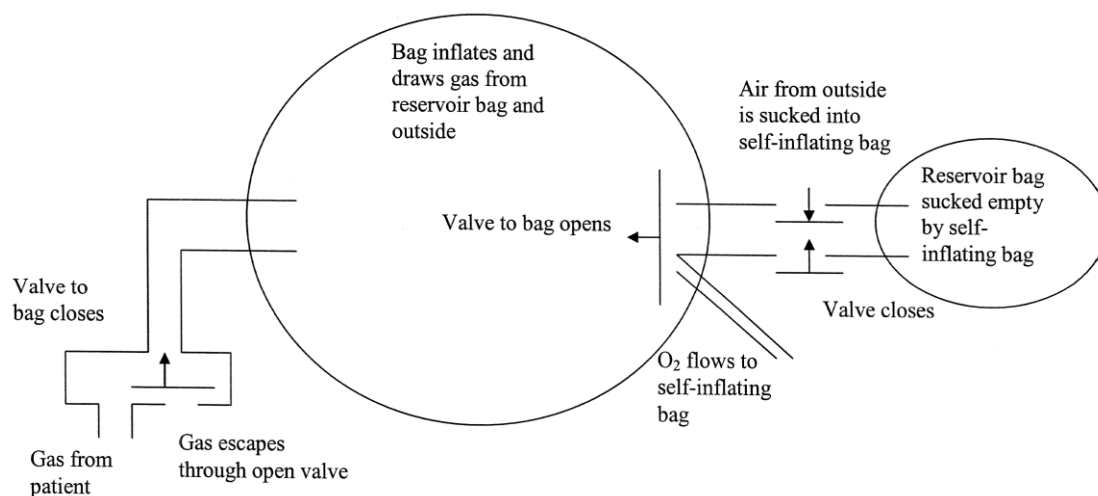
Ambu bag during inspiration

Valve closes

Bag is compressed

Bag is filled with O_2

Valve to reservoir bag closes

Valve from bag opens

O_2 flows to reservoir bag

Valve prevents over-inflation of reservoir bag

Gas flows into lungs

Valve closes
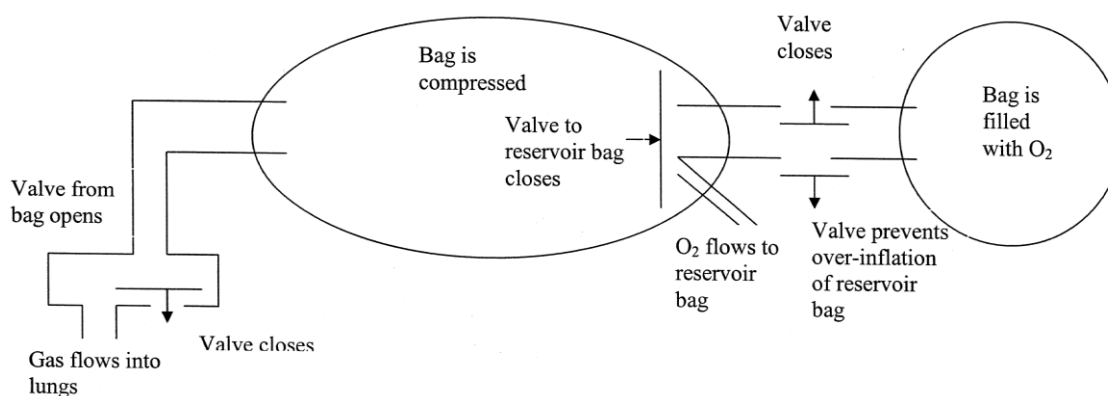
Figure 2 The Ambu bag.

The non-rebreathing circuit (circle system)

The circle system does not remove CO_2 by flushing it out of the system with high FGFs, but by removing the CO_2 with a chemical reaction. Theoretically, only the oxygen and the little nitrous oxide and vapour not breathed out by the patient needs to be replaced. Therefore, much lower FGFs are used (*low flow anaesthesia*). FGFs of between 500 ml min^{-1} to 1 l min^{-1} are safe. For low flow anaesthesia, *monitoring of oxygen, CO_2, and inhalation agents, is mandatory*. The construction of the circle system is illustrated in Figure 3.

This CO_2-removing chemical reaction takes place in a canister containing a solid granular (granule size of between 4 mesh and 8 mesh) substance consisting of:
- $Ca(OH)_2$ (about 80%),
- KOH (about 1% as activator),
- water (about 10%),
- a small amount of hardening agent (usually silicate),
- an pH sensitive indicator (ethyl violet in soda lime), and
- either NaOH (*soda lime*), $Ba(OH)_2$ (*Baralyme*), or calcium hydroxide lime (*Amsorb*).

The absorbent must not be too hard (decreases absorbing capacity), too fine (increases gas flow resistance), or too dry (forms CO with anaesthetic vapours).

Soda lime is the absorbent most commonly used in South Africa. The reaction is as follows:

$CO_2 + H_2O \leftrightarrow H_2CO_3$
$\downarrow$
$H_2CO_3 + 2NaOH (KOH) \leftrightarrow Na_2CO_3 (K_2CO_3) + 2H_2O + heat$
$\downarrow$
$Na_2CO_3 (K_2CO_3) + Ca(OH)_2 \leftrightarrow CaCO_2 + 2NaOH (KOH)$
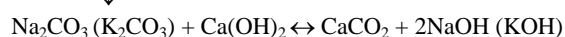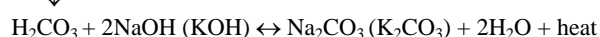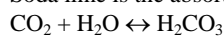
The pH of the absorbent mixture decreases during the reaction, causing the *ethyl violet indicator* changes from *colourless to violet*.

Soda lime reacts with anaesthetic vapours. Sevoflurane forms *Compound A*, an olefin compound, which is nephrotoxic in rats but not in humans. Dry soda lime and Baralyme degrades anaesthetic vapours to produce clinically significant quantities of *CO*. carboxyhaemoglobin concentrations as 30% have been reported. Rarely, *fires can occur in a rebreathing circuit absorbent canister*. This poorly understood chemical reaction has been described for sevoflurane in combination with *dry absorbent* (especially Baralyme).

The following factors enhance the production of CO:
- Desflurane > enflurane > isoflurane > halothane > sevoflurane
- High vapour concentrations
- Dry absorbent: FGF left open without a patient, e.g. during the weekend. If the FGF has been open for an unknown period, it is safer to replace the absorbent.
- Soda lime < Baralyme
- Eliminating NaOH and KOH (Drägersorb, Sofnolime)
- High temperature

Advantages of the circle system:
- *Economical*: less FGF and inhalation agent is used.
- *Pollution* of the theatre environment is reduced.
- Inspired gases are *heated and humidified*.

What is the FGF necessary for the circle system? See appendix
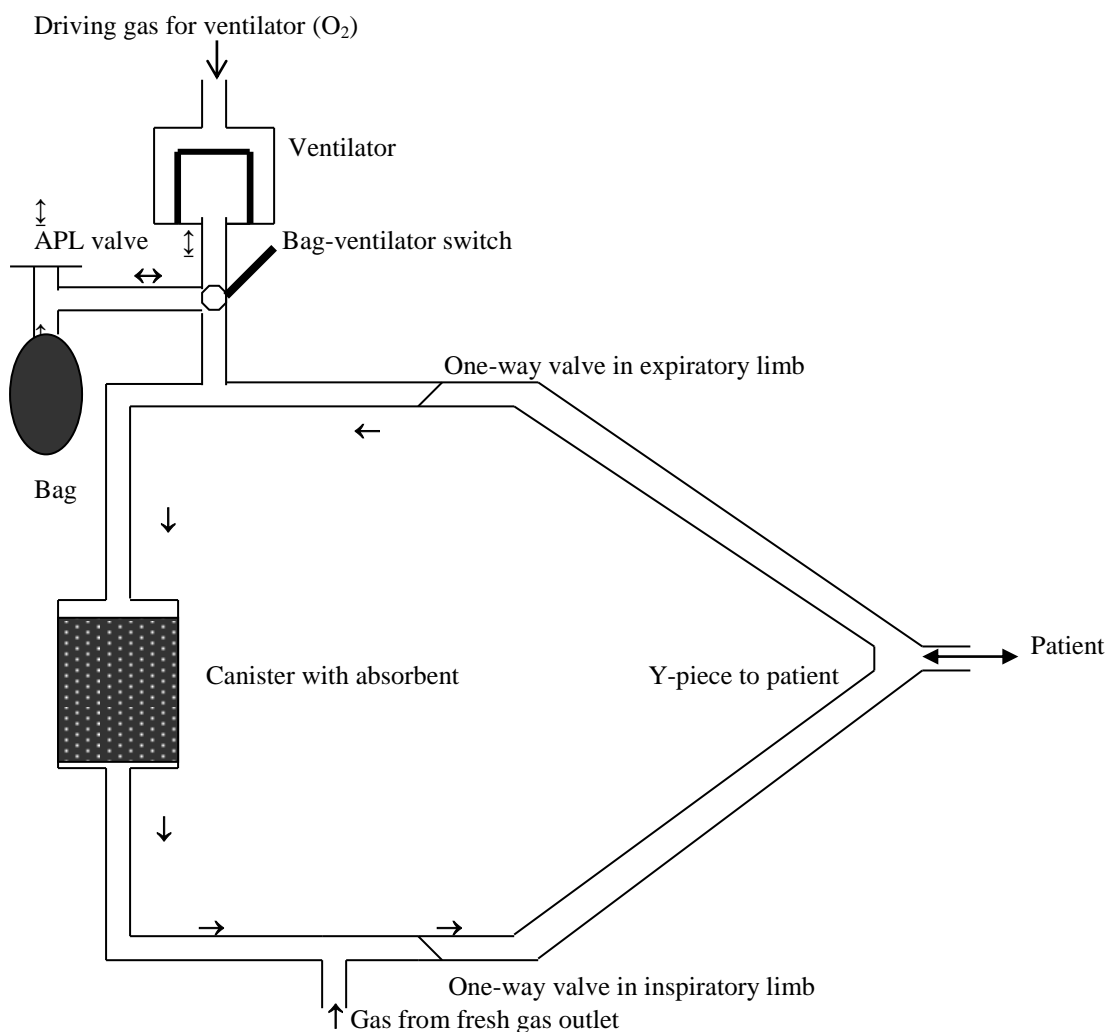
Figure 3 The circle system

The ventilator and artificial ventilation

The function of the ventilator is ventilation of the patient, which is not capable of adequate spontaneous ventilation. It is not expected from the student to know the design and function of anaesthetic ventilators.

Previously, ventilators were only substitutes of the reservoir bags of the Bain and circle systems. Currently, ventilators are built-in components of anaesthetic machines.

Anaesthetic ventilators can broadly be divided into three groups:

- *Minute volume dividers*. These ventilators receive the whole FGF and divide it into tidal volumes, which are delivered to the patient. The *Manley* is an example of this ventilator type and may still be found in old rural hospitals. It is a pneumatic (mechanical) ventilator that does not need electricity to function. It can be switched between controlled and spontaneous ventilation. The FGF is equal to minute volume, which flows into the ventilator. The filling volume of the bellows of the ventilator is set to deliver the tidal volume. The FGF is thus divided into a number of tidal volumes. Another example of a ventilator which divides the FGF into tidal volumes is the sophisticated electronic Siemens Elema 900C. This ventilator is an intensive care ventilator, but may still found in operating theatres. These ventilators need very high FGFs.
- *Bag-in-the-bottle ventilators*. These ventilators are very commonly part of modern anaesthetic machines and used in conjunction with circle systems. These ventilators are driven by oxygen, which compresses a bellows inside a transparent container. The bellows are filled by fresh and exhaled gas. If the bellows are filled during expiration, they are called *standing or ascending bellows*. If they fill during inspiration, they are called *hanging or descending bellows*. The standing bellows setup is usually preferred since a leak in the "bottle" that exceeds the fresh gas flow, will prevent the bellows to fill during expiration. With hanging bellows, gravity of the bellows may entrain gas through the leak and fill the bellows during expiration. There is no mixing between the driving gas and the bellows gas. Therefore, these ventilators are called *double-circuit systems* (see Figure 3). The Datex anaesthetics machines are fitted with these ventilators.
- *Piston ventilators*. These *single-circuit systems* employ a computer-controlled piston mechanism that moves gas in the system. In these systems, e.g. the Dräger anaesthetic machines, the fresh gas and exhaled gas is propelled by a piston mechanism. These ventilators are also part of a circle system.

Ventilation modes of anaesthetic ventilators

Patients ventilate (breathe) to supply O_2 and to excrete CO_2. Whether the patient is ventilating spontaneously, or is being ventilated mechanically, hypoventilation causes hypoxia and hypercapnia, while hyperventilation causes hypocapnia. All ventilation modes (including spontaneous ventilation) are characterized by the following entities:

- *Respiratory drive.* This determines the choice between spontaneous and controlled ventilation. *All sedatives and drugs used for general anaesthesia suppress respiration.*
- *Minute volume (Vm).* Vm is set according to the production of CO_2. It is calculated according to ideal body mass (IBM), or in obese patients according to the *obese dose-determining mass* (ODDM),[ii]
- and is about 100 ml kg^{-1} in adults and 150 ml kg^{-1} to 200 ml kg^{-1} in babies.
- *Tidal volume (Vt)* is normally 6 ml kg^{-1} to 8 ml kg^{-1} ideal body mass.
- *Peak inspiratory pressure* must be limited to less than 30 35 cm H_2O to prevent barotrauma.
- *Rate (frequency).* This is normally 8 min^{-1} to 12 min^{-1}, but varies with Vm.
- *Positive end-expiratory pressure (PEEP)* is the pressure that remains in the alveoli at the end of expiration. During normal spontaneous breathing, the resistance exerted by the vocal chords causes a PEEP of about 2 cm H_2O, and is also the minimum amount of PEEP given by most anaesthetic ventilators. The *advantage of PEEP* is the prevention of alveolar atelectasis. The *disadvantages of PEEP* are increased inspiratory pressure (barotrauma), and an increased intrathoracic pressure, which causes a decreased venous return (decreased cardiac output and increased physiological dead space).
- *The mechanical characteristics* of the respiratory system are determined by the airways, lung, and thoracic borders, i.e. diaphragm, pleurae, thoracic cage. These anatomical components determine the work of breathing, namely elastic (compliance of lung and chest wall) and non-elastic (mainly airway resistance). Compliance refers to the ability of the lung to receive a particular volume at a particular pressure, i.e. $C = \Delta V/\Delta P$ (Figure 4). The lower the compliance, and the higher the

---

[ii] ODDM = ideal body mass + 0.4(total body mass – ideal body mass)
IBM (kg) in men = height (cm) – 100, and IBM (kg) in women = height (cm) – 105, or
IBM (kg) in men = (height in m)^2 × 22.2, and IBM (kg) in women = (height in m)^2 × 21.9

airway resistance, the higher the *inspiratory pressures,* and *vice versa.*

- *In- and expiratory flow* is determined by the inspiratory: expiratory time ratio (I:E ratio) and is set according to the mechanical characteristics of the respiratory system. The I:E ratio is set to allow an adequate Vt at the lowest peak pressures and to allow complete expiration of the Vt during the available expiratory phase. Therefore, a stiff lung (low compliance) is ventilated at a high I:E ratio (long inspiratory time × lower inspiratory flow = adequate Vt), e.g. 1:2, or even 1:1. In patients with asthma or chronic obstructive airways disease (COPD) expiratory flow resistance is increased. Therefore, more time for expiration is required to prevent in complete emptying of the lung (auto-PEEP) and the I:E ratio is decreased, e.g. 1:3 or 1:4. Consequently, there is always a trade-off between in- and expiratory times: the smaller the I:E ratio, the higher the peak inspiratory pressure, and *vice versa.*
- *Monitoring of the ventilation* is done by spirometry (monitors Vt, rate, Vm, compliance, and airway resistance), pulse oximetry (arterial haemoglobin O_2 saturation), capnography (end-tidal PCO_2), blood gas analysis (PCO_2, PO_2, pH), and of course, cardiovascular function.
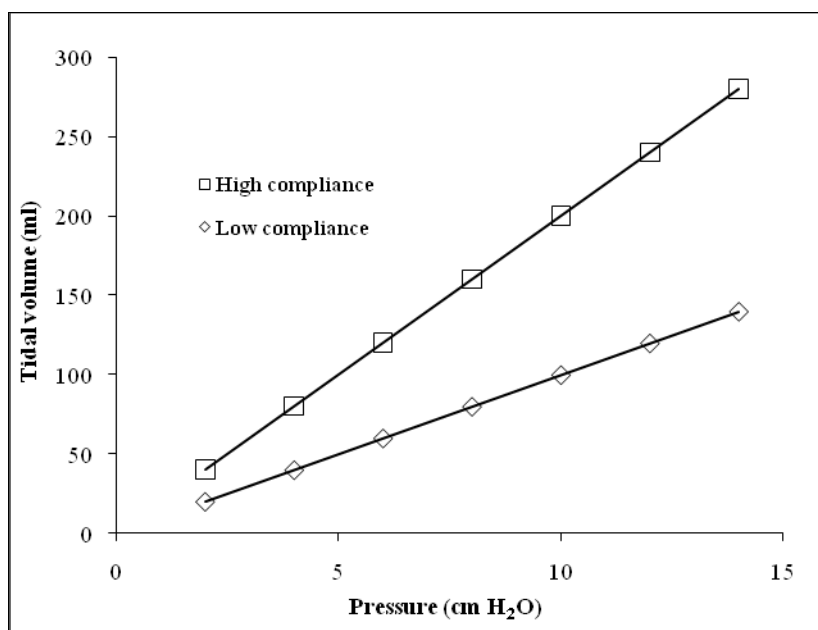
Figure 4 Compliance = $\Delta V/\Delta P$

Apart from spontaneous ventilation, the following modes are available on modern anaesthetic ventilators:

- *Volume-controlled ventilation*

  In *volume-controlled ventilation* (VCV), tidal volume (Vt) and ventilation rate are setto ensure a required minute ventilation (Vm). The ventilator cycles (changes from inspiration to expiration) when the Vt has been delivered. The Vt is delivered regardless the pressure created (up to a pre-set pop-off pressure, usually 40 cm H_2O).

  The *advantages* of VCV are that the delivery of a particular Vt is ensured and that the ventilator will alarm when the inspiratory pressure rises too high (usually > 30 cm H_2O). The *disadvantage* is that very high inspiratory pressures may result in barotrauma of the lung.

  The pressure reached as soon as the set volume has been delivered, is called the *peak inspiratory pressure (PIP)*. Thereafter, the PIP is dissipated through the lung and the pressure decreases the *plateau pressure*. It the lungs are "stiff" due to pathology distal to the airways, both PIP and plateau pressures are increased. However, when the lungs are stiff due to pathology in the airways, PIP >> plateau pressures since the high pressures are distributed slowly to the alveoli and the pressures decreases. Therefore, a condition such as *pulmonary oedema* causes and increase in both PIP and plateau pressures, while *bronchospasm* causes in increased PIP, while plateau pressures

are much lower.

- *Pressure controlled ventilation*
  During pressure-controlled ventilation (PCV) the lungs are inflated until a pre-set peak pressure is reached, after which the ventilator cycles to expiration. Therefore, the Vt delivered is determined by the pressure in the circuit; if the pre-set inspiratory pressure ___**above PEEP**___[iii] is reached soon after inspiration has begun, Vt will be small. PCP is therefore sensitive to changes in circuit or airway resistance or changes in lung or chest compliance (Figure 4).

  The advantage of PCV is that the lungs are protected from high pressures, which prevents barotrauma. PCV is therefore often used in babies, patients with lung bullae, and during one-lung ventilation to protect the lungs from high pressures. Since the pressure delivered during PCV is sustained over the whole inspiratory phase, the Vt is larger than during VCV with the same peak inspiratory pressure.

  The *disadvantages of PCV* are that
  o the *Vt may become very small* if the peak inspiratory pressures are set too low, which causes hypercapnia;
  o *an obstruction* in the circuit or patient a *decreased lung or chest wall compliance* my go unnoticed giving rise to low Vts;
  o the *Vt may become very high* if the lungs with a normal or high compliance. This may lead to hypocapnia.

- *Assist controlled ventilation modes*
  Assist controlled ventilation (ACV) combines characteristics of spontaneous ventilation with VCV or PCV. The clinician sets the minimum (mandatory) ventilation (frequency and volume or pressure) but the ventilator allows the patient to breath in-between ventilator-initiated breaths. The ventilator-initiated breaths are synchronized with those of the patient. Therefore, this mode is called *synchronized intermittent mandatory ventilation (SIMV)*.

  The advantage of SIMV is improved patient-ventilator interaction in patients with respiratory failure. SIMV has been used to wean patients from mechanical ventilation (*weaning*); the SIMV is gradually decreased while the patient-initiated ventilation gradually increases. Hypoventilation can be prevented intraoperatively by using SIMV, e.g. when a patient has not received a muscle relaxant or when a muscle relaxation has started to reverse. *The disadvantages of SIMV* are that the patient may still *hyperventilate* in-between, causing hypocapnia and an increased work of breathing, fatigue and *failure to wean*.

- Other ACV modes include *pressure-support ventilation (PSV)* and *bi-level positive airway pressure (BiPAP)*. These options are however not commonly available on anaesthetic ventilators.

SCAVENGER SYSTEMS

Gas consumption is determined by the amount of gas needed to drive the ventilator and the FGF. The fate the gas supplied to the anaesthetic machine is as follows:
- It may be directed into the anaesthetic circuit, inhaled, and exhaled by the patient.
- It may escape from the anaesthetic circuit through the Heidbrink or APL valve.
- Some gas (50 ml min^{-1} to 200 ml min^{-1}) is sampled from the Y-piece at the patient end of the circuit to the gas analyser (capnograph, O_2, anaesthetic gasses).
- It may be used to drive the ventilator.

These four gas components of used gas must be prevented from polluting the theatre environment. During spontaneous ventilation, gas escapes from the open valves in the anaesthetic circuits, e.g. the Jackson Rees system as well as from leaks in the system, e.g. faces masks and endotracheal tubes.

[iii] Example: If PEEP is, say 7 cm H_2O, pressure for PCP is set at say 15 cm H_2O, the peak pressure will be about 22 cm H_2O.

During controlled ventilation, the circuit valves are closed and driving gas (O_2) from the ventilator and excess fresh gas from the anaesthetic circuit is channelled to the scavenger system. Newer anaesthetic machines release the ventilator driving gas directly into the theatre and evacuate only the circuit gas.

Pollution can be limited by keeping the FGFs as low as possible to prevent overflow of gas out of the anaesthetic circuit. The gas from the capnograph outlet can be redirected to the anaesthetic circuit. Little can be done to evacuate gas that escapes from a mask or the valves during spontaneous ventilation. However, during spontaneous and controlled ventilation overflow gas is directed to an outlet that is connected to a scavenger system, which prevents the gas from escaping to the theatre atmosphere. *This is the scavenger system.*

A scavenger system consists or the following five components (Figure 5):
- A *collecting system* from the APL valve and ventilator at the anaesthetic machine outlet (1)
- *Tubing to transfer* gas from the collecting system (2) to *scavenger interface*
- *The scavenger interface* is *open with a reservoir* or *closed without a reservoir but with a relief valve* (3)
- Gas *disposal tubing* (4)
- Gas *disposal assembly*, which is *active (vacuum) or passive* (5)

The scavenger interfaces are either *open* to the atmosphere (valveless) and should be used with an active system, or *closed*, and can be used with a passive or active system. A *passive scavenger* system consists of tubing that is connected to the anaesthetic machine outlet. In *active scavenging*, the scavenger tube is connected to a suction system that allows flow equal to peak expiratory from the anaesthetic machine, i.e. about 30 l s^{-1}. The scavenge systems must comply with the following safety requirements:
- The diameters of the connecting tubing must not fit to any other outlet of the anaesthetic machine.
- The scavenger must be fitted with an interface to prevent negative or backpressure in the anaesthetic machine (-0.5 cm H_2O to about 5 cm H_2O).

In the closed interface, this reservoir of the open interface, is replaced by a relief valve, which prevents positive (> 5 cm H_2O) and negative (< 0.5 cm H_2O) pressure.
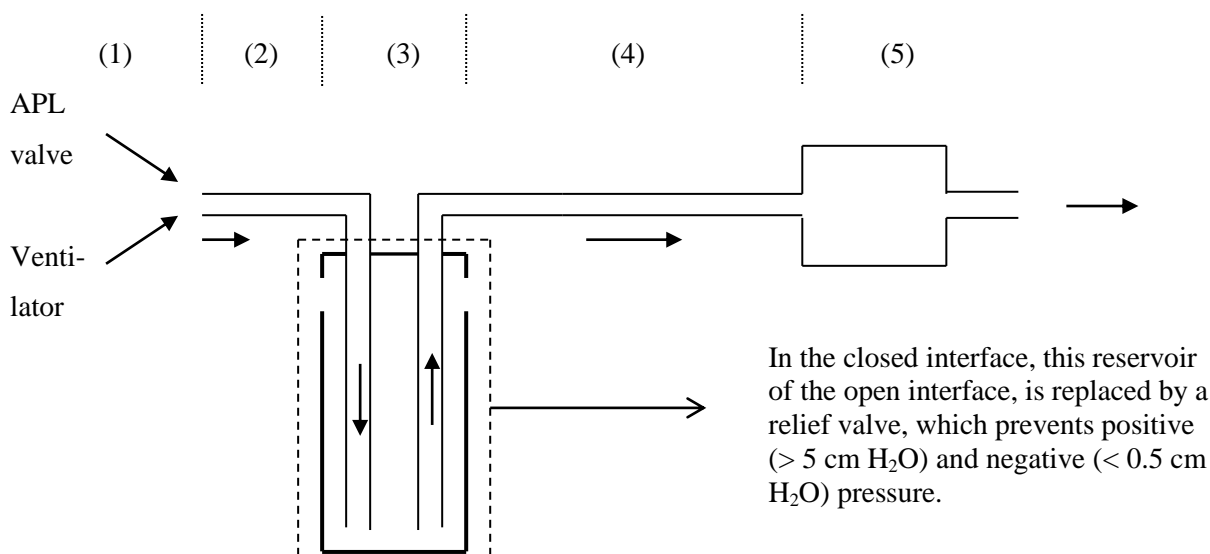
Figure 5 The components of a scavenger system

Thus far, we have dealt with the safe supply and removal of gas to the patient. We now turn to a piece of hardware, which is often neglected by the anaesthetist. It forms part an important part of patient management and comfort. This is the theatre table.

THE THEATRE TABLE

The theatre table has the following functions:
- It *supports* the patient during a procedure
- It is adjustable to position the patient to make the relevant *anatomy more accessible* to the surgeon, endoscopist, radiologist, etc.

- Different segments of the table can be manipulated relative to the horizontal plane. These positions are often used by the anaesthetist *to improve cardiovascular and ventilatory function*, and include the following:
  - The Trendelenburg position (feet higher than the head) improves venous return to the heart and prevents aspiration of regurgitated matter.
  - The ante-Trendelenburg position (head higher than the feet) decreases venous return to the heart.
  - Elevation of the legs and trunk horizontal increases venous return to the heart.
  - Elevation of the trunk and legs horizontal decreases pressure of the abdominal content on the lungs. The extreme of this position is the sitting position.
  - Lateral tilt is used to prevent aorta-caval compression in the presence of large intra-abdominal masses (pregnancy, tumours, ascites). It may also be necessary to remove pressure of mediastinal masses on the heart and great vessels.

The *anaesthetist must know* that the table is *functional* and know *how the controls work* before the patient is transferred to it.

SUCTION

Suction is an indispensable part of the anaesthetic equipment. Without good suction no procedure must be allowed to commence. "No suction; no induction!" Suction is essential to clear the airway and to prevent pulmonary aspiration during induction, maintenance, and end of anaesthesia. Suction is necessary to remove gastrointestinal fluid via a stomach tube and secretions and foreign matter from the lungs using bronchial suction catheters.

MONITORS

Monitors are used to ensure vital organ function. Monitors are often part of the anaesthetic machine, but may be separate units. Patient wellbeing is the primary responsibility of the anaesthetist. Monitors may facilitate perioperative patient safety, but do not replace *the presence or clinical acumen and vigilance of the anaesthetist*. The following monitors are regarded essential:
- Electrocardiography
- Non-invasive arterial blood pressure meter
- Pulse oximetry
- Capnography
- Temperature monitoring
- Peripheral nerve stimulator (neuromuscular monitor)

THEATRE PREPARATION AND CHECKING OF EQUIPMENT

Safety in the theatre is comparable to that in an aircraft. Like the passengers, patients must be confident the equipment and anaesthetist is in good working order.

The following items must be present on the working area of the anaesthetic machine:
- **Five metal objects:** Laryngoscope, Magill forceps, stylet for tube, artery forceps, and infusion stands.
- **Five plastic objects:** Face mask, tracheal tube, Guedel airway, airway filter, and suction tip.

Routine checking of the anaesthetic machine
All the components thus far discussed must be checked. Each functional group of components of the anaesthetic machines has to be assessed:

Gas supply
- In the case of piped gas, the anaesthetist must pull on the pipes where they are plugged into

pendant to ensure that they fit properly and that there are no leaks. When gas is supplied from cylinder, the filling pressures should be assessed.

- There should be a back-up cylinder of oxygen on the anaesthetic machine.
- Pressures of the gas supply must be checked on the pressure meters on the anaesthetic machine. If the oxygen pipe is unplugged, the nitrous oxide gas must be shut down in the anaesthetic machine and an oxygen gas failure alarm must sound.

The anaesthesia machine is tested for gas supply, fresh gas flow, vapour supply, fresh gas outlet.

- *Open the flow meters.* Detach the gas supply. There should be no flow in the flow meters. Reattach the gas pipes. Flow should be possible over the whole range of the flow meters. Pull out the oxygen pipe; the flow in the nitrous oxide flow meter must shut off immediately and a pneumatic alarm (whistle) must sound. Open the back-up oxygen cylinder. Flow in the oxygen flow meter must return and the whistle must stop blowing. It should not be possible to get any flow in the nitrous oxide flow meter when the oxygen flow meter is closed.
- *Vaporizers* should be firmly inserted. Fill them up if necessary. Do not proceed without a stock of anaesthetic vapour in your theatre.
- Check your *anaesthetic breathing circuit*. It should be complete. Connect the breathing circuit to the fresh gas outlet. Replace the soda lime of a non-rebreathing circuit (circle circuit) is necessary.
- *Test for leaks in the anaesthetic circuit*. Open the fresh gas flow to about 10 litres occlude the circuit at the patient end and then close the circuit valve and. Reduce the FGF to 200 ml min^{-1}. The reservoir bag should not deflate. Compress the reservoir bag and listen for leaks.
- *Test for leaks in the machine proximal to the fresh gas outlet*. To this end, you must know if the machine has a check vale before the fresh gas outlet. This valve prevents retrograde flow into the machine. To test for leaks in a machine with a check valve, the FGF is closed and a compressed auto-inflating bag is attached to the fresh gas outlet. If there is a leak, the bag will be able to suck air through the leaks is the system into the machine, which will enable the bag to suck in gas and inflate. Nowadays, most anaesthetic machines have a check valve before the fresh gas outlet.
- Switch the machine to *the ventilator* mode, switch on the ventilator, occlude the patient end of the ventilator or attach a test lung and ensure that there are no leaks in the ventilator.
- The *scavenger system* must work.
- Ensure that *the suction* is working.
- *The theatre table* must be in working order.

ESSENTIAL EQUIPMENT FOR EVERY THEATRE COMPLEX

- Emergency trolley with a defibrillator.
- Difficult intubation trolley.
- Ambu bag and masks if the anaesthetic gasses or anaesthetic machine fails during a case.

Appendix

FRESH GAS AND THE CIRCLE SYSTEM: FRESH GAS FLOW AND COMPOSITION[iv]

Fresh gas flow (FGF) supply = patient's oxygen consumption + leak + gas analysis flow = VO_2 + L + A
VO2 = [Inspiratory minute volume – (L + A)] × difference between in- and expiratory O_2 fractions
    = Expiratory minute volume × $(FiO_2 – FeO_2)$ = VE X FdO_2
(Please note that this is only a rough estimate; it is not necessary that you know the real Haldane transformation.)

The amounts of O_2 lost to L and A for the Datex anaesthetic machines are < 200 ml min^{-1} and 200 ml min^{-1} respectively.
 The FO_2 of gas that is lost to L and A varies between that of gas going to the patient (FiO_2) and of gas returning from the patient (FeO_2). Since the difference between FiO_2 and FeO_2 is small (usually between 3 and 5 percentage points, e.g. 50% and 46%) we may keep it simple and take it as FiO_2.

If one assumes that A + L = 200 + 200 = 400 ml min^{-1}, the amount of O_2 lost = 400 ml min^{-1} × FiO_2 = 400 × FiO_2.
Therefore, the minimum amount of oxygen in the FGF for a Datex machine = VO_2 + (400 × FiO_2).

What is the composition of the FGF if using O_2 and air, i.e. what are the fractions of air (F) and O_2 (1 – F) in the FGF?
The amount of O_2 supplied by air flow = FGF(0.2)(F) and by O_2 flow FGF(1.0)(1 – F)
Therefore, FGF(0.2)(F) + FGF(1.0)(1 – F) = (FiO_2)(FGF) and (0.2)(F) + (1.0)(1 – F) = (FiO_2) = 0.2F + 1 – F = 1 – 0.8F
Therefore, F = 1.25 - 1.25(FiO_2)

Example:
VE = 7000 ml min^{-1}
FiO_2 = 0.5 (50%)
FeO_2 = 0.45 (45%)
FdO_2 = 0.5 – 0.45 = 0.05

How much O_2 is required?
Total O2 requirements = VE X FdO_2 + 400 X FiO_2 = (7000 × 0.05) + (400 × 0.5) = 350 + 200 = <u>550 ml/min</u>

What is the fraction of air in the FGF?
F = 1.25 - 1.25(FiO_2) = 1.25 - 1.25(0.5) = 1.25 - 0.625 = 1 – 0.625 = 0.375

Each 100 ml of gas with an FO_2 of 0.5 contains 50 ml O_2 and is made up of 62.5 ml air + 37.5 ml O_2.
Therefore, for an O_2 requirement of 550 ml min^{-1} O_2, the FGF = 62.5 (550/50) ml min^{-1} air + 37.5(550/50) ml/min O_2.
                                            = 687.5 ml/min lug + 412.5 ml/min O_2
                                            = <u>VGV of 1 100 ml/min</u>

air fraction = -1.25(FiO_2) + 1.25

(x-axis: FiO_2, y-axis: Fraction of air)
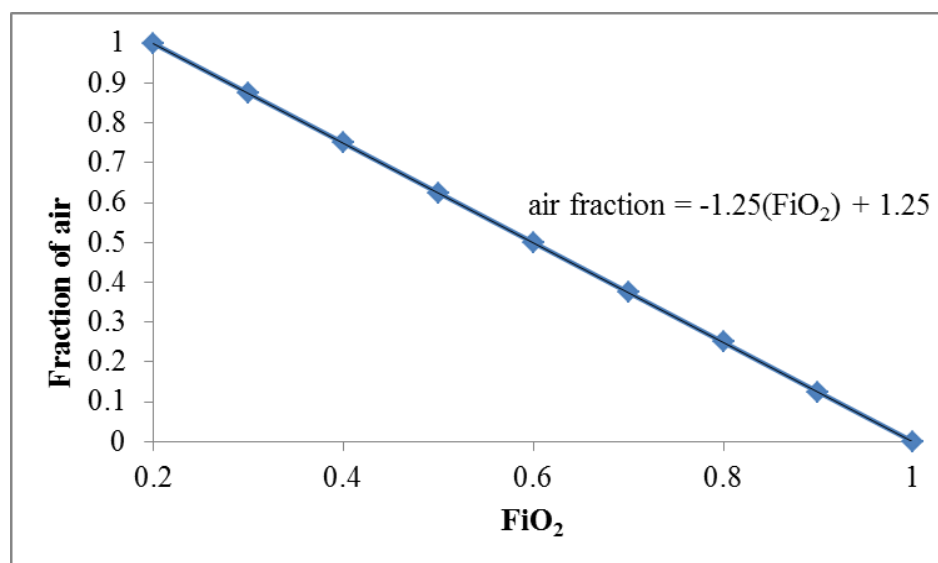
[iv] Thanks to Andrew Ferreirinha and Jo Goldman for their input.

CHAPTER 5

INTRAVENOUS INDUCTION AGENTS

Key points:
- Induction agents need to be known in detail
- Definition
- Classification
- Ideal agent
- All side effects
- Injudicious use can kill a patient – beware of hypovolaemic, shocked, elderly patients
- Ketamine and Propofol can be used for induction and maintenance

Definition

These drugs are given to induce a state of unconsciousness rapidly.

Use of intravenous anaesthetic drugs:
1. Induction of anaesthesia
2. Sole agent in short procedures
3. For sedation, e.g. to supplement regional anaesthesia

The ideal induction agent
- Safe
- Has minimal cardiovascular and respiratory effects. Most of these drugs, except, perhaps ketamine, cause a dose-dependent and potentially disastrous depression of both the cardiovascular and respiratory centres.
- Has rapid redistribution and metabolism without active metabolites
- Has analgesic properties
- Does not cause allergic reactions, pain on injection, involuntary muscle movements, or nausea and/or vomiting
- Is pleasant for the patient due to the rapid initiation of anaesthesia and the exclusion of an excitatory phase
- Easy to use and inexpensive

Common pharmacodynamic and -kinetic properties and considerations regarding intravenous induction agents
- They are *lipophilic agents* with a large volume of distribution.
- They cause loss of consciousness (induction of anaesthesia) by *equilibration between the blood and the richly perfused organs*, namely the lungs, heart, and brain (effect site). This process is indicated by the $t_{1/2}\alpha$.
- *Wakening follows distribution* from the brain and central compartment to less richly perfused tissue (muscle), followed by distribution to poorly perfused tissue (fat). During this phase metabolism and excretion contributes to the decline in blood levels. This process is indicated by the $t_{1/2}\beta$. Thereafter, the drug is released from all tissue, metabolised, and excreted. This process is indicated by the terminal $t_{1/2}$ or $t_{1/2}\gamma$.
- The small amounts of drug released from the muscle and fat are responsible for the *residual sedation (hang-over) following recovery from anaesthesia*. Therefore, patients who have received induction agents *must not drive a motor car or embark on activities requiring vigilance for at least 24 hours.*
- If the induction dose is followed by an infusion of the drug to maintain anaesthesia, muscle and fat stores act as reservoirs of the drug. Therefore, *patients awake much slower after infusions of induction agents than after a single induction dose* (see TIVA and TCI below).
- All induction agents (except ketamine) cause *dose-dependent cardiovascular depression*; that means myocardial suppression and vasodilatation. In this regard, *etomidate is the safest* drug. The cardiovascular effects of induction agents are attenuated by pre-induction administration of an opioid, followed by a much lower dose of the induction agents (this is called co-induction – see below).

- All induction agents (to a lesser extent ketamine), often cause *hypoventilation or apnoea and loss of airway and thoracic muscle tone*. <u>**Therefore, it is dangerous to administer these drugs if you foresee difficulty in maintaining an open upper and lower airway, and ventilation**</u>.
- *The cerebral, cardiovascular, and ventilatory effects are determined by* the:
  o Dose and rate of administration,
  o Central volume of distribution (blood volume),
  o Free (active) fraction of the drug,
  o Cardiovascular reserve,
  o Presence of other cerebral and cardiovascular depressants,
  o Ability of the stress response to compensate for a decrease in cardiovascular function.
- Therefore, the dose required to attain loss of consciousness and to cause a decrease in cardiovascular function (hypotension due to myocardial suppression and/or vasodilatation) is decreased in the following situations:
  o A decrease in *blood volume* decreases the central volume of distribution into which the dose is administered (increased concentration in the plasma), e.g. old age (the percentage of body water decreases with increasing age) and hypovolaemia.
  o *Hypoproteinaemia and anaemia* (larger free fraction)
  o *Low myocardial reserve* (cardiac suppression from any cause, e.g. ischaemia, any negative inotrope, extremes of age, etc.)
  o *Vasodilatation* (aggravated by vasodilatory effects of induction agents, antihypertensive agents, e.g. ACE inhibitors and angiotensin receptor blockers).
  o Inability of the *autonomic nervous system* to compensate for a decrease in blood pressure (cardiac output × peripheral resistance), e.g. extremes of age, ACE inhibitors, other induction agents (except ketamine) and opioids (central sympatholysis), autonomic neuropathy (diabetes mellitus), etc.
  o The *presence of other anaesthetic agents* with similar cerebral and cardiovascular effects, e.g. the co-administration of GABA agonists (all the anaesthetic vapours and induction agents, except ketamine) and opioids. Therefore, the cardiac (suppression, bradycardia), vascular (vasodilatation, hypotension), and respiratory (loss of muscle tone and loss of ventilatory drive) are strengthened. These effects must be taken into account to avoid severe cardiovascular and ventilatory suppression. *These additive or synergistic effects* (see below) are often harnessed; when much *smaller doses* of different agents are *co-administered* avoid the side-effects of large doses of a single agent are avoided. When different agents are used to accomplish loss of consciousness, it is called *co-induction*, e.g. a small dose of midazolam followed by a low dose of propofol, or an opioid followed by propofol or midazolam. In anaesthetic practice, *co-induction is the rule rather than the exception*.
  o *What about the dose of induction agents in obese patients*?
  Although these patients have an increased total blood volume, the blood volume per body mass is relatively lower than expected. On the other hand, the volume of distribution of lipophilic drugs is increased. However, perfusion of fat is less than muscle. The induction dose is usually based on the *obese dose-determining mass (ODDM)*, not ideal body mass. Remember, in obese patients, lean body mass > ideal body mass (see Chapter 18).
  o In general, a patient that suffers from <u>***ANY***</u> *disease that decreases exercise tolerance or the ability to compensate for a decrease in cardiovascular function*, are very sensitive to the cardiovascular effects of induction agents. These diseases include endocrine hypofunction, anaemia, hypovolaemia, cardiac failure, extremes of age, autonomic neuropathies, electrolyte disturbances, etc., etc.

In our hospital, phenylephrine and adrenaline solutions *are prepared routinely to manage cardiovascular collapse following induction of anaesthesia*. Ephedrine is also used:
- The vasotrope (α1 agonist) phenylephrine 10 mg in 200 ml saline (50 µg ml^{-1}) and
- The vasotrope-inotrope (direct α + β agonist) *adrenaline* 1 mg in 200 ml saline (5 µg ml^{-1})
- The vasotrope-inotrope (indirect α + β agonist) *ephedrine* 50 mg in 10 ml water (5 mg ml^{-1})
The dose of phenylephrine is about 1 µg kg^{-1}. If hypotension is *accompanied by a slow heart rate*, say

< 60 min^{-1}, *adrenaline* is given at a dose of about 200 ng kg^{-1} or *ephedrine* 0.1 mg kg^{-1}. (Please note that the increase blood pressure following phenylephrine administration gives a false sense of improvement since the pure vasoconstrictive effect is accompanied by a *decreased (not an increased) cardiac output*. Therefore, indirect α + β agonist such as ephedrine, adrenaline and noradrenaline are better choices.)

Example:

In an adult with a lean body mass of 70 kg,

The *phenylephrine dose* will be 70 kg × 1 µg kg^{-1} = 70 µg = about 1.5 ml of the 50 µg ml^{-1} solution, or

The *adrenaline dose* will be 70 kg × 200 ng kg^{-1} = 14 000 ng = 14 µg = about 3 ml of the 5 µg ml^{-1} solution, or

The *ephedrine dose* will be 70 kg × 0.1 mg kg^{-1} = 7 mg = about 1.5 ml of a 5 mg ml^{-1} solution.

Prolonged infusions of all induction agent into peripheral veins cause irritation of the vein and may be followed by *thrombophlebitis*.

Induction agents are divided into two groups:
- *Barbiturates*
  - Sodium thiopentone
- *Non-barbiturates*
  - Propofol
  - Etomidate
  - Benzodiazepines
  - Ketamine
  - Opioids (see Chapter 7)

The pharmacokinetic properties of commonly used induction agents are summarised in Table 1.

Table 1 Doses and pharmacokinetic properties of induction agents. You must know the induction doses and PPB; the other information is for is given for the sake of completeness only.

Drug	Dose (mg kg^{-1})*	PPB (%)	T$_{1/2}$α (min)	T$_{1/2}$β (min)	T$_{1/2}$γ (h)	Waking after induction (min)
Thiopentone	**4 - 6**	85	5 (2 -7)	50 (42 -59)	8 (5 - 12)	10 (5 - 15)
Propofol	**2 – 2.5**	98	2.5 (1 - 4)	37 (5 - 69)	32 (1.6 - 63)	5 (3 - 7)
Etomidate	**0.2 – 0.3**	76	2 (1 - 3)	20 (12 - 29)	4.2 (2.9 - 5.5)	4 (3 - 5)
Ketamine	**2**	27	2 (1 - 3)	13 (8 - 18)	1.6 (2.2 - 3.0)	10 (5 - 15)
Midazolam	**0.2 – 0.3**	98	10 (5 - 15)	28 (25 - 30)	23 (1.5 - 3.0)	15 (10 - 20)

PPB Plasma protein binding

* Doses are for intravenous induction of anaesthesia; doses are for healthy subjects who have not received any other sedative or opioids before induction.

Barbiturates: Sodium thiopentone (STP)

Physico-chemical properties
- STP is an ultra-short acting thiobarbiturate. It is a sulphur analogue of pentobarbitone.
- The injection is unstable in water and therefore marketed as 500 mg of powder, which is mixed with 20 ml of water. After reconstitution, it contains 25 mg ml^{-1}. Although soluble in water it is not very stable in solution, it can be safely used up to 24 hours after reconstitution, if the solution remains clear.
- To improve *solubility* of this acid substance, the injection contains 6% sodium carbonate. Therefore, the pH of the *injection is very alkaline*, i.e. 10.5.
- Remember, STP injection is *incompatible with pancuronium and vecuronium* injections; they form a white precipitate.

Pharmacokinetics (see also Table 1)
- Thiopentone is rapidly *distributed* to all well-perfused organs. Thereafter *redistribution* occurs to other tissues (muscle and fat).
- Due to its very high lipid-solubility, the blood-brain concentration reaches equilibrium within 1

minute.
- The *short duration* of action is mainly due to *redistribution*.
- This binding is decreased in acidotic patients. This is important because the *unbound fraction is the active component*. Therefore, myocardial depression, for example, will be aggravated in these patients.
- Metabolism of STP occurs in the liver.
- A small amount is excreted unchanged by the kidney.

Pharmacodynamics (see also general considerations)
- *Central Nervous System*
  - o Induction occurs in one arm-brain circulation time. In a young person with a normal cardiac output, this is 10 s to 20 s and in a person with a lower cardiac output, e.g. the elderly, 45 s to 60 s.
  - o STP causes sedation, hypnosis and has anticonvulsant effects.
  - o It has beneficial effects in patients intracranial pathology since it *decreases cerebral oxygen consumption* ($CMRO_2$). This provides brain protection in focal ischaemia (not global ischaemia). The decrease $CMRO_2$ causes cerebral vasoconstriction, which decreases intracranial pressure.
- *Cardiovascular system*
  - o A decrease in the cardiac output occurs due to peripheral *vasodilatation* and a depression of the *myocardial contractility*.
  - o *Hypotension* transiently occurs and depends on the dose and rate of administration.
  - o Cardiovascular suppression is not important in healthy patients but may be *life-threatening in a patient who has a fixed cardiac output*, e.g. constrictive pericarditis, tight mitral or aortic valve stenoses, a complete heart block, hypovolaemia, etc. This drug should be used circumspectly in people with *ischaemic heart disease* as a decrease in coronary circulation may occur (due to hypotension).
- *Respiratory system*
  - o Respiratory depression is dependent on the dose, rate of administration and the presence of other central nervous system depressants
  - o The sensitivity of the respiratory centre to CO_2 is decreased
  - o Respiratory depression is self-limiting
- *Airway*
  Thiopentone may sensitise the larynx and bronchi to reflex activity. During light levels of anaesthesia or incomplete muscle relaxation, stimuli such as mucous, blood, laryngoscopy, or intubation may cause laryngospasm (see Chapter 3) and bronchospasm (see Chapter 13).
- *Eyes*
  - o Initially mydriasis, followed by miosis
  - o Decreases intra-ocular pressure
- *Uterus*
  - o It has no effect on uterine tone.
  - o It crosses the placental barrier shortly after intravenous induction and may cause sedation of the neonate.

Indications for STP (for doses, see also Table 1)
- Induction of general anaesthesia (4 mg kg^{-1} to 6 mg kg^{-1} in healthy young patients)
- Control of convulsions (eclampsia and epilepsy) 6 mg kg^{-1} h^{-1}
- Electro-convulsive therapy 4 mg kg^{-1} to 6 mg kg^{-1}
- Sustained infusions in head injured patients with raised intra-cranial pressure and are being ventilated in an intensive care unit. The dose is < 40 mg kg^{-1} day^{-1}.

Advantages of STP
- Pleasant, reliable, and rapid induction
- No delirious phase
- Rapid recovery

Side effects of STP
- *Local side effects of sodium thiopentone*
  - *Extravenous injection is complicated* by ulceration and damage to the surrounding tissues in the antecubital fossa e.g. median nerve and thrombophlebitis**.** This is treated by infiltration of area with 1% lignocaine to dilute the thiopentone and anaesthetize the area.
  - *Intra-arterial injection causes immediate ischaemia in the limb distal to the point of injection.* Thiopentone injection is a strong irritant alkali, which precipitates when mixed with arterial blood. These crystals cause the local release of noradrenalin, which in turn contributes to microvasculature obstruction. The full extent of the injury is only evident after 15 days of the initial insult. The clinical picture consists of *immediate* whitening of and intense burning pain in the limb distal to the point of injection, e.g. the hand. This is followed by discolouration of the skin. Induction of anaesthesia is delayed. *Late signs* are oedema, blisters, ulceration, gangrene, and loss of a limb.
  - *Treatment of an intra-arterial injection of STP***:**
  - PREVENTION IS BETTER THAN CURE!!! Always ensure that you are injecting any drug into a free-flowing drip. To determine if your drip is free flowing always connect an administration set to the cannula in the vein. *Prevention of arterial thrombosis* is attempted with the administration of intravenous heparin 100 IU kg^{-1}. Promote *vasodilatation* by sympatholysis (brachial plexus blockade or stellate ganglion block), or intra-arterial papaverine (40 mg to 80mg in 10 ml to 20ml of NaCl 0.9% in an adult).

- *Systemic side effects of STP*
  - *Respiratory*: Apnoea, obstruction of airway by tongue, laryngospasm, bronchospasm, hiccoughs (if you inject it too rapidly), and cough
  - *Cardiovascular*: Circulatory collapse may occur due to vasodilatation and depression of myocardial contractility

Absolute contraindications to the administration of STP
- Circulatory *shock*
- *Fixed cardiac output* e.g. mitral or aortic stenosis and constrictive pericarditis. However, caution must be used in all patients with cardiac disease e.g. angina, cardiac failure etc. Hypotension can decrease coronary perfusion.
- Inability to manage the *airway* and airway obstruction e.g. Ludwig angina
- *Porphyria variegata*

Relative contraindications to the administration of STP (use smaller doses)
- See common properties of induction agents above.
- Status asthmaticus
- Severe liver disease
- *Dystrophia myotonica* patients remain apnoeic for several hours after an induction dose of STP.
- Endocrine disease, including hypothyroidism and Addison's disease. The thiourea group of STP decreases the iodine uptake by the thyroid for up to 7 days.

NON-BARBITURATES

Propofol (Diprivan)
Physico-chemical characteristics:
- Propofol is an alkyl phenol (2,6 diisopropyl phenol)
- Its water-solubility is very low. Therefore, it is dissolved in a white emulsion similar to Intralipid, consisting of 10% soybean oil, 2.2% glycerol, and 1.2% egg phosphatide. It is marketed as a 1% (10 mg ml^{-1}) and 2% (20 mg ml^{-1}) solution.
- Although some preparations of propofol may contain EDTA (a preservative) this product, *__like all injections__*, should never be left open or the same syringe used in more than one patient. Once drawn up, the needle should be capped and the contents used within 6 hours.

Pharmacokinetics (see also table 1)
- Propofol has a large volume of distribution (females > males).
- Propofol is rapidly conjugated in the liver to form inactive glucuronides and sulphates.
- The clearance of propofol exceeds hepatic blood flow, suggesting extra hepatic clearance (probably in the lungs).
- The kidneys excrete 1% and faeces 2%
- Renal disease does not influence the kinetics of propofol.

Pharmacodynamics (see also general considerations)
Central nervous system
- Propofol is primarily a hypnotic. Hypnosis occurs in one arm-brain circulation time. Lower doses can cause induction but the onset is delayed. Rapid administration is more potent than the same dose over 60 seconds (can you figure out why?).
- Propofol is used for *sedation, induction of anaesthesia, as well as for maintenance* of anaesthesia (see TIVA and TCI below). The onset of action is slightly slower than with thiopentone. The induction dose in healthy unpremedicated patients is 2.0 mg kg^{-1} to 2.5 mg kg^{-1}; in premedicated patients, 1.5 mg kg^{-1} to 2.5 mgkg^{-1}; and in patients older than 60 years, 1.0 mg kg^{-1} to 1.75 mg kg^{-1}. Since propofol is cleared rapidly, it is the ideal drug for *total intravenous anaesthesia*.
- Subhypnotic doses provide sedation and amnesia, as well as a feeling of general well-being.
- Intracranial pressure is reduced by about 30%.
- Propofol decreases systemic blood pressure. Therefore, cerebral perfusion pressure may be reduced by about 10%. Consequently, propofol must be administered carefully in the presence of raised intracranial pressure.
- It lowers the CMRO$_2$ by about 36%.
- It lowers intra-ocular pressure by about 35%.
- Hallucinations and opisthotonus have been reported.

Cardiovascular system
- The most prominent effect of propofol is a *decrease in systolic, mean, and diastolic blood pressure* of about 30% after induction. The cause of this drop of blood pressure is primarily due to a decrease in *systemic vascular resistance* (decreases pre- and afterload), but also some myocardial suppression. Continuous infusion with propofol maintains the systolic blood pressure 20% to 30% below pre-induction values.
- *Heart rate* does not change significantly after induction with propofol, but a decrease in heart rate occurs when administered with and opioid.
- Propofol decreases *myocardial oxygen consumption and lowers myocardial blood flow* (due to a decrease in blood pressure).

Ventilatory effects of propofol
- *Apnoea* occurs in about 30% of patients. It lasts about 30 seconds. This is dose dependent, as well as dependent on the rate of injection and also on the type of premedication that the patient may have received. The incidence of prolonged apnoea is greater than that seen with other induction agents.
- Respiratory rate is significantly decreased for at least 2 minutes.
- Minute volume is decreased for as long as 4 minutes.

Advantages and uses of propofol
- Induction and recovery after propofol anaesthesia is rapid and pleasant.
- The rapid clearance of the drug makes it the induction agent of choice in *outpatient anaesthesia*.
- Since propofol is a *potent suppressant of airway reflexes*, it allows fairly good *intubating conditions* when a muscle relaxant is not used, as well as for *placement of a laryngeal mask*
- *Safe in malignant hyperthermia and porphyria.*

- No influence on the synthesis of corticosteroids, hepatic, haematological or fibrinolytic functions
- Propofol can be used in young *patients older than 3 years* – if steps are taken to prevent pain on injection.
- For total intravenous anaesthesia, propofol is not only used to induce anaesthesia, but also to maintain anaesthesia using an infusion (see TIVA and TCI below).

Other *non-hypnotic uses* of propofol:
- Anti-emesis
- Anti-pruritic

Side-effects of propofol
- Propofol causes *pain in the vein into which it is injected*. This can be decreased by preceding the propofol with an fast acting opioid such as alfentanil, injecting the propofol into a fast-flowing infusion into a large vein, or by the addition of 1 ml 2% lignocaine, or 1 ml ketamine 50 mg ml^{-1} to 20 ml of propofol injection.
- Apnoea
- *Hypotension and bradycardia* occur commonly, especially when co-administered with opioids.
- *Propofol can cause erotic hallucinations*. This should be kept in mind in patients how are receiving propofol sedation or how have received propofol. This effect can last for several hours after discontinuation of the drug, and may have legal consequences.
- *The propofol infusion syndrome* follows infusion of propofol as sedative in intensive care and was first reported in children, but has also been observed in adults. The syndrome has been observed mostly in patients who had received > 4 mg kg^{-1} h^{-1} for about 48 hours, but has also been reported a child after an infusion of only 6 hours. Patients die from cardiac, renal, and liver failure. The cardiac failure was accompanied by a bradycardia, associated with a lactic acidosis, myoglobinaemia and -uria, lipaemic plasma renal failure and fatty liver.

The *pathogenesis* probably involves *inhibition of a muscle mitochondrial cytochrome oxidase, which inhibits the respiratory chain.* This explains the rhabdomyolysis, myoglobinaemia, cardiac failure, lactic acidosis, and renal and liver failure. The only successful treatment is supportive, including haemodialysis. Propofol should therefore not be used over prolonged periods, and doses of infusions should be kept to a minimum.

Etomidate
Physico-chemical characteristics
Etomidate is a carboxylated imidazole derivative. It is dissolved in propylene glycol and marketed as a 10 ml ampoule containing 20 mg, i.e. 2 mg ml^{-1}.

Pharmacokinetics of etomidate (also see Table 1)
- The clearance of etomidate is very rapid
- Increasing age is associated with a smaller volume of distribution and a decrease in the clearance.
- It is metabolized by the liver. The main metabolite is inactive. Cirrhosis doubles the $t_{1/2}$.
- The metabolized fraction is excreted by the kidney (85%) and in the bile (13%).
- Only 2% of the substance is excreted unchanged.

Pharmacodynamics (see also general considerations)
Central nervous system
- It induces anaesthesia within 1 arm-brain circulation time.
- It lowers the CMRO$_2$ with about 45%, cerebral blood flow with about 34% and intracranial pressure with about 30%.
- Since blood pressure is usually preserved, cerebral perfusion pressure is well maintained.
- The *EEG following induction* with etomidate induction resembles that of *grand mal epilepsy*.
- Induction of anaesthesia with etomidate is often followed by *myoclonic movements*.

Respiratory system
- After induction, a brief period of hyperventilation followed by apnoea is often observed.
- There is a high incidence of *coughing and hiccoughing.*
- The ventilatory *response to a raised CO$_2$* is diminished.
- This drug does not release histamine and is safe to be used in asthmatics.

Cardiovascular system
- One big advantage of etomidate is *the minimal depression of the cardiovascular system*. With an induction dose of 0.3mgkg^{-1} in patients for non-cardiac surgery, the *blood pressure and heart rate changes with <10%.*
- Therefore, the myocardial oxygen supply/demand ratio is well maintained.

Endocrine effects
A big disadvantage of etomidate is that it *inhibits the synthesis of cortisol and aldosterone for up to 8 hours following induction of anaesthesia.* Sedation with etomidate infusion has been associated with increased mortality in the intensive care unit. When etomidate is used solely as an induction agent, the reduction in cortisol production is probably of no clinical importance. Morbidity and mortality has only been reported in compromised patients who received *prolonged infusions* lasting hours or days. This side-effect has lead to the withdrawal or this drug form the market in several countries.

Other side effects
- Pain on injection
- Myoclonic movements
- It causes postoperative *nausea and vomiting* in 30% to 40% of patients.

Uses (for dose, see Table 1)
Since etomidate is *cardiovascularly a clean drug*, some anaesthetists prefer to use the drug in cardiovascular compromised patients. The effect on steroid synthesis must however by kept in mind. In this regard, it is probably not wrong to administer cortisol postoperatively to overcome this side-effect. The prevalence of cortisol deficiency in critically ill patients is high, which may contraindicate the use of etomidate in this population of patients.

Benzodiazepines
Physico-chemical characteristics
Two benzodiazepines are commonly used, namely diazepam and midazolam
Diazepam
- 5mgml^{-1} in a 2ml ampoule.
- Since this drug is poorly soluble in water, it is dissolved in 40% propylene glycol
- Intramuscular injections are painful and poorly absorbed

Midazolam
- Midazolam is water-soluble but cyclisizes at a pH > 4 to form an imidazole ring after injection. This compound is a highly lipophilic, potent substance.
- It is marketed as 5 mg in 5 ml and 15 mg in 3 ml ampoules.
- Intramuscular and intravenous injection is usually not painful.
- Midazolam is the most lipid-soluble and also the most potent benzodiazepine available.

Pharmacokinetics of benzodiazepines (also see Table 1)
- Midazolam is metabolised in the liver by microsomal oxidation or glucuronide conjugation
- Benzodiazepine metabolism is influenced by the following: genetic difference, liver disease, inhibition of oxidative enzyme function (cimetidine, erythromycin), enzyme induction (ethanol, smoking increases clearance), age, hepatic and renal disease.
- Diazepam has a T$_{1/2}$ of about 30 hours, but it has *two long-acting active metabolites,*

desmethyldiazepam ($T_{1/2}$ about 3 days) and oxazepam ($T_{1/2}$ = about 10 hours).

- Midazolam undergoes rapid oxidation of the imidazole ring. It has a high clearance and no active metabolites.

Pharmacodynamics
Central nervous system
- Sedation, hypnosis, anxiolysis, amnesia, central muscle relaxation (via spinal GABA receptors) depending on the dose (receptor occupancy) (Table 2). Although induction with midazolam is lower than with STP, amnesia is more reliable. Anterograde amnesia occurs after an induction dose and lasts for up to 2 hours.
- Increased threshold for convulsions after local anaesthetics administration
- Lowers the $CMRO_2$ and the cerebral blood flow
- Less is less brain protective than STP

Table 2 Dose-dependent effects of benzodiazepines

Effect	Receptor occupancy
Hypnosis	60%
Sedation	30% to 50%
Anxiolysis	20%
Amnesia	
Anticonvulsive	
Central muscle relaxation	

Cardiovascular system
- As sole agents, benzodiazepines do not cause major changes in cardiovascular parameters.
- The most consistent haemodynamic change is a slight dose-dependent decrease in arterial blood pressure due to a decrease in systemic vascular resistance. This occurs to a greater extent with midazolam.
- Benzodiazepines do not attenuate the intubation response or any other stress response.
- In combination with any opiate, especially the short acting ones such as fentanyl, sufentanil and alfentanil, the decrease in blood pressure is more pronounced.

Respiratory system
- *Dose-dependent respiratory depression.* This is exaggerated in patients with COAD since these patients rely on peripheral hypoxic drive of ventilation in the carotid body and aortic arch. A dose of midazolam 0.2mgkg^{-1}, has a peak onset of respiratory depression after 3 minutes, which is sustained for approximately 15 minutes.
- There is a synergistic action on the respiratory system if an opiate (central sensitivity to an increase in $PaCO_2$, which decreases cerebrospinal fluid pH) is added to the benzodiazepine.
- Smaller doses of benzodiazepines cause respiratory depression in aged patients.

Uses (also see Tables 1 and 2)
- The benzodiazepine of choice is midazolam as it has the shortest onset of action, less venous complications and the highest clearance.
- *Anxiolysis* in the form of preoperative medication. The dose of midazolam is 0.1 mg kg^{-1} to 0.2 mg kg^{-1} (7.5 mg and 15 mg tablets), of oxazepam about 0.2 mg kg^{-1} (10 mg, 15 mg, and 30 mg tablets), and of temazepam 0.2 mg kg^{-1} (10 mg and 20 mg capsules).
- *Sedation.* The depth of sedation must be monitored. Sedation must allow constant communication with the patient (conscious sedation). Monitoring of ventilation is essential, including pulse oximetry. Intravenous sedation with midazolam can be done with 0.02 mg kg^{-1} to 0.05 mg kg^{-1} and the same dose per hour for prolonged sedation.
- *Induction and maintenance* of anaesthesia. The intravenous dosage is 0.2 mg kg^{-1} followed by an infusion of 0.2 mg kg^{-1} h^{-1}. Midazolam is not analgesic and concomitant use of a short-acting opioid may be necessary. ***Beware of the synergistic effects of these drugs on consciousness,***

blood pressure, and ventilation.
- Benzodiazepines *increase the threshold for convulsions* of local anaesthetics. Remember, since a central nervous system effect (convulsion) of an overdose of local anaesthetic may be masked by a benzodiazepine, the first sign of toxicity may be cardiovascular compromise (bradycardia, asystole, and hypotension).

Side-effects
- The most significant problem with midazolam (all benzodiazepines) is interindividual variation i.e. the dose to reach a particular endpoint is extremely variable.
- Prolonged post-operative amnesia, sedation, and respiratory depression especially if combined with an opiate.
- Synergism occurs with induction agents, opioids, and sedatives in combination with benzodiazepines to give severe respiratory depression and drop in arterial blood pressure.

Flumazenil (Anexate) is a specific benzodiazepine receptor antagonist. The disadvantage of this drug is that it has a relatively short half-life (60 minutes) compared to the agonists. Therefore, resedation and ventilatory suppression may occur. It can precipitate withdrawal in patients addicted to benzodiazepines. It should only be used as a diagnostic agent to exclude a benzodiazepine as a cause of sleep/coma. The dose is about 3 μg kg^{-1} intravenously over 1 min, followed by 1.5 μg kg^{-1}. The usual total dose is 4 μg kg^{-1} to 8 μg kg^{-1}. If the patient does not wake up from this dose, the diagnosis of benzodiazepine-induced sleep should be reconsidered.

Ketamine
Physico-chemical properties
- Derivative of phencyclidine. LSD is also a phencyclidine derivative.
- Its lipid solubility is 5 times to 10 times that of STP.
- It is marketed in various strengths, i.e. 10 mg ml^{-1}, 50 mg ml^{-1}, and 100 mg ml^{-1}.

Pharmacokinetics (see also table 1)
- Changes in liver blood flow affect clearance.
- Hepatic microsomal enzyme metabolism by N-demethylation forms norketamine, which has about 25% of the activity of ketamine. Norketamine is hydroxylated to hydroxyl-norketamine which is excreted by the kidney.

Pharmacodynamics (see also general considerations)
- *Central nervous system*
  - *Site of action*
    Ketamine acts as a non-competitive antagonist of the excitatory ligand glutamate on the *NMDA receptor*. This suppresses neuronal function subcortical, including the thalamus, but stimulates parts of the limbic system, including the hippocampus. Ketamine causes inhibition (*dissociation*) of the thalamo-neocortical projection system. It may induce a *cataleptic state* (wax-like stiffness of the limbs and trunk and insensitivity to stimuli), but this is not often observed.
  - Induction with intravenous ketamine is slower than with thiopentone. The onset of action is within 30 s with maximal effect within 1 minute. The onset of action is characterised by *nystagmus, mydriasis, and increased lacrimation*.
  - Complete analgesia occurs even with light sleep i.e. dissociative anaesthesia.
  - Ketamine causes *amnesia*.
  - The *protective reflexes* (corneal, most importantly cough and swallowing reflexes) are retained to an extent, but *not guaranteed*.
  - Skeletal muscle tone may increase and *movements* of the head, limbs, and torso may occur.
  - Unwanted *psychological phenomena* often occur on emergence. These include hallucinations, "floating out of the body" and dreams. Benzodiazepines, possibly due to sedative or amnesic characteristics can lower the incidence and severity of these post-operative reactions. There is a low incidence of these unwanted reactions in paediatric patients

- o Petite mal-like activity is observed on the *EEG*
- o Ketamine is not the ideal drug for use in neurosurgical cases as it has a number of unwanted side effects, namely increased regional $CMRO_2$, blood flow, and intracranial pressure, especially in spontaneously breathing patients (All sedatives depress ventilation and may increase intracranial pressure in spontaneously breathing patients)

- *Respiratory system*
  - o Ketamine has minimal dangerous respiratory effects. It suppresses ventilation (response to CO_2) less than other induction agents. Apnoea only occurs at very high doses.
  - o It is a very good bronchodilator (sympathomimetic effect)
  - o Reflexes such as the cough, swallowing etc. are relatively well maintained. However, ketamine does not guarantee a patent airway and does not necessarily prevent pulmonary aspiration after loss of consciousness. Beware of airway obstruction in children.
  - o Increased upper and lower airway secretions. This can be prevented with anticholinergic agents such as atropine and glycopyrrolate.

- *Cardiovascular system*
  - o Stimulation of the cardiovascular system occurs. Ketamine releases noradrenalin centrally and inhibits neuronal uptake of catecholamines.
  - o The increased noradrenalin causes hypertension, tachycardia and an increased cardiac output.
  - o Ketamine has direct negative inotropic effects *in vitro*.

Indications
- *Induction of anaesthesia in high* risk patients, especially those with a cardiac tamponade or constrictive pericarditis.
- Induction and maintenance of anaesthesia or sedation when inhalants are contraindicated, e.g. *malignant hyperthermia* (see Chapter 11)
- Emergency conditions at *accident scenes*
- *Multiple anaesthetics* for changing bandages, radiotherapy, bone marrow punctures
- *Analgesia*
- *Asthma*
- Children with *cyanotic congenital heart disease*
- Paediatric cardiac catheterization
- Before performing a painful local anaesthetic block

Dose and route of administration of ketamine
- Intravenous induction of anaesthesia: 1 mg kg^{-1} to 2 mg kg^{-1}
- Intramuscular and subcutaneously induction of anaesthesia: 5 mg kg^{-1} to 10 mg kg^{-1}
- Sedation: Oral 5 mg kg^{-1} to 10 mg kg^{-1}
- Analgesia: 0.1 mg kg^{-1} to 0.2 mg kg^{-1} every hour.
- Total intravenous anaesthesia: 2 mg kg^{-1} followed by 2 mg $kg^{-1}h^{-1}$ to 3 mg $kg^{-1}h^{-1}$

Side effects and contra-indications
- In *critically ill patients* who have depleted catecholamine stores, the negative inotropic effect of ketamine causes a severe drop in blood pressure. (This has been disputed and ketamine has been used safely in these patients. All sedatives, including opioids may result in profound cardiovascular depression in critically ill patients.)
- Contra-indications
  - o Untreated hypertension
  - o In unventilated patients with increased intracranial pressure
  - o Penetrating eye injuries
  - o Aneurysms of all types

Total intravenous anaesthesia (TIVA)
TIVA does not fall in the scope of this course. Those who are interested in the topic, are referred to standard text books.

Air pollution, myocardial suppression, and vasodilatation have shifted the choice of anaesthetic technique to TIVA. A loading dose (induction dose) of and intravenous induction agent is followed by a maintenance dose to sustain blood (brain, i.e. effect site) levels to maintain a particular level of suppression of consciousness (sedation, hypnosis, or general anaesthesia). At present, no drug provides all the modalities to give a complete (balanced) anaesthetic on its own, namely hypnosis, muscle relaxation, and analgesia.

Drugs used for TIVA include propofol, ketamine, and the opioids sufentanil, fentanyl, alfentanil, and remifentanil. Very often, the additive (2 + 2 = 4) or synergistic (2 + 2 >>> 4) properties of combinations of these drugs are utilised. These lower doses of the individual drugs used in combination decrease their side effects. However, drug combinations become very potent and should be regarded as a "different drug".

A different approach to TIVA is to use pharmacokinetic models that have been developed to predict plasma and effect site concentrations that result in a particular depth of anaesthesia, i.e. *target controlled infusions (TCI)*. These TCI models (computer programs) take into account anthropometric variables that influence drug effect, including age, gender, body mass, and height.

Since these models also work with the statistical mean person (like minimum alveolar concentration of vapours, MAC50%), it is necessary to *monitor unconsciousness* with EEG-based monitors such as spectral entropy or bispectral index (BIS).

For TIVA and TCI, a drug must have a predictable effect at a particular concentration and a fast decline in plasma levels after an infusion is stopped after a particular duration of the infusion, i.e. in the context of time of infusion (*context sensitive half-life*). The only drugs that come close to these criteria and allow rapid arousal and ward-readiness are remifentanil and propofol.

CHAPTER 6

INHALATION AGENTS

Key points
- *Physics*: Saturated vapour pressure, Minimum alveolar concentration (MAC), blood/gas partition coefficient
- *Pharmacokinetics*: Uptake of anaesthetic vapour and recovery from vapour: Concepts of F_A/F_i, second gas effect, blood/gas partition coefficient (BGPC), tissue solubility, metabolic breakdown, and diffusion hypoxia
- *Individual agents*
- *General considerations*
    - o Physico-chemical parameters
    - o Mechanism of action
    - o Effect on the Cardiovascular system, central nervous system and respiratory system
- o Pharmacokinetic principles regarding breakdown and excretion
- o Toxicity
- o Myocardial preconditioning
- o Malignant hyperthermia and masseter muscle spasm
- o Carbon dioxide response curve
- *Two groups of inhalational anaesthetics*: vapours and gases
- *Inhalation induction*
- *Effect of altitude* and inhalation agents

Introduction

Students often wonder why general anaesthesia is usually started (induced) with an intravenous agent (induction agent) but then maintained with an inhalational agent. I think that this sequence of anaesthesia is fortunate (or fortuitous). Historically, modern anaesthesia started with an inhalational agent (nitrous oxide around 1850). This was followed by more inhalational agents (chloroform, ether), which were replaced with the fluorinated vapours (halothane, metoxiflurane, enflurane). The intravenous agents appeared much later. Metoxiflurane has been withdrawn due to toxicity and halothane and enflurane are dwindling – at least in the developed world.

The development of the syringe and hollow needle (around 1900) opened the way to the intravenous route with the first successful (and still in use) intravenous anaesthetic, hexobarbital and later, sodium thiopental in 1934. Several intravenous agents followed but were discontinued due to allergic reactions, e.g. althesin. However, none of the intravenous agents had the kinetic advantages of the rapid-in-rapid-out kinetics of inhalational agents, until the development of propofol and remifentanil. With these two agents, the rapid-in-rapid out principle does apply to a large extent when using target-controlled infusions (TCI). TCI uses pharmacokinetic models that take into account several biographical variables (age, gender, mass, etc). The TCI devices administer the drugs at an infusion rate that result in plasma or brain drug concentrations (according to the model) to ascertain a particular depth of anaesthesia or sedation. This method is analogue to the end-tidal concentrations (see below) read on the monitor with inhalants.

With the availability of rapid-acting and *relatively* short-acting intravenous agents and the safer vapours, the advantages of the two groups were harnessed, namely rapid induction with an intravenous agent, followed by the inhalational agent. While the intravenous agent was disappearing (patient is waking up), the concentration of the inhalant is being introduced to keep the patient asleep. While the procedure is being performed, the intravenous agent is being eliminated, while the inhalant is maintaining unconsciousness. At the end of the procedure, the inhalant is switched off, is eliminated mainly by the lungs (and to a large extent by the liver with older inhalants) and the patient regains consciousness (Figure 1)

With the availability of the rapid acting inhalants with an acceptable odour (halothane, but especially sevoflurane), induction of anaesthesia using an inhalant instead of an intravenous drug is often done. This is the routine in patients who do not tolerate insertion of an intravenous cannula (children) and when an intravenous agent is contraindicated), e.g. patients (children and adults) with a compromised airway (see Chapter 3).
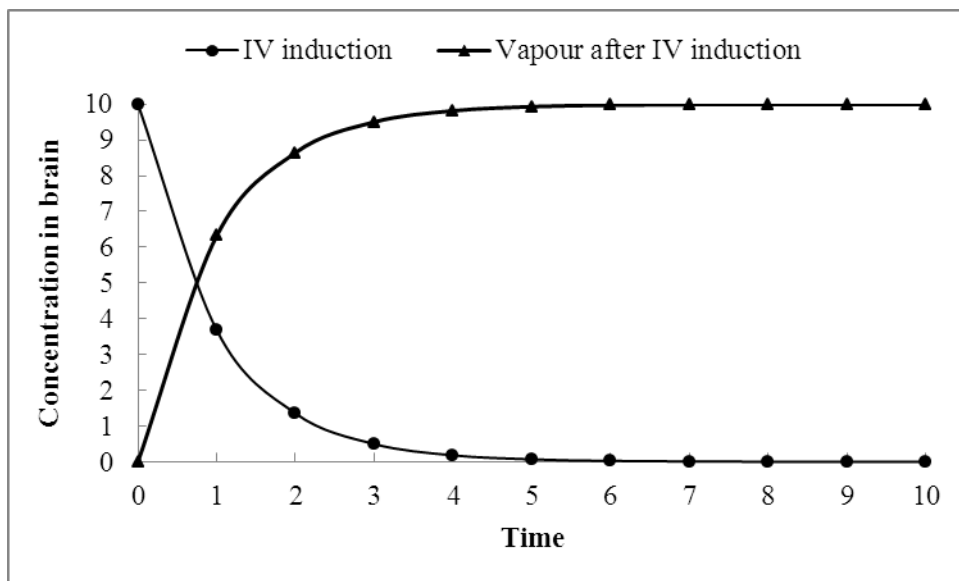
Figure 1 Concentration of induction agent and inhalant in brain over time

Definitions

- Drugs that are *inhaled* to reach the *blood stream* and then diffuse over the *blood-brain barrier* to the *brain* to exert an *action*.
- *Inhalants* are either *gases or vapours*.
- *Vapour pressure* is the partial pressure of gas particles that have escaped from a liquid by evaporation in a closed rigid container.
- When equal numbers of particles are evaporating and are condensing (return to the liquid), i.e. there exists equilibrium between evaporation and condensation, the vapour (evaporated liquid) is said to be saturated, this vapour pressure is called the *saturated vapour pressure*. Since this occurs in a closed rigid container, it is isolated from and is not influenced by ambient pressure. Therefore, the published saturated vapour pressures of liquids are *independent of ambient pressure*. However, saturated vapour pressure is *dependent on temperature*; the higher the temperature, the higher the saturated vapour pressure.
- The *boiling point of a liquid* is the temperature at which the vapour pressure of a liquid in an open container (in contact with ambient pressure) equals ambient pressure. Therefore, boiling point is dependent on ambient pressure; the lower the ambient pressure, the lower the boiling point. For example, the boiling point of water at sea level is 100°C, but about 94°C in Pretoria.
- If one would put a gas in a compressible container, and decrease the volume of the container, the partial pressure of the gas will increase. With increasing pressure, the particles will collide with each other and the walls of the container and dissipate some of their kinetic energy to the container, which becomes hotter (if you fill a syringe with air, occlude the outlet and compress the plunger, the temperature of the syringe increases). Therefore, they will have less energy and will liquefy. However, **above** a certain temperature, the molecules will have so much kinetic energy that it will become impossible to liquefy the gas, no matter how high the pressure. This is called the *critical temperature*.
- *Critical pressure* is the vapour pressure of a substance **at** its critical temperature, i.e. the pressure needed to liquefy the gas *at* its critical temperature.
- *A gas* is a substance above its critical temperature. Referring back to the air-filled syringe above: you will not be able to liquefy the air inside the syringe, no matter the pressure you apply, since the critical temperatures of oxygen and nitrogen are <<< 20°C. Therefore, medical gases are kept in high pressure metal containers at usual working temperatures of about 20°C, since their critical temperatures are << 20°C. E.g. the critical temperature of oxygen is very low, i.e. -118°C.
- When gases are mixed, the critical temperature of the gas mixture differs from those of the constituent gases. This is called the *pseudocritical temperature*. E.g., the critical temperature of nitrous oxide (N_2O) is 36.5°C and that of oxygen, -118°C. However the critical temperature of Entonox (50% N_2O:50% O_2) is -5.5°C.
- *A vapour* is a substance below its critical temperature (see Table 1). Therefore, the vapours can be kept in glass or plastic bottles from which the anaesthetic vaporizers are filled.

Uptake and distribution of the inhalants: Physical and physiological principles

The gas laws

- *Henry's law*
  The concentration of a gas in solution is directly proportional to the partial pressure of the gas above the solution: Cgas ∞ Pgas
- *Graham's law*
  The rate of diffusion of a gas is inversely proportional to the molecular weight of the gas.

- *Ostwald's solubility coefficient*
  The uptake of gas into a medium is proportional to the solubility of the gas in that medium.

Classification of inhalation agents
- *Vapours (**SHIED**)*
    o *Halogenated hydrocarbons***: H**alothane
    o *Ethers***: E**nflurane, **I**soflurane, **S**evoflurane, and **D**esflurane
- *Gases*
    o Nitrous oxide
    o Xenon

The inhaled anaesthetic vapour crosses the alveolar-capillary membrane to the blood. From here it is transported to the brain where it interacts with receptors. The change of a rousable state (awake or sedated) to the *anaesthetic state* (not rousable by painful stimuli) is called *induction* of anaesthesia.

The time it takes for a gas to have an effect on the brain depends on the rate at which the gas is *washed into* the body – particularly the brain. The concentration of vapour in the brain is directly proportional to the partial pressure of the vapour in the alveolus (PA). The sooner equilibrium is reached between the partial pressure of the gas in the alveolus (PA), in the capillary blood from the lungs (Pc), and in the brain (Pb), the quicker the induction of anaesthesia:

$$PA \leftrightharpoons Pc \leftrightharpoons Pb$$

Remember, gas molecules diffuse to the blood. Therefore, the fraction of the gas that the patient exhales from the alveoli (FA) is smaller. Therefore, at the start of induction, the FA/FI ratio is low, but as the blood stores are saturated with gas molecules, FA/FI will approach unity (FA/FI = 1).[6] You can read these ratios on the anaesthetic monitors.

The rate at which FA/FI increases is described by the following differential equation:
$dFA/dFI = -t/\tau$,
where t is the time until equilibrium is reached (FA/FI = 1), and τ is the time constant.
The time constant is the ratio of the *volume* of the reservoir into which the gas is delivered and the *rate* at which the gas is delivered to the reservoir. In the case of the lungs, the volume is the functional residual capacity (FRC) and the flow is the alveolar ventilation (VA):
$\tau = FRC/VA$.
To describe FA/FI from t = 0 to t = ∞, the above equations are solved to:
$FA/FI = 1 - e^{-t/\tau}$
Remember, e = 2.718 (≈ 2.7).
Therefore, if t = τ, FA/FI = $1 - 2.7^{-1} = 1 - 0.37 = 0.63$ or 63%.
FA/FI nears unity in about 4 × τ; then FA/FI = 96%.

Example:
How long will it take (induction time) in an adult with an FRC of 2 L and a VA of 4 L min⁻¹?[v]
$\tau = FRC/VA = 2$ L/4 L min⁻¹ = 0.5 min.
Therefore, induction will take about 0.5 min × 4 = 2 min (see Figure 2).

---

[v]Tidal volume = alveolar volume + dead space. Therefore, alveolar ventilation = (tidal volume – dead space) × ventilatory rate. Consequently, increased dead space ventilation decreases alveolar ventilation.
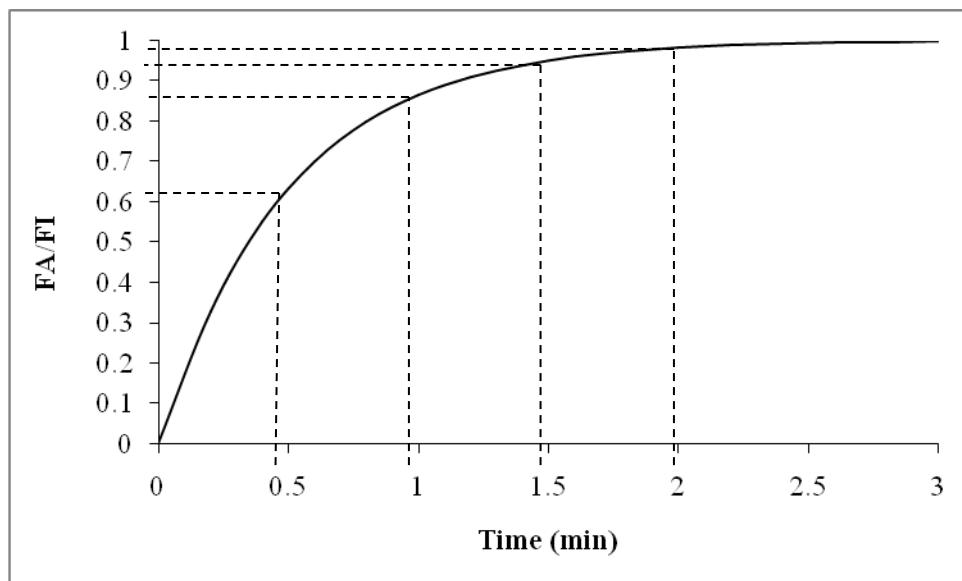
Figure 2 Uptake of anaesthetic gas
FA/FI ratio of fraction of gas in alveolar to fraction of gas in inspiratory gas

The rate at which the gas is washed into the body determines the rate at which FA/FI increases. This is determined by two opposing phenomena, namely the delivery to the lungs and removal from the lungs by the blood. *Wash-in is determined by six factors*; three that influence *delivery* to the alveoli, and four that influence *removal* from the alveoli by the blood:

- *Delivery to the alveoli (wash-in)* :
  - Alveolar ventilation (not minute ventilation).v
  - FRC
  - Inspiratory concentration of the gas (FI). See foot note[vi]
- *Removal from the alveoli by the blood*:
  - The alveolo-capillary partial pressure difference (PA – Pc)
  - Solubility of the vapour in blood (blood/gas solubility coefficient, BGPC)
  - Cardiac output
  - Metabolism of the inhalant

Delivery to the alveoli
- *Alveolar ventilation (VA)*
  If unopposed, ventilation produces a rapid change (in and out) of gases in the lungs. The higher VA, the more gas is delivered to the alveolus. Therefore, the rate of FA/FI increases (shorter τ). This explains the observation that patients with a high alveolar ventilation relative to FRC, e.g. *infants* (4:1), fall asleep more rapidly than adults (2:1) or patients that hypoventilate. Furthermore, a gas induction will be prolonged in patients with increased dead space ventilation (parts of the lung that does not take part in transfer of gas to blood due to decreased perfusion, i.e. alveolar dead space). Although *hyperventilation* may increase delivery of gas to the alveolus, it may also decrease cardiac output and $PaCO_2$, both of which decrease cerebral perfusion (see effect of cardiac output below). Therefore, hyperventilation does not affect delivery of gas to the brain significantly.

[vi]FI can be kept high (and replace the vapour that has been taken up from the alveoli), by increasing FI (setting on vaporiser) and the fresh gas flow until the required FA has been reached (the vapour is *washed in* at a high concentration and flow). Thereafter, the FI and fresh gas flow can be reduced. The same principle applies at the end of the anaesthetic; FI is reduced to zero (vaporiser is switched off) and the fresh gas flow increased to keep FA and FI low (*wash out* the vapour). See Figure 1.

- *Functional residual capacity (FRC; see Chapter 13)*
  The larger the FRC, the larger is the volume which must be filled with gas (longer τ). Therefore, wash-in is more rapid in patients with restrictive lung functions, e.g. obesity and restrictive lung diseases. However, this is only true if the disease does not decrease VA.
- *Inspiratory concentration (the overpressure technique, concentration effect and the second gas effect)*
  The higher the concentration in the fresh gas from the anaesthetic machine to the patient (inspiratory fraction, FI), the larger the differences in partial pressure between the alveolar gas (PA) and that in the capillary blood (Pc), the more rapid is the rise in the F_A/F_I ratio (the less the impact of uptake of inhalant from the alveoli) the more *rapid the induction* or the *deeper the level of anaesthesia* will be. This is called the *concentration effect, or rather the pressure effect*. This difference between pressure and concentration is stressed since it is not the "concentration" that has the anaesthetic effect, but the partial pressure (number of molecules).

Why is the distinction between concentration and pressure clinically important? Since altitude (ambient pressure) has an influence on partial pressure. Remember, the ambient pressure at sea level is 101.3 kPa (or let us say 100 kPa). Therefore, in any container not completely isolated from the environment (including the anaesthetic machine and alveoli), the total pressure in that container is 100 kPa. The sum of the partial pressure of all the gases in a gas mixture, such as air and an anaesthetic gas mixture is 100 kPa. Air consists of 20% of O_2 and 80% of N_2. Therefore, their respective *partial pressures at sea level* are 20% of 100 kPa, i.e. 20 kPa and 80% of 100 kPa, i.e. 80 kPa. However, the ambient pressure in Pretoria is about 87 kPa but air still consists of 20% of O_2 and 80% of N_2. Therefore, their respective partial pressures are 17 kPa and 70 kPa.

The same applies to anaesthetic gas mixtures. Remember, that the dose of any drug, including anaesthetic gases is determined by the number of molecules. It is not the size of the tablet that determines the effect, but the number of molecules of the active ingredient. Therefore the number of anaesthetic gas molecules to have a particular effect, is the same at sea level and at altitude – but the concentration in the gas mixture at sea level and altitude differs. For example, at sea level the partial pressure of the anaesthetic vapour isoflurane to allow skin incision in 50% of patients is 1.15 kPa, or a concentration (%) of
$(1.15 \text{ kPa}/100 \text{ kPa}) \times 100 = 1.15\%$.
In Pretoria, the dose of isoflurane for skin incision is still 1.15 kPa, but the concentration is
$(1.15 \text{ kPa}/87 \text{ kPa}) \times 87 = 1.32\%$.

This is clinically important since the gas analysers of anaesthetic machines measure the partial pressure of gases as well as ambient pressure and then gives the percentage of gas as a percentage of ambient pressure. Therefore, 1.15% of isoflurane in Pretoria is not 1.15 kPa, but 1.15% of 87 kPa, which is 1.00 kPa. However, the anaesthetic monitors do not display the anaesthetic gases in kPa but in %. *Therefore, to obtain the same effect, anaesthetists working at altitude, such as Pretoria, must know their ambient pressure.*

The higher the concentration of vapour in the fresh gas, the faster the concentration will rise in the alveoli (PA). This in turn, will increase the rate at which brain concentration will rise. The faster brain concentration rises, the faster the onset of unconsciousness will be. *This is the overpressure technique.*

N_2O is administered at high concentrations (usually between 50% and 70%). At these high concentrations, the difference between PA and Pc is so large, that diffusion is so rapid from the alveoli that the FRC shrinks. Therefore, if N_2O is administered at a concentration of say 50%, its concentration (volume of N_2O per volume of FRC) will increase, i.e. it becomes more concentrated to say 60%. If a vapour is administered with N_2O, say 1% isoflurane and 60% N_2O, the concentration effect of N_2O will not only cause a concentration effect, but will also increase the concentration of the other (second) gas. This is the *second gas effect*. This effect is often used during vapour (gas) inductions, e.g. halothane plus N_2O or *sevoflurane plus N_2O* (the latter is the most patient-friendly vapour induction). Can you understand that the concentration effect of N_2O causes the second gas effect? The concentration effect of vapours that are administered at far lower concentrations, also occurs, but is clinically insignificant.

Removal of gas from the alveoli by the alveolar capillary blood
Uptake of gas from the alveoli is dependent on the product of three factors, namely the solubility of the gas in the blood (blood/gas partition coefficient, BGPC), the difference in partial pressure of the gas in the alveoli and the alveolar capillary blood, and the cardiac output:

$$BGPC \times (PA - Pc) \times \text{Cardiac output.}$$

If any one of these factors decreases, uptake decreases and no gas is removed from the alveoli. Consequently, FA/FI will increase more rapidly (shorter τ).

- *Solubility of the gas in the blood and tissue*
  Wash-in time is inversely related to solubility. When anaesthetic gas enters the blood, it occurs in two forms; dissolved in plasma water (aqueous phase), and bound to plasma lipids and proteins (bound phase). The solubility of the gas in plasma lipids and proteins is expressed by the *BGPC*. *The BGPC is the ratio of the amount (partial pressure, not concentration) of gas dissolved in blood to that in alveolar gas at equilibrium*. The higher the BGPC, the more gas dissolves in the plasma lipid/protein. Therefore, the ratio (coefficient) of the concentrations of a gas in the lipid/protein phase relative to the aqueous phase is higher in a more soluble gas than a less soluble one, e.g. halothane vs. sevoflurane (see Table 1).

Table 1 Characteristics of inhalants

Drug	MAC* (%)	BGPC	Boiling point (°C)	Saturated vapour pressure (mm Hg) at 20°C (degree of volatility)
N_2O	105	0.47	-88.5	-
Halothane	0.77	2.43	50.2	243
Enflurane	1.68	1.9	56.5	175
Isoflurane	1.15	1.4	48.5	240
Sevoflurane	2.0	0.64	58.5	168
Desflurane	6.0	0.42	22.8	681

MAC minimum alveolar concentration (inversely proportional to potency) at sea level;
*These values are for vapours in the absence of N_2O at sea level and are numerical about equal to kPa;
BGPC Blood/gas solubility coefficient (inversely proportional to rate of induction and emergence)

The *higher the BGPC* (e.g. halothane), the more gas molecules are mopped up by the plasma lipid/proteins. Therefore, the Pc of the gas will stay low, FA will constantly decrease since Pc stays low, and FA/FI will increase slowly (long τ and induction time). A gas that is *less soluble in plasma lipid/proteins* (the blood does not accommodate a lot of gas) has a *low BGPC* (e.g. N_2O and desflurane). This allows for a quicker rise in the Pc, less gas leaves the alveoli, PA increases more rapidly, as does FA/FI.

The BGPC varies with age. It is about *20% less in neonates and the elderly* than in young adults. These differences may be attributed to differences in plasma protein and lipid concentrations. The tissue fat and protein concentrations in infants are lower than in adults. Therefore, equilibrium is reached more rapidly and induction will be faster. In the elderly, the body consists of more fat, and equilibrium will take longer, resulting in a slower induction.

The rate at which FA/FI increases is also influenced by the *solubility in the tissue* of well-perfused organs (heart, liver, kidney, endocrine organs, and brain), medium-perfused organs (muscle), fat, and low-perfusion organs (bone). The sooner these tissues are saturated with gas, the sooner the partial pressure of the gas in the tissue (Pt), Pc, FA, and FA/FI will increase.

The rate at which the tissues take up gas molecules (the time constant τ) is dependent on the rate at which the gas is transported to the tissue (tissue perfusion, Q), the volume of the tissue (V), and the solubility of the gas in the particular tissue (tissue/blood partition coefficient, TBPC). *The TBPC is the ratio of the amount of gas (partial pressure) dissolved in tissue to that in blood at equilibrium*. The larger the tissue volume and the larger the TBPC, the longer it will take for

Pt, Pc, FA, and FA/FI to rise, and therefore the longer τ:

$$\tau \text{ for a particular tissue group} = (V \times TBPC)/Q$$

From this equation it is clear that Pt (the active form of the gas) will increase more rapidly (short τ) in the brain (relatively low volume, say 2% of body mass, and perfusion of about 15% of the cardiac output) than in fat (about 20% of body mass but 6% of cardiac output). Due to their lower muscle content, *the TBPC in neonates is about 50% of that in adults.* Some of the differences in wash-in times (τ) between adults and neonates may be explained by their differences in body composition (Table 2)

Table 2 Anatomical and physiological variables affecting wash-in time (τ)

Component	Adults	Neonate	Influence of an ↑ on τ*
Water (%)	55	80	↓
Blood (%)	65	90	↑
Fat (%)	16	16	↑
Muscle (%)	43	25	↑
Brain (%)	2	13	↑
Brain perfusion (% of cardiac output)	15	40	↓
Liver (%)	2	5	↑
Kidneys (%)	0.5	1	↑
Cardiac output (ml kg^{-1} min^{-1})	75	130	↓
Alveolar ventilation (L kg^{-1} min^{-1})	65	130	↓
FRC (ml kg^{-1})	30	35	↓
Alveolar ventilation/FRC ratio	2	4	↓
BGPC (except sevoflurane**)	Higher	Lower	↑

FRC, Functional residual capacity; BGPC, Blood/gas partition coefficient
*The smaller τ, the more rapid the induction and recovery
**BGPC is the same in adults and neonates

Since V and Q for a particular organ is relatively constant in a person and between persons, the main determinant of τ is the TBPC: the lower TBPC, the sooner Pt increases, and consequently, Pc, FA, and FA/FI.

- *Alveolo-capillary blood and blood-tissue differences in partial pressure*
When the difference between two adjacent compartments is high, the movement of gas is high, and *vice versa*. Once equilibrium has been reached between the capillary blood/alveolus and tissue/blood compartments, no net diffusion of gas occurs and FA/FI approaches unity. If the differences are maintained, diffusion is maintained and FA/FI stays low. The sooner diffusion decreases, the sooner FA/FI increases (shorter wash-in time and τ). Remember, the less space for the gas in blood (smaller BGPC) and in tissue (smaller TBPG), the quicker equilibrium increases, and therefore a more steep increase in FA/FI (shorter wash-in and τ).

- *Cardiac output*
Now you must read carefully! If the pulmonary capillary blood flow is low (low cardiac output or intracardiac right-to-left shunts), the time available for gas in the alveoli to be taken up by the blood (bound to lipid/protein and dissolved in water), increases. Therefore, the blood stores become saturated more rapidly followed by a rapid increase in the partial pressure of the gas in capillary blood (Pc). As Pc increases, less gas will diffuse over the alveolo-capillary membrane, and FA/FI will also increase sooner (low τ). The same applies to the movement of gas between blood and tissue.

However, does it matter? If a gas has a high BGPC and TBPC, the capacity of blood and tissue to take up the gas is large and uptake is more dependent on partial pressure difference. However, if the BGPC and TBPC are low, saturation occurs quickly and blood flow has little effect; whether the blood flow through the pulmonary capillaries is high or low, the blood is saturated rapidly in any case. Cardiac output affects gases with a high BGPC and TBPC much more; halothane > enflurane > isoflurane >> sevoflurane > N_2O > desflurane.

This phenomenon has very important clinical implications. If a patient has a *low cardiac output, breathes spontaneously*, and receives halothane, the effect depends on cerebral perfusion. *If cerebral perfusion is maintained*, blood with a high partial pressure of halothane reaches the brain, and depresses the brain (consciousness and vital functions) rapidly. This depresses ventilation, which attenuates the delivery of gas to the alveoli, and therefore to the capillary blood and *the level of anaesthesia will become lighter*. However, *if the patient is being ventilated*, the effect of the high partial pressure of halothane is maintained with a profound effect on vital functions. Not only is the attenuation of halothane delivery overcome, but the suppression of the cardiovascular centre in the brain is exacerbated. The lower cardiac output potentiates the maintenance of the high diffusion gradient between blood and brain more, which further depresses vital function. *Therefore, increasing the inspiratory concentration of a highly soluble vapour such as halothane and enflurane in ventilated patients with maintained cerebral perfusion may result in severe cardiovascular suppression – especially in patients with a low cardiovascular reserve.*

The effect of a low cardiac output on wash-in time into the brain (induction time) is less *if brain perfusion is also depressed.* Then, the increased diffusion gradient between blood and tissue (due to the low cardiac output) is counteracted by the low flow to the brain and wash-in to the brain increases (remember, τ for an organ = V $\times$ TBPC/organ perfusion).

From the above discussion, it is again clear that the cardiac output has little effect on the wash-in of gases with a low BGPC and TBPC.

- *Anaesthetic metabolism and inter-tissue diffusion*
  Anaesthetic metabolism and diffusion of inhalants between tissues increase the alveolo-capillary pressure difference (PA-Pc), which promotes uptake (delays the rise in the FA/FI ratio). This contributes to the rapid increase of the levels of desflurane and isoflurane (minimally metabolized), moderate rate of increase with sevoflurane and enflurane (5% metabolised) and slow increase with halothane (20% metabolised).

From the above discussion it should be clear that changes in physiologic variables ventilation, perfusion, distribution of circulation, ventilation-perfusion abnormalities influence the FA/FI ratio, and the magnitude of these influences is to a great extent determined by solubility in blood: the lower the solubility (BGPC), the less the influence.

Mechanism of action of the inhalants[7] (Table 3)
The inhaled anaesthetics are a structural *diverse group of drugs*. This suggests that they *do not interact with a single site* (receptor or membrane channel) but with different sites in different organs. Furthermore, many excitatory and inhibitory neurotransmitters (ligands) and their agonists and antagonists (drugs that interact with their specific targets (receptors or channels)) effect anaesthetic requirement. However, the predominant effects of inhaled anaesthetics cannot be explained by the depletion, production, or release of a single neuromodulator in the CNS. In addition, specific antagonists do not reverse the effects of the inhalants. These observations may explain the diverse effects they display at different sites in the central nervous system and outside the central nervous systems (systemic side effects). This may also explain the concentration dependent effect of an agent on the same organ as well as the differences in effects exerted by different agents (e.g. halothane, the ethers, nitrous oxide, and xenon).

Inhaled anaesthetics have *presynaptic and postsynaptic effects* in the brain, spinal cord, peripheral nervous system and neuromuscular junction. The ability of anaesthetics to prevent a motor response to painful stimulation results from an action in the spinal cord – not the brain. *Therefore, MAPP (MAC) is a spinal phenomenon*.

The Meyer-Overton rule describes the relationship between lipid solubility (TBPC) and anaesthetic potency. However, at clinical doses, inhalants produce only modest changes in membrane lipid structures and function.

What can be deduced from the effects of inhalants is that their ultimate action is directly or indirectly on specific neuronal membrane proteins (receptors, ion channels, or surrounding membrane areas) that facilitate or inhibit the translocation of ions during membrane excitation. These points to the possibility that inhalants act indirectly through production of a second messenger.

Despite a remarkable accumulation of knowledge, a comprehensive *theory of general anaesthetic action* has not come forth. There is agreement that the state of anaesthesia consists of two main components, namely the behavioural (amnesia,

decreased consciousness, and immobility) and peripheral (immobility), which are separable states in vivo, but not in vitro. Of the multiple molecular and cellular anaesthetic effects identified, it is unclear which are critical for the behavioural end points, which are harmless or beneficial side effects (e.g., preconditioning before ischaemic insults to organs, such as the heart and the brain), and which, could have long-lasting or delayed adverse consequences (e.g., apoptotic cell death leading to cognitive dysfunction).

Table 3 Possible sites of anaesthetic action

Macroscopic	Central nervous system	Anaesthetics disrupt transmission throughout the CNS
	Brain vs. spinal cord	Decerebration does not alter MAC.
Microscopic	Axons vs. synapses	Higher concentrations of inhalants are required to disrupt axonal than synaptic transmission.
	Excitatory vs. inhibitory synapses	May block excitatory and enhance inhibitory transmission.
Molecular	Pre- vs. postsynaptic membrane	May alter release of presynaptic neurotransmitter (perhaps through changes in intracellular Ca^{2+}) and modify flow of ions through postsynaptic channels.
	Lipid vs. protein	*Lipid*: The *Meyer-Overton rule* implies a hydrophobic site of membrane action. The *critical volume hypothesis* explains action through membrane expansion. Possible importance of membrane-aqueous interface. The lipid fluidization theories cannot account for the production of the anaesthetic state. *Protein*: Evidence is accumulating for direct binding of anaesthetics to excitable membrane proteins.

MAC minimum alveolar concentration

Potency of the inhalation agent (Table 4)
The anaesthetic vapours and gases work at hydrophobic sites in the brain. Therefore, the higher the fat solubility of the agent is, the higher its potency (Meyer-Overton rule). This entity is expressed as the *oil/gas partition coefficient (OGPC)*. Remember that the same number of molecules must occupy the receptors (probably glycine-gated chloride channels) to give a certain effect size. The higher the OGPC, the more gas molecules dissolves in the brain for a particular partial pressure. Therefore, a lower partial pressure of the gas is needed to supply a particular number of molecules to occupy a certain number of receptors.

It is customary to express the MAPP as a percentage of ambient pressure at sea level, and is known as the *minimum alveolar concentration* (MAC). *These are also the MAC values that are always published and taught*. Since ambient pressure decreases with increasing altitude, the MAC of a gas also increases. Therefore, MAC values at higher altitudes are always higher than the published values. Anaesthetists must take cognisance of these differences lest they under-dose their patients and the level of anaesthesia will be too light. (See *Inspiratory concentration above*.) *There are different doses (multiples of MAC) of the gases to obtain a particular effect or endpoint (Table 5).* There is a *great deal of uncertainty about these figures*, since study sample sizes were small, some used the vapours in combination with N_2O, different endpoints were used, etc.

What are the disadvantages of the entity "MAC"?
- It refers to only *50% of subjects*; about 49% need less and about 50% need more. Therefore, MAC represents only the mean or concentration at the peak of the normal distribution curve.
- *Movement does not depend on cortical function* but is a brainstem nocifensive reflex (defensive response to pain). Therefore, if a patient makes non-purposeful movements during surgical stimuli, it does not necessarily mean that he/she is awake.
- It is *influenced by several factors* (see Table 6).

How is the uncertainty about the depth of anaesthesia dealt with? By monitoring brain cortical function. These include EEG-base monitors such as spectral entropy of the EEG and bispectral index of the EEG (BIS). The scales of these monitors run from 0 to about 100; it has been established that values of < 50 depict an adequate depth of surgical anaesthesia.

Table 4 Pharmacokinetics and potency of anaesthetic inhalants

Characteristic	Halothane	Enflurane	Isoflurane	Sevoflurane	Desflurane	N$_2$O
Potency[a]	224	99	91	53	19	1.4
MAPP (kPa)[b]	**0.74**	**1.68**	**1.15**	**2.05**	**6.00**	**104**
Potency × MAPP[c]	168	165	104	109	112	146
MAC (%) at sea level[d]	0.74	1.68	1.15	2.05	6.00	104
MAC (%) in Pretoria[e]	**0.86**	**1.93**	**1.32**	**2.35**	**6.90**	**120**
Metabolism (%)	20	5	0.2	5	0.02	0

a Expressed as the *olive oil/gas partition coefficient*. A better correlation between oil solubility and potency may be obtained if physiological oil such as lecithin is used.
b *Minimum alveolar partial pressure*; the same at all altitudes
c This *product (Meyer-Overton rule)* is fairly constant for a particular species; the higher the potency, the lower the MAPP.
d *Minimum alveolar concentration:* fraction of MAPP of 101.3 kPa (ambient pressure at sea level)
e *Minimum alveolar concentration*: fraction of MAPP of 87 kPa (ambient pressure in Pretoria)
The partial pressure in the alveoli that results in a level of anaesthesia that suppresses movement during skin incision in 50% of patients is called *the minimum alveolar partial pressure (MAPP)* and is expressed as kPa (or mm Hg). Since the same number of molecules (dose of the gas) causes the same effect at all altitudes (ambient pressures), the MAPP is also the same at all altitudes.

Table 5 MAPP (MAC at sea level) and response in the absence of other anaesthetics*

Type of MAC	Effect	Multiple of MAPP
Awake	Opens eyes on verbal command; recall possible	≤ 0.3
Asleep	Does not open eyes on verbal command; no recall	> 0.3
Laryngoscopy	Inhibits movement during laryngoscopy	0.9
Skin incision	**Inhibits movement during skin incision**	**1.0**
Surgery	**Inhibits movement during surgery**	**1.3**
Intubation	Inhibits movement during tracheal intubation	1.6
BAR	Inhibits increase in blood pressure and heart rate	1.7

BAR: **B**locks **A**utonomic **R**esponse during painful stimuli, e.g. tetanic electrical stimulation of the ulnar nerve, surgical manipulation of tissue, e.g. gut.
*You must know what needs less and what more anaesthetic; do not memorize the figures

Table 6 Factors affecting MAC

Increase	Decrease
Alcoholism Hyperthyroidism Hyperthermia Infants and puberty	Analgesics, sedatives: opioids, benzodiazepines, ketamine, dexmedetomidine. Hypothyroidism Hypothermia The elderly Hypotension, low cardiac output Hypoxaemia Severe anaemia Pregnancy Chronic use of central nervous stimulants such as amphetamine Antihypertensives such as α-methyldopa and reserpine
	Deafferentation*, i.e. muscle relaxation, neuraxial blockade

Deafferentation means that the central nervous system (spinal cord and brain) does not receive impulses from the sensory (afferent) peripheral nervous system. Therefore, the reticular activation system that keeps the brain cortex alert is not stimulated.

The ideal inhalational anaesthetic agent
- It must have a *balanced effect*, i.e. good analgesic, hypnotic, amnesic, and muscle relaxant properties, but
- It must have a *high therapeutic index, with no systemic side effects*, i.e. cardiac, vascular, ventilatory, renal, hepatic, and metabolic.
- Low BGPC, which ensures *rapid induction and emergence*
- High OGPC, which increases potency and a *low MAPP (and MAC)*. The low MAC should decrease *cost and pollution*, since lower concentrations are needed.

- It must be *stable in vitro* (inert), i.e. non-flammable, stable at a wide range of ambient temperatures, stored in convenient bottles, have a boiling point higher than commonly occurring ambient pressures, have a long shelf life, and is stable in anaesthetic equipment, including vaporisers and soda lime CO_2 absorbers (see Chapter 4).
- It must be *stable in vivo*, i.e. it must not break down spontaneously or be metabolised. If it does decompose spontaneously or is metabolised, it must be minimal and to non-toxic products, which do not accumulate.
- No *drug interactions*

Most important systemic effects of the inhalants
- *Central nervous system*
  SHIED decrease the cerebral metabolic rate of oxygen consumption ($CMRO_2$). Remember, if the $CMRO_2$ decreases, the brain needs less blood, the blood vessels constrict, and the cerebral blood flow (CBF) decreases (remember, this is called autoregulation; see Chapters12 and 29). This is called *CMRO$_2$-perfusion coupling*. This vasoconstrictory effect of SHIED is blunted by their direct vasodilatory effect, which decreases *CMRO$_2$-perfusion coupling*. The pressure where the vasodilatory effects of these agents overwhelm the constrictor effect differs amongst the vapours; with halothane and enflurane it is > 0.6 MAPP and for isoflurane, sevoflurane, and desflurane it is > 1.5 MAPP. However, in certain conditions, autoregulation is blunted. Then, the vasodilatory effect of isoflurane (and all the other vapours) supervenes at lower concentrations. These conditions include injury, severe hypertension, infection, ischaemia, etc.

  Cerebral vasoconstriction is also caused by *hypocapnia*. The vapours, except sevoflurane, blunt the vasoconstrictory effect of hypocapnia. That means that sevoflurane does not cancel the vasoconstrictory effect of hypocapnia. Therefore, sevoflurane is useful in decreasing ICP in the presence of hypercapnia.

  SHIED decreases the set point of thermoregulation. Therefore, patients cool down intraoperatively. As soon as the vapour is washed out, the set point increases, the thermoregulatory centre in the hypothalamus receives the cold impulses from the skin and internal organs, and immediately starts thermoregulation, including vasoconstriction and shivering. *Shivering* is therefore commonly observed postoperatively if steps are not taken intraoperatively to prevent cooling (covering the patient) and/or warming the patient actively. In the case of halothane, this is called *halothane shivers*.

  All inhalants stimulate the *chemo-emetic trigger receptor zone* and therefore may be responsible for *postoperative nausea and vomiting*. *Nitrous oxide* causes intestinal distension and contributes to postoperative nausea and vomiting.

- *Cardiovascular effects[8]*
  SHIED and N_2O are direct cardiovascular suppressants. SHIED alter the Ca^{2+} homeostasis within the cardiomyocyte and vascular smooth muscle (they are calcium channel blockers). Therefore, they exert profound effects on the cardiovascular system by *decreasing calcium ion-dependent phenomena*, namely inotropy (contractility), chronotropy (heart rate), dromotropy (conduction), lusitropy (diastolic function, ability or the ventricles to relax and receive blood), afterload (arterial dilatation), and preload (arterial and venous dilatation as well as lusitropy). SHIED depress the *autonomic control* (baroreceptor reflexes) of blood pressure.

  Therefore, *all inhalants can cause a decrease in cardiac output*. *However, the net effect of anaesthetics is complex and determined by interaction between the direct (primary) effects, i.e. cardiac (depression) and vascular (dilatation), and the secondary effects, i.e. on the autonomic nervous system (activation due to cardiovascular changes).*

  SHIED are *coronary vasodilators*. In ischaemic myocardium, the coronary arteries supplying that

area dilate maximally (remember, it happens in all autoregulating organs) to increase flow to ischaemic tissue. However, if coronary arteries in non-ischaemic myocardium also dilate, blood will be stolen from the ischaemic myocardium since pressure and resistance to normal areas decreases. This is called "*coronary steal*".

Although coronary steal has been well described, it has not been substantiated in humans, and probably *not clinically important*. However, you must remember that any condition that decreases blood pressure, and therefore, coronary perfusion pressure, and any condition that increases heart rate, and therefore, decreases coronary artery filling time (short diastole), will aggravate myocardial perfusion. *On the other hand, the reduced inotropy, preload, afterload, and heart rate decreases myocardial oxygen consumption*; these effects are harnessed in patients with ischaemic heart disease and cardiac failure. These effects account for all anaesthetic drugs – vapours as well as intravenous agents (except ketamine).[vii]

SHIED affect heart rate and rhythm. They suppress the electrical activity of the myocardium and conduction system; probably due to their effects on calcium channels. This gives rise to altered automaticity, refractory periods, and conductivity. These changes are complicated by bradycardia (halothane) and re-entry tachycardia. Supraventricular tachycardias occur very commonly with the use of SHIED, is characterised by changes in the P wave or absence of the P wave (junctional rhythms), and probably originate re-entry circuits.

SHIED, particularly halothane, *sensitize the myocardium to the dysrhythmogenic effects of adrenaline*. These agents promote the development of supraventricular and ventricular dysrhythmias, especially during myocardial ischaemia or infarction.

These effects may be *profound in patients with cardiovascular disease*. The *interaction between the inhalants and cardiovascular drugs* (β blockers, α blockers, calcium blockers, ACE inhibitors, angiotensin receptor antagonists, etc.) must also be kept in mind.

The cardiovascular effects of N_2O are mild in comparison with SHIED. *Xenon* has essentially no cardiovascular effects.

SHIED and xenon (but not N_2O) exert important cardioprotective effects against reversible and irreversible myocardial ischemia by activating intracellular signal transduction pathways involving adenosine (A_1) receptors, protein kinase C, Gi proteins, mitochondrial or sarcolemmal ATP-dependent K channels, and reactive oxygen radicals. These effects may attenuate the consequences of ischemia and reperfusion injury (effect oxygen free radicals during re-oxygenating ischaemic myocardium).

- *Respiratory system[9]*
  Inhalants influence *all aspects of ventilatory function*: from the outside (brain, airways, muscles of ventilation) to the inside (alveoli, pulmonary perfusion). SHIED (especially enflurane and desflurane) have an *unpleasant odour* and can irritate the airway. Airway irritation can cause coughing, breath-holding, and laryngospasm – especially during the second stage of anaesthesia (see Chapter 3). Sevoflurane and halothane are the only vapours that are tolerated during inhalation inductions.

  Many of the pulmonary effects of SHIED are a result of their effect of calcium channels, which are involve in bronchial and vascular smooth muscle tone, ciliary action, and mucus production. SHIED are *bronchodilators* (distal > proximal airways), even in *β₂ agonist-resistant bronchospasm*. These agents attenuate bronchoconstriction due to *chemical or mechanical stimuli*. In this regard, sevoflurane and halothane are the most useful since they are the least irritant to the

---

[vii]This consideration demonstrates the difficulty to describe the effects of vapours on different organs; the effect in the isolated organ where blood flow is maintained, and the organ in the intact human (not animal). Conflicting information in the literature regarding anaesthetic agents probably stems from these factors: who was tested, what was tested, and what was regarded as a significant change.

airways.

SHIED decreases *ciliary movement and therefore, mucus clearance*. They also alter the quality of mucus as well as a reduction in *surfactant production* by the Type II pneumocytes.

SHIED are all *pulmonary vasodilators* and may therefore affect pulmonary vascular resistance (PVR). *PVR* is determined by cardiac output and *hypoxic pulmonary vasoconstriction (HPV)*. If cardiac output is maintained, blood flow recruits the pulmonary vascular bed, which results in a decreased pulmonary vascular resistance. Hypoxic areas in the lung undergo vasoconstriction (HPV). This prevents blood flow to poorly ventilated lung units (wasted perfusion), or put another way, it decreases the shunt fraction. However, lung units can also become hypoxic if it receives venous blood from the right heart (mixed venous blood) with very low oxygen saturation. This happens when the body has extracted a large fraction of blood oxygen, such as conditions complicated by a low oxygen flux (supply) (see Chapter 14). Therefore, HPV is mainly caused by a low alveolar PO_2 (PAO_2), but also by a low mixed venous saturation ($SmvO_2$). Therefore, the shunt fraction increases if cardiac output is maintained since under-ventilated areas are still perfused well. On the other hand, if the inhalant decreases cardiac output, the vascular recruitment, which decreases pulmonary vascular resistance, is decreased. In addition, the effect of decreased $SmvO_2$ on HPV is also decreased. Therefore, it seems if though inhalants have clinically little effect on pulmonary vascular resistance.

SHIED, especially the ether derivatives decrease the tone of skeletal muscle, including muscles of ventilation. Therefore, they can cause loss of upper airway tone leading to airway obstruction. The decreased tone in muscles of ventilation causes a decrease in *thoracic volume*, resulting in a decreased *functional residual capacity* (FRC), smaller *tidal volumes* and *micro-atelectasis*, especially in dependent (the posterior in the supine, anterior in the prone, and the lower lung in the lateral position).

The clinical effects of the decreased muscle function are *decreased lung compliance*, increased shunting (collapsed alveoli), and compression of large intrathoracic structures (heart, large airways, and blood vessels). The latter effect is usually of little consequence, but can have grave consequences (airway obstruction, cardiovascular collapse) in patients with *mediastinal masses* (masses between the lungs surrounding the airways and great vessels) or pericardial constriction (effusions, constrictive pericarditis).

SHIED depress the *ventilatory responses to hypercapnia and hypoxaemia* by decreasing the sensitivity of the central and peripheral chemoreceptor sensitivity in a dose-dependent fashion. The degree of increases in $PaCO_2$ with SHIED is as follows: enflurane > desflurane > isoflurane > sevoflurane > halothane. They almost completely eliminate the response to hypoxaemia at as little as 1 MAPP. Breathing is also mediated by direct effects on lung parenchyma and indirectly through actions on afferent, central, and efferent neural pathways.

The effects of inhalants on hypoxaemia is *aggravated in patients where the response to an increase in $PaCO_2$ is also blunted*, namely by *opioids and chronic hypercapnia* (chronic obstructive airways disease). Immediately after emergence these patients may breathe due to pain, extubation, movement, etc., but become apnoeic as soon as external stimuli cease. The depressant effects of these agents are further enhanced in *patients with pulmonary disorders*. These findings may have important clinical implications during the perioperative period.

The net effect of SHIED on ventilation is a decrease in tidal volume, an increase in ventilatory rate, but a decrease in minute volume. This is accompanied by an increase in shunt fraction, i.e. increase in the number of alveoli that are perfused but not ventilated (see Chapter 13), which is *a common cause of a decrease in oxygen saturation and is evident minutes after induction of anaesthesia. All these factors* give rise to hypoventilation, with hypoxic hypoxia and hypercapnia, especially in patients breathing spontaneously. *Nitrous oxide and xenon* affect the ventilation much less.

- *Effect on skeletal muscle and myometrium*
  As pointed out above, SHIED, especially the ether derivatives *decrease skeletal muscle tone*. This is caused by central (spinal cord and brain) and peripheral mechanisms (neuromuscular junction). Therefore, they potentiate the effect of non-depolarising muscle relaxants.

  Uterine tone is reduced. The pregnant uterus is relaxed and this can cause increased bleeding during evacuations and caesarean sections. At pressures of > 1.5 MAPP uterine hypotonia is

resistant to the effects of oxytocic drugs. This effect of the anaesthetic vapours is however utilised for the manual removal of a retained placenta. However, it is preferable to relax the uterus using a short-acting smooth muscle relaxant such as nitro-glycerine (50 μg). But remember, this small dose of nitro-glycerine **_can cause severe hypotension_**, especially in hypovolaemic patients. SO BE CAREFUL!

- *Renal effects*
  Kidney perfusion is normally determined by *autoregulation*. At blood pressures below the autoregulatory limit, renal ischaemia occurs. All inhalants cause a dose-dependent decrease in blood pressure and can therefore cause renal hypoperfusion. This is particularly important in hypertensive patients (higher autoregulatory limits) and patients with renal impairment.

- *Liver effects*
  Except during the postprandial phase, liver perfusion is not subject to autoregulation and is *pressure-dependent*. Since *SHIED can decrease blood pressure and cardiac output, they can all cause liver ischaemia, especially in patients with liver pathology*. Halothane and enflurane decrease both portal and arterial contribution to liver perfusion, while *isoflurane seems to maintain arterial liver blood flow better*. The effect of sevoflurane decreases the oxygen supply/demand ratio in animals. Little is known about desflurane and liver perfusion. Remember that abdominal surgery per se decreases liver perfusion. *Therefore, isoflurane is probably the vapour of choice in patients with liver pathology.*

- *Metabolism and toxicity of inhalants[10]*
  The liver metabolises substances (endogenic and drugs) to inactive (*phase I metabolism*) and more soluble substances (*phase II metabolism*), which can be excreted. However, some of the metabolites are *reactive toxic substances*. *The main phase I enzymes* are the *cytochrome P450* (CYP) mono-oxygenases, of which CYP2E1 is the most important isoform involved in the metabolism of SHIED. The *main phase II enzyme* is *uridine diphosphate glucuronosyl-transferase (UGT)*.

  Halothane, enflurane, isoflurane and desflurane are all metabolized to *trifluoroacylated hepatic protein adducts (bind to liver proteins)*, which can induce liver injury in susceptible patients (genetic factors may play a role). The tendency of a vapour to cause liver injury appears to parallel to fraction of the drug metabolised, namely halothane (20%) > enflurane (5%) > isoflurane (0.2%) > desflurane (0.02%). The incidence of halothane hepatitis is about 1 in 200 000 and rarer in paediatric patients. Liver injury occurs after repeated exposure on subsequent occasions to *different* fluorinated vapours (cross-sensitization).

  The inorganic fluoride is produced from the fluorinated ethers during metabolism in the liver. Since *enflurane and sevoflurane* are metabolised to a larger extent than isoflurane and desflurane, inorganic fluoride levels exceeding 50 μM may occur. Although fluoride is nephrotoxic, these low levels are safe – even in patients with impaired renal function. Fluoride levels may increase in patients with liver enzyme induction, for example in patients receiving isoniazid.

  Dry carbon dioxide absorbents and SHIED interactions can lead to the production of *carbon monoxide* in the anaesthesia circuit (desflurane > enflurane > isoflurane). The absorbent is dried by high fresh gas flows or when the fresh gas is not closed after it was increased at the end of the procedure. CO production is *more with Baralyme* than with soda lime. Negligible amounts of CO are formed from halothane and sevoflurane. If you find the fresh gas open and the absorbent is dry, you can either replace the absorbent, add water to the absorbent (about 200 ml per kg of absorbent), or use very low flows until the absorbent is wet.

  There appears to be no risk associated with brief occupational low-level exposure to anaesthetic gases in the operating room. However, prolonged exposure to high concentrations (10^3 ppm) may be associated with *abortions and decreased fertility*. Individuals with vitamin B_{12} deficiencies may develop a *neuropathy and megaloblastic anaemia from N_2O*.

All inhalants, including N_2O depress leucocyte migration and the phagocytic process. This may *decrease their antimicrobic and antitumor effect* and has been implicated in an increased susceptibility to infection and the development of malignancies.

Specific inhalational anaesthetic agents (see also general effects above, Tables 3 and 7)
Nitrous oxide (**see also Chapter 4**)
Nitrous oxide is colourless, odourless, and not flammable, but supports combustion. It analgesic; at sea level, 20% of nitrous oxide is equivalent to 15 mg of subcutaneous morphine. However, to acquire anaesthetic properties (loss of consciousness), 105 kPa (> 100% at sea level) is needed. Therefore, pure nitrous oxide anaesthesia is only possible under hyperbaric conditions. Consequently, nitrous oxide is always used in conjunction with oxygen and other volatile anaesthetics.

Entonox is a mixture of 50% of oxygen and 50% of nitrous oxide (see Chapter 4). Entonox is used for minor painful procedures such as dentistry and trauma units. Entonox is also used during labour. Entonox works within about 30 s and has a duration of action of about 60 s after it has been stopped.

Nitrous oxide is an anaesthetic gas working at subcortical level, probably by blocking *NMDA receptors*, similar to ketamine. Since nitrous oxide has a MAPP of 104 kPa, it is not used as a sole anaesthetic, and always used in conjunction with vapours at pressures of < 80 kPa at sea level (but less at altitude). It was previously called a *"carrier gas"* for the vapours. Since nitrous oxide is analgesic at pressures of ≥ 20 kPa, and sedative at pressures ≥ 30 kPa, it is often used for short painful procedures in anxious patients, e.g. dental work.

This inhalant has a low potency, but potentiates other inhalants or intravenous anaesthetics. Therefore, it is usually used in conjunction with these agents. N_2O increases the potency of anaesthetic vapours with a % per %.
Example: You are working at sea level. What is the effective (equivalent) number of MACs of 0.6% (or 0.6 kPa) isoflurane administered with 50% (or 50 kPa) of N_2O? On its own, the isoflurane is administered at 1.15 kPa/MAPP of isoflurane= 0.6 kPa/1.15 kPa = 0.5 MAC.

On its own, the N_2O is administered at 50 kPa/MAPP of N_2O = 50 kPa/105 kPa $\approx$ 0.5 MAC. Therefore, the effective MAC is 0.5 MAC + 0.5 MAC = 1 MAC. Can you work out what the effective MAC of the same concentrations of isoflurane and N_2O will be in Pretoria? Hint: work with MAPP.

Can you see that the *potency of N_2O* administered at the same concentration (% of ambient pressure) is *lower than at sea level*, but that N_2O administered at the *same partial pressure* has the *same potency than at sea level*? Therefore, to have the same analgesic effect than at sea level, the gas must be administered at a higher concentration (but the same partial pressure) at altitude. For example, the analgesic potency of 50% (50 kPa) at sea level is equivalent to 100×50 kPa/87 kPa = 57% in Pretoria.

The additive effect of N_2O on other vapours is advantageous since it has a very low BGPC, which shortens induction with and emergence from the other vapours. The second gas effect also facilitates induction and emergence with other vapours.

Since N_2O diffuses back to the alveoli very rapidly at the end of anaesthesia, it dilutes the alveolar oxygen (the reverse of the second gas effect). This may cause hypoxaemia and is called *diffusion hypoxia*. Diffusion hypoxia is prevented by increasing the FiO_2 for about 5 minutes when N_2O is switched off.

Isolated gas-filled spaces, e.g. gut, pneumothorax, lung bullae, pneumoperitoneum, intracranial gas, and air in the cuff of the tracheal tube contain air that is in equilibrium with the O_2 and N_2 in blood and alveolar gas. Since the *N_2 is about 25 times more soluble in blood than N_2O*, N_2O diffuses into these spaces at a much faster rate than the rate at which N_2 can be eliminated. Therefore, these spaces

will expand and cause compression of the surrounding tissue. *Therefore, N_2O is contraindicated in patients where expansion of gas-filled cavities* can cause harm, e.g. pneumocephalus, intraocular air or gas (retina surgery), gas in the middle ear (middle ear surgery), pneumothorax, lung bullae, bowel obstruction, air emboli, etc. You must also remember to check the tracheal tube cuff pressure.

N_2O is mildly negative inotropic, especially in patient with cardiac failure. The cardiac suppressing effect is compensated for by an increase in peripheral vascular resistance due to some sympathetic stimulation. It may increase pulmonary vascular resistance and should be avoided in patients with pulmonary hypertension.

Nitrous oxide decreases the *ventilatory response* to hypoxaemia but not to hypercapnia. It causes a slight decrease in tidal volume, slight increase in ventilatory rate with maintenance of minute ventilation. Although nitrous oxide does not irritate to the airway, it is not suitable for an inhalation induction since the MAPP is so high (105 kPa). This can only be reached in hyperbaric conditions, e.g. 200 kPa. Then you can administer 1 MAPP (105 kPa) of nitrous oxide plus 95 kPa of oxygen; this gives a gas mixture consisting of 52.5% N_2O + 47.5% O_2.
Nitrous oxide decreases airway *mucociliary function* for hours after exposure.

N_2O *suppresses bone marrow* (megaloblastic anaemia with prolonged exposure) since it inhibits methionine synthase involved in vitamin B_{12} metabolism. The gas is associated with spontaneous abortion in animals. It is safe in malignant hyperthermia-sensitive patients. Postoperative *nausea and vomiting* is increased after a nitrous oxide-containing anaesthetic technique.

Halothane
Halothane is a halogenated hydrocarbon containing F, Br, and Cl. Halothane is stabilised with thymol, which is responsible for clogging of vaporizers.

- *Effects on the central nervous system.*
  See above.
- *Autonomic nervous system*
  Both the *sympathetic and parasympathetic* tone is decreases. Halothane suppresses the sympathetic response (tachycardia and hypertension) to *hypoxaemia*.
- *Cardiovascular system*
  Halothane is *negative inotropic* but *has little effect on systemic vascular resistance* since it causes vasodilatation in the skin and brain but vasoconstriction in splanchnic and muscle blood vessels. Blood pressure is decreased by about 20%. It maintains *coronary autoregulation. Heart rate decreases* as a result of sympathetic suppression. Halothane is renowned for its *dysrhythmogenicity* due to sensitisation of the myocardium the *effect of catecholamines, as well suppression of conduction* from the SA node, AV node, and Hiss-Purkinje system.
- *Respiratory system, muscle tone and myometrium, kidneys*
  See above
- *Liver*
  Liver *blood flow* decreases, with arterial supply impaired more than the venous supply. *Halothane hepatitis* is a *very rare* complication of halothane anaesthesia. It is characterised by fever, anorexia, nausea, vomiting, rash, and eosinophilia several days after exposure to halothane. This is followed by obstructive jaundice and hepatic failure. The mortality is as high as 50%. It is postulated that enzyme induction and hypoxia increases the production of reductive (instead of oxidative) metabolites, including the trifluoroacetyl free radical. This radical acts as a haptene, which activates the *immune-mediated hepatitis*. Although hepatitis has been reported after other vapours also, it is more common after halothane due to its extensive hepatic metabolism (20%) as compared to 0.2% of isoflurane. Factors that increase halothane metabolism may therefore increase the occurrence of this complication. These include:
  o Women
  o Middle aged
  o Obesity

o Exposure within the previous six weeks
o Enzyme induction levels (alcohol, barbiturates)
The following steps can be taken to avoid halothane hepatitis:
o *Avoid halothane in obese middle aged women who have been previously* exposed to halothane or enzyme induction.
o Maintain *hepatic oxygen delivery*: avoid hypoxia, hypotension anaemia, and unnecessary traction on the liver.
o Protect the liver by the *administration of carbohydrates* during the fasting period.

Enflurane
Enflurane is a non-flammable halogenated ether derivative.
- *Central nervous system effects*
  It causes *EEG changes consistent with epilepsy*, especially at *high concentrations* and if the patient is *hypocapnic*. This does not contraindicate its use in patients suffering from epilepsy. Enflurane increases cerebrospinal fluid secretion and decreases CSF reabsorption. Therefore, enflurane increases intracranial pressure.
- *Cardiovascular system*
  Enflurane is *negative inotropic* and causes generalised vasodilatation. Therefore, arterial pressure decreases. It maintains *coronary autoregulation. Heart rate* changes little, and the vapour is *not as dysrhythomogenic* as halothane. Myocardial oxygen requirements are decreased.
- *Respiratory system*
  Enflurane is irritating to the airways and is therefore not suitable for inhalation induction.
- *Liver, renal, skeletal muscles and myometrium*
  See above.

Isoflurane
Isoflurane is an ether derivative.
- *Central nervous system effects*
  Isoflurane has no effect on the production of CSF, but increases the rate of CSF reabsorption
- *Cardiovascular effects*
  Isoflurane is negative inotropic and causes vasodilatation, particularly in muscle and skin. The decreased blood pressure is accompanied by an increase in heart rate. Therefore, blood pressure decreases, while cardiac output is maintained. Isoflurane is a potent coronary vasodilator.
- *Respiratory system*
  Isoflurane is irritating to the airways and not suitable for inhalation induction.
- *Skeletal muscle and myometrium, renal, liver*
  See above

Sevoflurane
Sevoflurane is an ether derivative.
- *Central nervous system effects*
  Like enflurane, it can produce an epileptiform EEG but not contraindicate the drug in epileptics. Sevoflurane does not blunt the cerebrovascular response to hypocapnia (vasoconstriction) and is therefore useful in patients where hyperventilation is needed for acute lowering of increased intracranial pressure. The most distinct central nervous system effect of sevoflurane is the *emergence delirium*. The delirium is more common in small children and lasts about 30 minutes. This emergence phenomenon may also occur with other vapours.
- *Cardiovascular system*
  Sevoflurane causes dose-dependent negative inotropy, but the main effect is that of peripheral vasodilatation, but with less of an increase in heart rate than the other ether derivatives. It causes a mild decrease in blood pressure. Apart from a slight tachycardia, dysrhythmias are uncommon with sevoflurane.
- *Respiratory system*, s*keletal muscle and myometrium, renal effects*
  See above.

- *Metabolism and toxicity*
  About 5% of sevoflurane is metabolised in the liver to hexafluoro-isopropanol (potentially hepatotoxic), formaldehyde, inorganic fluoride, and carbon dioxide. As is the case with enflurane, the levels of fluoride are not clinically nephrotoxic.

  Sevoflurane *decomposes in soda lime* at about 6% per hour at 22°C to several decomposition products, including *Compound A*. Decomposition is more with low fresh gas flows (< 1 L min^{-1}). Compound A is nephrotoxic in rats, since they have high levels of the enzyme β-lyase, which converts Compound A to a nephrotoxic substance. However, blockade of β-lyase does not protect rats from renal injury. Compound A has not been shown to be nephrotoxic in humans, but may become important after prolonged exposure.

Desflurane

Desflurane is an ether analogue, but has physical properties that should be taken into account.
Desflurane has a very low boiling point (22.8°C) and a very high vapour pressure (681 mm Hg). These characteristics pose two problems. Firstly, when theatre temperature exceeds 22.8°C, the desflurane in the bottle and TEC vaporiser starts boiling with a large increase in the vapour output. Secondly, the fluid vaporises so rapidly that the vaporiser temperature decreases to below the dew point (temperature at which ambient air is fully saturated and condensation starts). Do you remember the experiment to demonstrate latent heat where air is blown over a container with ether? Evaporation of the ether decreases the temperature of the system (container and ether) to the extent that condensation starts on the walls of the container and eventually freezing of the water vapour occurs. To overcome this vaporisation problem, the desflurane vaporiser is heated to 39°C. At this temperature, desflurane is a gas under pressure in the vaporiser. The gas is then injected into the fresh gas. This warming feature of the desflurane vaporiser obviates the need for temperature compensation of the splitting ratio, e.g. a bimetallic strip to regulate flow through the vaporisation chamber. Furthermore, theatre temperature must be kept below 22.8°C.

- *Nervous system*
  The *biggest advantage of desflurane* is the rapid recovery from anaesthesia. However, recovery time is clinically only significant different from over vapours if exposure lasts more than 2 hours.
- *Cardiovascular effects*
  Desflurane activates the *sympathetic nervous system activation* during abrupt increases in the inspiratory concentration (2 min to 4 min after intravenous induction of anaesthesia).
- *Respiratory effects*
  See above.

The *biggest disadvantage of desflurane* is *irritation of the airways,* which makes it unsuitable for inhalation induction. Airway irritation causes coughing and laryngospasm if the anaesthetic level lightens. Airway irritation contributes to activation of the activation of the sympathetic nervous system by desflurane. Since desflurane has a very low BGPC, the level of anaesthesia can be deepened rapidly. Other than the properties mentioned, the pharmacodynamic profile is very similar to that of isoflurane. Desflurane is very stable and is almost inert. Less than 1% is metabolized.

Possible adverse effects in theatre staff
- Addiction
- Adverse effect on mental abilities
- Increased incidence of malignancy
- Toxic effect on liver and kidneys
- Increased incidence of abortions and congenital abnormalities.

Table 7 Pharmacodynamics of inhalants (at 1 MAPP for vapours and ≤ about 60 kPa for N_2O)

Effect	N_2O	Halothane	Enflurane	Isoflurane	Sevoflurane	Desflurane
Inotropy	↓	↓	↓	↓	↔	↔
SVR	↑	↔	↓	↓	↓	↓
PVR, cardiac output maintained	↓	↓	↓	↓	↓	↓
PVR, cardiac output decreased	↔	↔	↔	↔	↔	↔
MAP	↔	↓↓	↓↓	↓	↓	↑↑
Heart rate	↑	↓↓	↑	↑	↔	↑
Cardiac output	↓	↓↓	↓↓	↔	↔	↔
Dysrhythmogenic	↔	↑↑	↑	↑	↑	↑
Coronary autoregulation[a]	↔	↔	↔	↓	↔	↔
Renal perfusion	↔	↓↓	↓↓	↓	↓	↓
Splanchnic autoregulation[a] and liver perfusion	↔	↓↓	↓↓	↔	↓?	↓?
Liver perfusion	↔	↓↓	↓↓	↔	↑	↑
Sympathetic nervous system	↑	↓↓	↓↓	↓↓	↓↓	↑↑[c]
CVR, cerebral autoregulation[a]	↓↓	↓↓	↓↓	↔	↔	↓
ICP	↑↑	↑↑	↑↑	↔	↑	↑
Analgesic	direct	indirect	indirect	indirect	indirect	indirect
Anaesthesia (non-hyperbaric)	0	+++	+++	+++	+++	+++
Thermoregulation set point[b]	↓	↓↓	↓↓	↓↓	↓↓	↓↓
Pupil size	↓↓	↓↓	↓↓	↓↓	↓↓	↑↑
Irritates airway	↔	↔/↑	↑↑	↑↑	↔/↑	↑↑
Inhalation induction	No	Yes	No	No	Yes (choice)	No
Ventilatory response to ↓PaO_2	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓
Ventilatory response to ↑$PaCO_2$	↓	↓↓	↓↓	↓↓	↓↓	↓
Tidal volume	↓	↓↓	↓↓	↓↓	↓↓	↓↓
Ventilatory rate	↑	↑↑	↑↑	↔	↑↑	↑↑
Minute volume	↔	↓↓	↓↓	↓↓	↓↓	↓↓
Airway reflexes	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓
Bronchodilator	↔	↑↑	↑↑	↑↑	↑↑	↑↑
Mucociliary function	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓
Surfactant production	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓
HPV	↓	↓	↓	↓	↓	↓
Muscle tone	↔	↓	↓↓	↓↓	↓↓	
Uterus tone	↔	↓↓	↓↓	↓↓	↓↓	↓↓
MH	Safe	Avoid	Avoid	Avoid	Avoid	Avoid

↔ No effect; ↑ Slight increase; ↑↑ significant increase; ↓ Slight decrease; ↓↓ significant decrease

SVR Systemic vascular resistance

PVR Pulmonary vascular resistance

HPV Hypoxic pulmonary vasoconstriction

MH Malignant hyperthermia

MAP Mean arterial pressure. A decrease in MAP will decrease the blood pressure and blood flow in all organs, especially in organs without autoregulation of perfusion, if vasodilatation interferes with autoregulation (such as vapours), and in organs where blood pressure has declined below the autoregulatory limit (see Chapter 12)

CVR Cerebral vascular resistance

ICP Intracranial pressure

a Vasodilator; decreased autoregulation leads to hypoperfusion during hypotension.

b Since the set point is decreased to about 34°C, patients cool down to this temperature before thermoregulation starts. In the awake state, the set point is 36.5°C to 37.3°C for vasoconstriction and 36.2°C for shivering.

c During light level of anaesthesia and abrupt increases in the delivered concentration. This causes an increase in heart rate and blood pressure.

CHAPTER 7

OPIOIDS

Main points
- Opioid receptors in brain & spinal cord
- Uses of opioids
- Commonly used opioids and their potencies and

doses
- Metabolism of opioids
- Effect on organ systems

Opioids are the mainstay of providing analgesia in perioperative period. Their action and side effects are mediated via activation of specific opioid receptors (μ, δ, κ, σ) in the central nervous system (CNS) and peripherally. Opiate receptor activation inhibits presynaptic release and postsynaptic response to excitatory neurotransmitters from nociceptive neurons. The choice of opioids in the perioperative period depends on their pharmacodynamic (potency) and pharmacokinetic properties (Table 1). (See also Chapter 10)

Table 1 Opioids and their properties

Drug	Lipid solubility	Relative potency	IV Dose*	Duration of action
Morphine	+	1	50 μg kg^{-1} to 300 μg kg^{-1}	1 h to 2 h
Alfentanil	++	10	10 μg kg^{-1} to 20 μg kg^{-1}	5 min to 10 min
Fentanyl	+++	100	1 μg kg^{-1} to 3 μg kg^{-1}	20 min to 30 min
Sufentanil	+++++	>1000	0.1 μg kg^{-1} to 0.3 μg kg^{-1}	30 min to 45min
Remifentanil	++++	300	0.1 to 1.0 μg kg^{-1} min^{-1}	1 min to 3 min after infusion stopped

*These dosages (especially the lower end of the dose ranges) are analgesic and are used to strengthen (additive or synergistic) the effects of inhalants and sedatives.

Pharmacokinetics of opioids
- Except for remifentanil, all opioids rely on the liver for biotransformation. Morphine relies on renal excretion of active metabolites for elimination.
- Morphine is conjugated in the liver to glucuronic acid to form active metabolites morphine-3-glucuronide (an antagonist) and morphine-6-glucuronide (a potent agonist).
- Alfentanil, fentanyl and sufentanil are metabolized by the liver but their metabolites are not active.
- Remifentanil undergoes rapid ester hydrolysis by non-specific esterases in the red cells. It has no active metabolites.

Effects of opioids on organ systems
- *Cardiovascular*
  - o No effects on myocardial contractility
  - o Decreased sympathetic outflow may result in bradycardia and hypotension
  - o Histamine release (morphine) can cause cardiovascular collapse
  - o Blunts the sympathetic response to intubation
- *Respiratory system*
  - o Depressed sensitivity of respiratory centre to increased $PaCO_2$
  - o Hypoxic drive is decreased
  - o Rapid injection of the potent opioids may cause chest wall rigidity with inability to ventilate
  - o Blunt the bronchoconstrictive response to intubation
  - o Opioids decrease airway patency (see below).
- *Central nervous system*
  - o Reduced cerebral oxygen consumption, cerebral blood flow, and intracranial pressure (if ventilation is maintained), but less than the benzodiazepines or barbiturates
  - o Analgesic doses have causes little EEG changes but large doses when an opioids is the only anaesthetic (cardiac surgery), causes slow-wave sleep.
  - o Miosis
  - o Nausea (stimulation of the chemo-emetic trigger zone)

- o Intrathecal opioids are analgesic
- *Gastro-intestinal system*
  - o Decreased gastric emptying
  - o Spasm of sphincter of Oddi
  - o Constipation
- *Endocrine system*
  - o Decreases the release of stress hormones
  - o Attenuates the intubation response

Side effects of opioids

- Respiratory depression. Opioids suppress minute volume (hypoventilation) by decreasing tidal volume (hypopnoea) and/or respiratory rate (bradypnoea). ***Therefore, a normal respiratory rate does not exclude respiratory depression.***
- Opioids depress the hypoglossal nerve nucleus directly, which leads to relaxation of the mylohyoid muscle. ***This causes narrowing of the pharynx and even airway obstruction, especially in patients that suffer from sleep apnoea.*** This effect is aggravated by the sedatory effect of opioids and other sedatives.
- Postoperative nausea and vomiting
- Tolerance to the analgesic effects (acutely during remifentanil infusion), and to the side effects, except to constipation and miosis
- Histamine release
- Pruritus, especially if used intrathecally
- Chest wall rigidity if used in high doses
- Addiction potential
- Constipation with long term use.

All the side effects of μ opioids (hypoventilation, pruritus, hypotension, etc.) are reversed by the *μ antagonist naloxone*. Since the $t_{1/2}$ of naloxone is shorter than most opioids, i.e. about 60 minutes, the anaesthetist must keep in mind that μ effects, most importantly hypoventilation and sedation, may return. The dose of naloxone is 5 μg kg^{-1} titrated at 1 μg kg^{-1} to 2 μg kg^{-1} every 2 minutes IVI to reverse opioid effect. The dose must be titrated to avoid sudden return of pain and sympathetic nervous system activity. This may be complicated by severe hypertension, tachycardia, and in vulnerable patients, myocardial ischaemia, cardiac failure, and pulmonary oedema. In the case of prolonged opioid effects (opioid toxicity and intrathecal morphine), an infusion may be used. The dose is about 1 μg kg^{-1} h^{-1}.

CHAPTER 8

ANAESTHESIA AND MUSCLE TONE

Key points

- Physiology of muscle contraction
- Effects of anaesthetic agents on motor pathways
- Distribution, anatomy and physiology of the nicotinic acetylcholine receptors (nAChRs) : neuromuscular, non-neuromuscular
- Up-and down-regulation of nAChRs
- Neuromuscular blocking agents: Pharmacokinetics and –dynamics
  o Depolarisers
  o Non-depolarisers: the benzylisoquinolines and aminosteroids
- o Concept of ED95 and dosing of neuromuscular blocking agents
- Reversal of non-depolarising muscle relaxants
  o The cholinesterases (AChE)
  o Reversible inhibitors of AChE
  o Adverse effects of AChE inhibitors and the use of antimuscarinic agents
- Allergic reactions to muscle relaxants
- Effect of neuromuscular blockade on the central nervous system
- The ideal muscle relaxant

The focus of this Chapter 9 is the effects of anaesthetic agents on muscle tone.

Activation of muscle contraction involves:

- Activation of upper motor neurons
- Transmission via the corticospinal tracts to α motor neurons and interneurons in the ventral spinal cord
- Conduction along the Aα fibres in the peripheral nerves to the nerve terminals
- Mobilization and release of acetylcholine (ACh) from vesicles into the neuromuscular junction (NMJ) (Figure 1)
- Activation of pre- and postjunctional ACh receptors and
- Muscle contraction

Anaesthetic agents affect each part of this motor pathway to some extent and may therefore affect muscle tone. The effects of anaesthetic agents are:

- Not limited to one anatomical structure or region, but have a wide range of effects
- Dose-dependent
- Neuronal (central or peripheral) or non-neuronal

The major receptor involved outside the spinal cord is the *nicotinic acetyl choline receptor (nAChR)*. However, the concept that different types of receptors, including different ACh receptors occur exclusively inside or outside the CNS, or in nerve tissue or muscle, has been rejected.

The effect of anaesthetic agents on motor pathways

- *Volatile anaesthetics* act on motor pathways at the *cortical level*. They may also depress transmission from the *corticospinal neuron to the α motor* neuron at synapse level.
- At subanaesthetic concentrations, *sevoflurane* has a potent and concentration-dependent inhibitory effect on spinal *nociceptive and non-nociceptive transmission*. At anaesthetic concentrations, sevoflurane produces an almost complete blunting of spinal responses. This is consistent with clinical experience that *very little neuromuscular blockers are required* to maintain immobility when *1 MAC sevoflurane is administered*.
- At the level of the *spinal cord, sevoflurane* has a much greater effect than *propofol*.
- At clinical concentrations, *propofol* inhibits spinal motor neuron activity; propofol reduces motor neuron action potential firing by about 50%.
- The inhibitory effect of *propofol on spinal nociceptive transmission* only appears at anaesthetic concentrations.
- Neurons in the *ventral spinal cord are more depressed* by isoflurane, halothane, and propofol than are neurons in the dorsal spinal cord.
- *Opioid-associated rigidity* is characterized by increased muscle tone during the administration of

opioids, particularly the lipophilic compounds fentanyl, alfentanil, sufentanil, and remifentanil. This adverse effect coincides with the onset of apnoea and loss of consciousness. The observation is not related to any neuromuscular or muscular effect since pre-treatment with a non-depolarising muscle relaxant (NDMR) prevents rigidity. Neither is it due to impairment of the monosynaptic reflex. It occurs more commonly in patients receiving drugs with antidopaminergic side effects such as the butyrophenones, animals with lesions in the corpus striatum, and in Parkinson's disease.

- *Neuraxis and peripheral nerve blockade* prevent all afferent and efferent nerve traffic. All local anaesthetic-induced lower motor neuron blocks (neuraxial and peripheral motor nerve block), attenuate or eliminate reflex activity and cause flaccid paresis or paralysis in the muscles innervated by the blocked neurons.
- *The effects of volatile anaesthetics on sodium and potassium channels* contribute to their overall depression of the central nervous system. This leads to a generalised decrease in muscle tone.
- *Ketamine* also blocks axonal conduction in peripheral nerve membranes, which decreases muscle tone.
- *Several anaesthetic agents affect γ amino butyric acid (GABA), glycine, and glutamate receptors.* Most general anaesthetics, including vapours and intravenous anaesthetic (barbiturates, propofol, benzodiazepines, etomidate, and ketamine) agents affect inhibitory transmission by enhancing $GABA_A$-receptor-mediated currents. However, the action of general anaesthetics is not limited to their effect on $GABA_A$ receptors. They also bind to glycine, NMDA, and nACh receptors. The effects of these agents inhibit the traffic to motor neurons and can therefore decrease muscle tone.

The acetylcholine receptors

The *distribution of ACh receptors* may explain some of the *side-effects of muscle relaxants and inhibitors of acetylcholinesterase (AChE)*. ACh receptors occur in:

- *Central nervous system* (M_1 and nicotinic)
- *Peripheral nervous systems*, namely
  - *Muscarinic* (M_2 in the heart; M_3 in smooth muscle and exocrine glands) and
  - *Nicotinic* at the *NMJ* (pre- and postjunctional) (Figure 1) and at *autonomic* ganglia (sympathetic and parasympathetic).

ACh increases the membrane permeability for different cations at different effector organs:

- At *autonomic ganglia and adrenal medulla*, and the *NMJ,* stimulation of nAChRs by ACh hypopolarizes the membrane (increased excitability) by increasing *permeability for Na^+*.
- At the *heart* M_2 receptors mainly occur supraventricularly in pacemaker cells and myocytes. Stimulation of these receptors increases *permeability for K^+*. This hyperpolarizes membranes resulting in negative chronotropy, bathmotropy (excitability), and inotropy.
- At *visceral smooth muscle and exocrine glands* (bronchial muscle and glands, gastrointestinal tract, urogenital tract, postganglionic sympathetic fibres to sweat glands) stimulation of M_3 receptors increases *permeability for Ca^{2+}* causing contraction and secretion respectively.

Nicotinic acetylcholine receptors and anaesthesia

Nicotinic AChRs play an important role in *the anaesthetic state* (See Chapter 1). Pancuronium decreases the MAC of Halothane by 25%. During a stable anaesthetic neuromuscular block gradually wears off (the patient becomes tight), which is accompanied by apparent lightening of the anaesthetic plane (increased heart rate and blood pressure, movement).

Structure, distribution, and function of nAChRs

Seventeen nAChR subunits have been cloned and are broadly divided into α and non-α subunits (β, γ, δ, and ε) in different combinations depending on their distribution and function. The α subunits have two adjacent cysteine groups, which form the main binding sites for ACh, whereas both the α- and non-α subunits contribute to the specificity of the different types of nAChRs.

Neuronal nAChRs
Neuronal nAChRs are widely distributed in the *central and peripheral nervous systems (PNS)*. They consist of five subunits forming a pore. Twelve different subunits have been identified in neuronal nAChRs, namely $\alpha2$ to $\alpha10$ and $\beta2$, $\beta3$, and $\beta4$. Neuronal nAChRs are homo- or heteromeric and are built up of different combinations of the subunits. When ACh binds to two α subunits of a nAChR receptor, cation channels are activated allowing the influx of Na^+ and Ca^{2+} followed by depolarisation of surrounding cell membranes.

The role of nAChRs in the CNS is less well defined than at the NMJ and PNS. Brain nAChRs are not crucial for survival but play a role in more subtle brain functions such as attention, vigilance, memorization, learning, behaviour, and addiction to nicotine. Another major CNS function of nAChR stimulation is transmission in the dorsal horn of the spinal cord and appears to be involved in pain processing and modulation. Intrathecal application of neostigmine is analgesic.

Volatile anaesthetics and ketamine are potent inhibitors of muscle and neuronal nAChR channels at clinical concentrations. The mechanism of these effects may include competitive antagonism, open channel blockade, allosteric changes of the receptors, and desensitisation. In general, the neuronal nAChRs are more sensitive than the muscle receptors to the effects of these non-relaxant anaesthetics. In the CNS, low concentrations of *atracurium and its degradation product laudanosine* stimulate nAChRs and synaptic activity.

NDMRs are highly polarized drugs, which prevents them from crossing the blood-brain-barrier (BBB). Due to its lipophilicity, laudanosine crosses the BBB. In pathological conditions, the *BBB may become more permeable* and NDMRs may reach the brain, e.g. sepsis and surgery. The clinical relevance of NDMRs reaching the CSF is *however unclear*.

Ganglionic type nAChRs in the carotid body is involved in stimulation of ventilation during hypoxia. The increase in ventilation during hypoxia is mainly controlled by afferent impulses from peripheral chemoreceptors in the carotid bodies, and, to a lesser extent, receptors in the aortic arch. While peripheral chemoreceptors react to hypoxia and hypercapnia, the acute ventilatory response to hypoxia is only dependent on stimulation of the peripheral chemoreceptors. The increase in ventilation following an increase in arterial CO_2 is less than 20% dependent on stimulation of peripheral chemoreceptors, while the remainder is dependent on stimulation of pH-sensitive receptors in the brain stem.

An intact cholinergic system is important for carotid body chemoreceptors response during hypoxia. Although ACh may not be the primary neurotransmitter responsible for chemoreceptor response in the carotid body, it may play a modulating feedback role. Substance P and dopamine are probably involved directly in neurotransmission in these receptors. *NDMRs* maintain hypercapnic ventilatory response during a partial neuromuscular block. However, chemoreceptor function is blocked by non-relaxant doses of NDMRs, which *decreases the ventilatory response to hypoxia*. At a mechanical adductor pollicis train-of-four (TOF) ratio of 0.70 (see below for explanation of TOF), the hypoxic ventilatory response is reduced by approximately 30% in the awake volunteer after both aminosteroids (pancuronium and vecuronium) and benzylisoquinolines (atracurium) and by both relaxants with (pancuronium) and lacking (vecuronium and atracurium) antimuscarinic properties.

NDMRs do not only reduce the hypoxic ventilatory response, but also the motor function of the pharyngeal function and therefore, of the upper airway. This is seen in partially relaxed patients with an adductor pollicis TOF ratio of 90%. In order to prevent hypoventilation, obstruction and aspiration patients should be ventilated and kept intubated until the TOF ratio has recovered to > 90%.

Neuronal nAChRs are also involved in the inflammatory reflex. This reflex consists of stimulation of the vagal nerve. The afferent impulse activates a neuronal muscarinic (M_1) brain network. Efferent impulses are conducted via the vagal nerve, which inhibits cytokine release by stimulation of $\alpha7$ nAChRs on macrophages. As some NDMRs also block the $\alpha7$ nAChR, their use in patients with inflammatory conditions may be contra-indicated. These conditions include sepsis, circulatory shock, ischaemia, and reperfusion.

Pre- and postjunctional nAChRs (also see **neuromuscular blocking agents**)
The most important receptors in the neuromuscular junction are pre- (neuronal) and postjunctional (mostly muscular) nAChRs. Muscle nAChRs are heteromeric consisting of $\alpha1$, $\beta1$, δ, and γ, or $\alpha1$, $\beta1$, δ, and ϵ subunits. Five subunits form a functional nAChR with a barrel-like shape surrounding the ionic pore (Figure 2). Adult muscle nAChRs (present in large numbers in the *Torpedo* electroplate) consist of two α, and one each of β, δ, and ϵ units, while the embryonic muscle receptor consists of two α, and one each of β, δ, and γ units.

The lower motor neuron synthesizes ACh, which is stored in vesicles in the nerve ending. The Aα fibres lose their myelin sheaths at the end-feet to allow unhindered release of ACh molecules into the neuromuscular cleft. Depolarisation of the *prejunctional membrane* opens voltage-gated Ca^{2+}

channels. This is followed by a cascade of events that cause mobilization of ACh to fill vesicles with quanta of ACh, fusion of the vesicle and cell walls, and release of ACh into the junctional cleft. Several toxins affecting neuromuscular transmission interfere with ACh release into the junctional cleft.

The mobilization and release of ACh is modulated by prejunctional nAChRs and muscarinic receptors. *Neuronal nicotinic autoreceptors* occur in the membranes of motor nerve terminals and are involved in a *positive feedback mechanism for ACh mobilization*. Whilst stimulation of the prejunctional nAChRs enhance release of ACh, stimulation of prejunctional muscarinic receptors inhibits mobilization and release of ACh. This was confirmed by the finding that pancuronium inhibits evoked release of ACh.
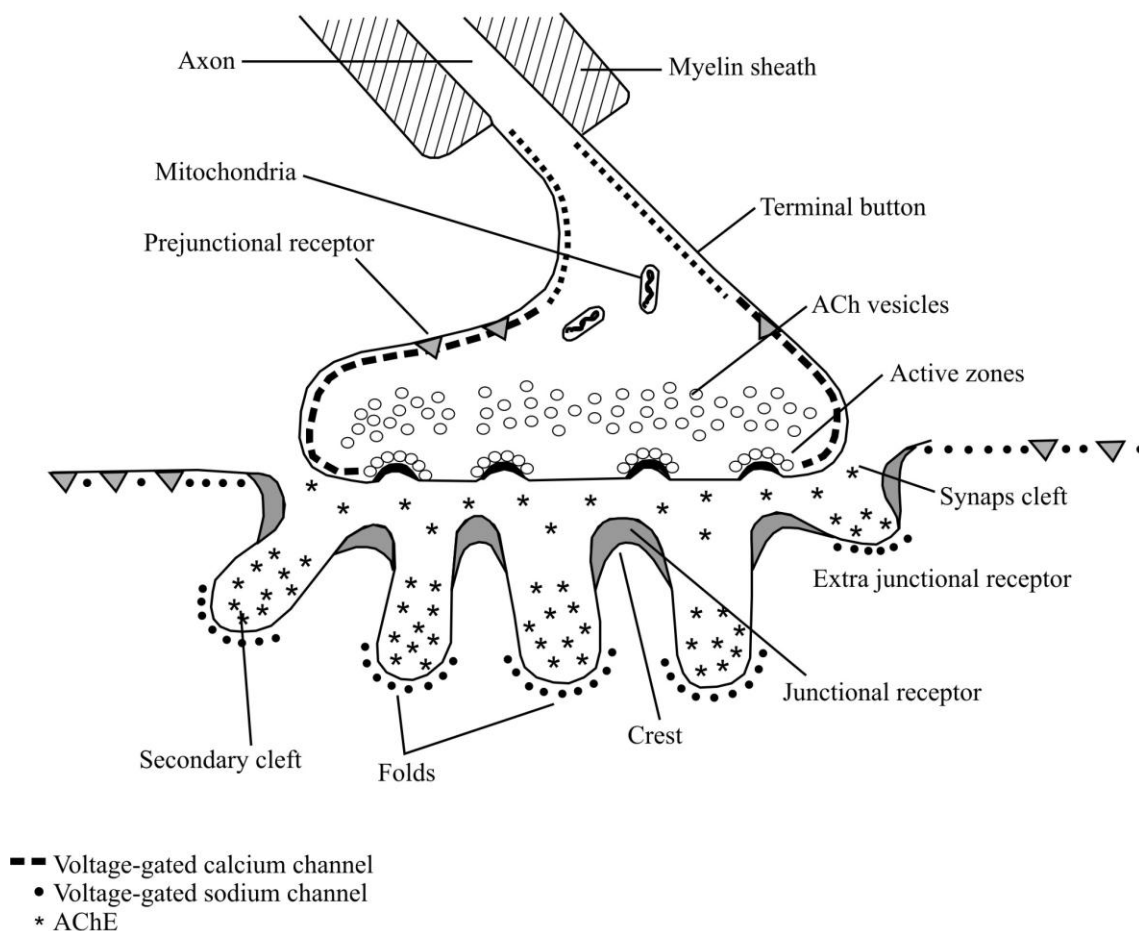
Figure 1 The neuromuscular junction
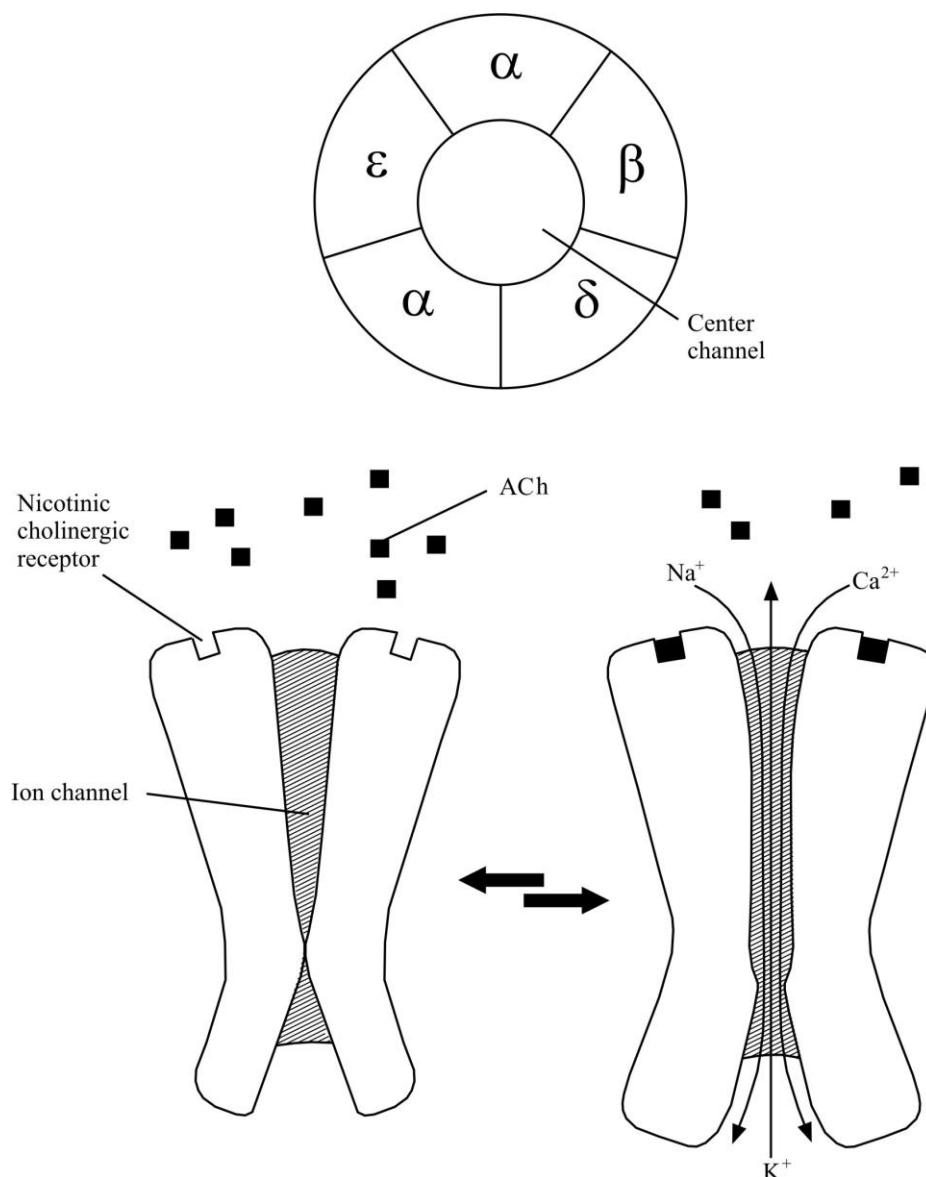
Figure 2 The adult postjunctional ACh receptor: Cross section above and longitudinal section below

Stimulation and blockade of prejunctional acetylcholine receptors

ACh stimulates prejunctional nAChRs, which causes a positive feedback on its mobilization and release during high frequency stimulation. *Agonists such as suxamethonium* stimulate these receptors, which may contribute to an initial increase in the response to nerve stimulation, followed by paralysis. Depolarising muscle relaxants do not inhibit prejunctional release of ACh and therefore do not cause fade with TOF or tetanic neuromuscular stimulation.

NDMRs are *competitive antagonists at these receptors*. They inhibit prejunctional release of ACh. The postjunctional effect of the NDMR is responsible for a reduction in tetanic tension, while *the prejunctional effect is responsible for fade during TOF stimulation*. NDMR cause fade at concentrations lower than those that decrease the single twitch. Therefore, *fade is indicative of residual NMB* (Figures 6, 7, and 8).

Postjunctional membrane nAChRs

Apart from the adult $\alpha1\beta1\delta\varepsilon$ nAChR, two more subtypes of nAChRs occur in the postjunctional membrane; the foetal $\alpha1\beta1\delta\gamma$ and neuronal $\alpha7$ nAChRs. *Mature muscle nAChRs are only found*

opposite the nerve terminal (perijunctionally), whilst foetal receptors occur perijunctionally as well as extrajunctionally in the muscle membrane.

After birth, the nerve axons grow into the developing muscle. These axons transport nerve-derived growth factors, including agrin and neuregulins, to the developing muscle. These growth factors are essential for maturation of muscle myotubules. The growth factors stimulate clustering of nAChRs at the junctional area, while other muscle-derived proteins are involved in the maturation and stabilisation of the nAChRs at the junction. Clustering is responsible for the migration of these proteins from the extrajunctional to the junctional region. *Shortly before and after birth*, *the γ-subunits in the nAChRs start to change to ε-subunits*. This transformation continues for more than two weeks after birth. In is unknown when postjunctional α7 nAChRs disappear.

In comparison to mature nAChRs, foetal receptor channels have a smaller conductance, a two- to ten-fold longer open time, and higher sensitivity and affinity for agonists. Therefore, agonists such as ACh and suxamethonium depolarise immature receptors easier; as little as 1% to 10% of the adult dose can cause depolarisation in foetal receptors. However, infants and children require larger doses of suxamethonium than adults because of their larger volume of distribution and larger number of receptors.

The *foetal α1βδγ and the postjunctional α7 receptors* have a lower affinity for NDMRs leading to resistance to these drugs. This is also the position when mature receptors are replaced by immature receptors, e.g. with immobilisation, denervation and burns. The synthesis of foetal receptors *starts within hours after immobilization* but it takes days to spread over the whole muscle.

The *junctional muscular nAChRs form Na$^+$ channels that are activated (opened) when ACh binds both α units*. Na$^+$ flows into the muscle cell and causes an endplate potential (EPP). If enough ACh quanta are released from prejunctional vesicles, sufficient channels (at least 20%) are opened and the EPP will reach a threshold, which will open voltage-dependent Na$^+$ channels in the surrounding cell membranes. This is followed by action potentials in the surrounding cell membranes, which spread over the entire muscle and *muscle contraction*.

The neuromuscular transmission with muscle contraction is measured in terms of motor response to different patterns of nerve stimulation, including response to a single supramaximal stimulus (single twitch, ST), double burst stimulus (DBS), or to a series of four stimuli (train-of-four, TOF). The response is graded according to the number of responses (train-of four count), presence or absence of fade, and the ratio of the last to the first response (TOF%). In the intact neuromuscular junction, the responses are normal and equal (Figure 3).
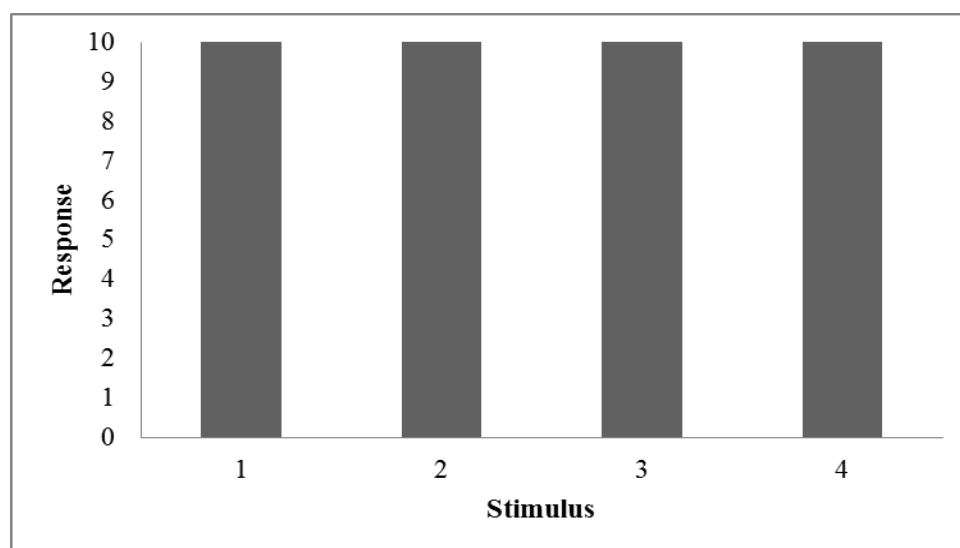
Figure 3 Train of four: Normal response: the TOF count = 4/4 and the TOF% > 90%.

ACh is hydrolysed rapidly (within about 1 ms) by AChE in the basal lamina in the junctional cleft and the receptor reverts to the resting state and is ready to be opened when a next nerve impulse releases ACh. Levels of junctional AChE activity may be decreased due to congenital defects of the enzyme, inhibition by AChE inhibitors (pesticides), or following denervation.

Up- and down-regulation of nAChRs

Up- and down-regulation is a *self-regulatory homeostatic mechanism*, which regulates receptor *density and type in the postsynaptic membrane*. Up- or down-regulation occurs when receptors are chronically exposed to their *antagonists or agonists*. In general (but not at all anatomical sites), chronic exposure to the agonist will result in a decline in the number of receptors (down-regulation), while chronic exposure to an antagonist (even at sub-paralytic doses) will cause an increase in the number of receptors (up-regulation). Up-regulation of muscle nAChRs can be prevented by nerve-mediated muscular stimulation, but not during competitive block when nerve-mediated neuromuscular stimulation is not possible.

Up-regulation of muscle nAChRs occurs in:
- Denervation states. Denervation of lower motor neurons and proliferation of muscular nAChRs occurs not only after lower motor neuron lesions but also after upper motor neuron injury (spinal cord injury, stroke).
- Long-term immobilization with atrophy (intensive care, unconsciousness)
- Thermal muscle trauma
- Infection (long-standing peritonitis)
- Long-term administration of drugs, including NDMRs, anti-epileptic drugs, theophylline, and dexamethasone

Up-regulation may have a *pre- and postjunctional component*, but the downstream effect is the same, namely decreased stimulation of postjunctional ACh receptors: Long-term lack of nerve stimulation as well as antagonism of prejunctional receptors by NDMRs will decrease the release of ACh, while chronic exposure to NDMRs will prevent the action of released ACh. The postjunctional component of up-regulation is the increased number of junctional and extrajunctional receptors as well as *appearance of foetal nAChRs* containing ε instead of γ subunits (*up-regulation*).

Denervation-related immobilization and immobilization due to sedation or prolonged administration of NDMRs cause up-regulation of postjunctional nAChRs. Postjunctional nAChRs are turned over by peripheral movement to the peri-junctional muscle membrane. These receptors are internalised and form the source of these additional receptors.

Up-regulation of receptors affects the pharmacodynamics of depolarising (increased sensitivity) and non-depolarising (resistance) neuromuscular blockers:
- Stimulation by suxamethonium causes massive depolarisation and efflux of K^+ through the upregulated nAChR pores.
- Upregulation of nAChR and resistance to NDMRs occur within a week after lower motor neuron injury.
- Resistance to NDMRs also occurs in patients with *cerebral palsy* (CP). However, they do not demonstrate the severe increased plasma potassium after the administration of suxamethonium, which occurs in patients with *lower motor neuron lesions*.

Down-regulation is seen with:
- Long-term *increase in junctional ACh* concentrations (long-term inhibition of AChE) results in internalisation of acetylcholine receptors.
- *Myasthenia gravis* where postjunctional nAChRs are destroyed.
- Both these conditions render the muscle *hyposensitive (tolerant) to suxamethonium but hypersensitive to NDMRs*.

THE NEUROMUSCULAR BLOCKING AGENTS

The Na^+ channels of the junctional and extrajunctional nAChRs occur in *three functional states*:
- *Resting* and the Na^+ channels can be activated (opened) by the ACh binding to the nAChRs.
- *Active* and the Na^+ channels are opened, Na^+ can enter the cell and depolarise the membrane.
- *Inactive* when ACh still occupies the receptor but the channel is inactive, i.e. it cannot be opened.

Neuromuscular blocking agents are generally divided into two groups, according to their effect on the nAChRs at the neuromuscular junction, namely agonists (depolarising) or antagonists (*NDMRs)*.

Depolarizing neuromuscular blockade: Suxamethonium (succinyldicholine)

As will be seen from the pharmacodynamics, suxamethonium is mostly referred to as a "neuromuscular blocker". It is, however, actually an "endplate blocker". Suxamethonium is unique in its action; it initially stimulates and subsequently blocks ionic (Na^+) traffic in the muscle Na^+ channels. The depolarising muscle relaxants are agonists (they have both affinity and intrinsic activity) at muscle nAChRs that are responsible for opening the gates in the Na^+ channels.

Suxamethonium is the only depolarising muscle relaxant in clinical use. It is a long molecule ('leptocurare') consisting of two conjoint ACh molecules. Suxamethonium binds to the α subunits of the *resting postjunctional nAChR*. This is followed by opening (*active state*) of Na^+ channels, EPP, and depolarisation of the muscle membrane. This is clinically observed as *fasciculations*. Fasciculations occur soon after injection, are fist recognized in the face and then spread over the chest, abdomen, limbs, and lasts a few seconds.

As long as suxamethonium molecules are *occupying the perijunctional receptors* (the nAChRs on the border between the end plate and the rest of the muscle membrane), the ion channels remain in an *inactive state*. A nerve-evoked ACh release will be unable to stimulate opening of the Na^+ channels until they have returned from the inactive to the resting state. Since the muscle cannot repolarise until the suxamethonium has been removed from the receptors the muscle remains insensitive to ACh and therefore paralysed. The channels outside the perijunctional zone are not occupied by suxamethonium, repolarise after the initial depolarisation (fasciculations), and are excitable by *direct electrical* stimulation. The allosteric interaction of *isoflurane* with muscle nAChRs *sensitise muscle to the effect of suxamethonium*.

The repolarised muscle is therefore paralysed. This is called *accommodation*. Paralysis is maximal within about one minute, and usually lasts less than eight minutes. This is the so-called *phase I block*. Since ACh released from the prejunctional fibre can activate only Na^+ channels that are not occupied (activated → inactivated) by ACh, the motor response to nerve stimulation will be less than when none of the channels are being occupied. A phase I block is therefore characterized by a decreased response to single twitch, TOF (Figure 4), and tetanic stimulation, but the absence of fade. When the postsynaptic receptors are freed from suxamethonium the membrane repolarises and ACh is able to activate the channels again.

Suxamethonium does not interact with the *prejunctional* nAChRs. If suxamethonium is not metabolized by plasma ChE (butyrylcholinesterase; BuChE), relaxation may last for several minutes to hours (*phase II block*). A phase II block may demonstrate the characteristics of a non-depolarising block, namely fade with TOF (Figure 5) and tetanic stimulation, which suggests a prejunctional effect. The mechanism of a phase II block is poorly understood.

The dose of suxamethonium

The dose of suxamethonium that decreases the single twitch with 95% (called the ED95 of a relaxant) is 0.3 mg kg^{-1}. The intubation dose in adults is 1 mg kg^{-1}. The dose of suxamethonium that produces a 90% decrease in twitch height is 0.5 mg kg^{-1} in neonates, 0.6 mg kg^{-1} in infants, and 0.4 mg kg^{-1} in children (Tables 1 and 3). Therefore, higher intubation doses are recommended, namely 3 mg kg^{-1} in

neonates and infants and 2 mg kg^{-1} in children.
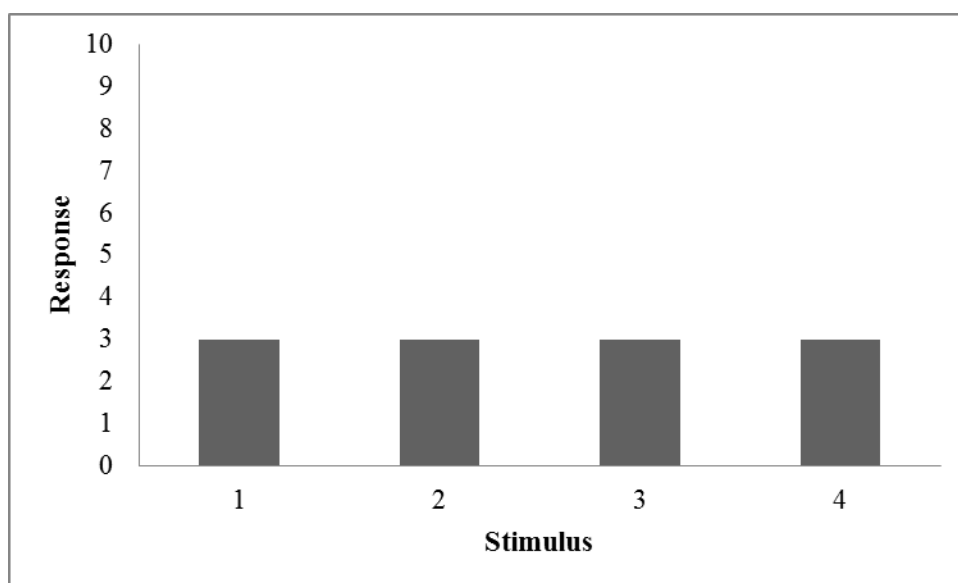
Figure 4 Train of four: Phase I depolarising block. All four responses are decreased but equal.
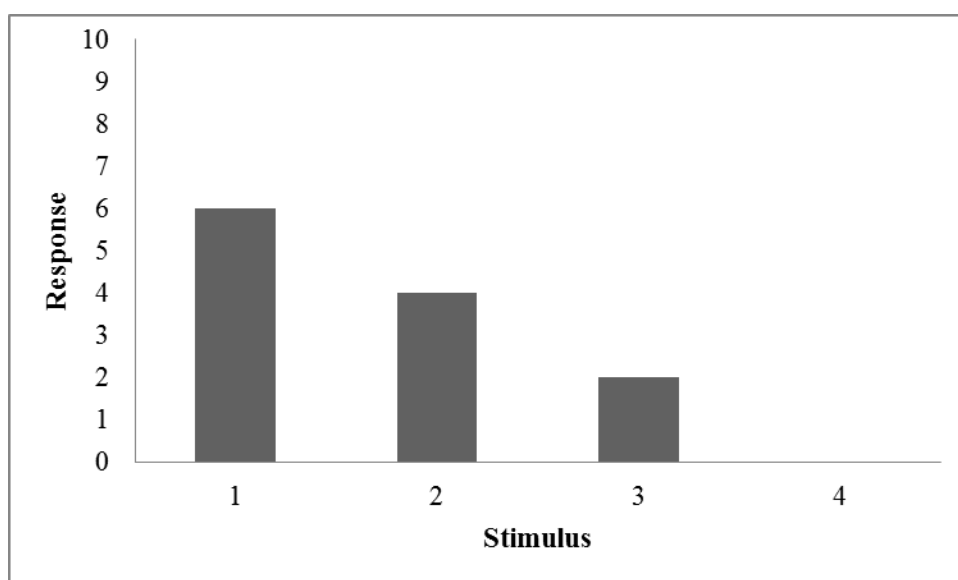
5 Train or four response with a phase II depolarising block and nondepolarising block. In this case the TOF count = 3/4 and there is fade of the responses with a TOF% = 0/60 = 0%.

Adverse effects of suxamethonium

- Suxamethonium may have several effects on the *autonomic nervous system*. It can stimulate nicotinic (ganglia) and muscarinic receptors. At clinical doses, suxamethonium does not bind to neuronal nAChRs in autonomic ganglia. *At high doses it may interact with these receptors in vagal ganglia causing a bradycardia, especially in infants and children*. Therefore, an antimuscarinic agent is usually administered before suxamethonium in infants and children, e.g. *atropine 20 µg kg^{-1}*. High doses may also affect *sympathetic ganglia* (including the adrenal medulla) causing increased catecholamine levels. The latter cause *tachydysrhythmias*, supraventricular and ventricular *ectopic beats*, and *hypertension*.
- *Increases in intraocular pressure* of more than 80% lasting a significant time occur in children following the administration of suxamethonium. Although the use of suxamethonium is not the drug of choice in the patient with penetrating eye injury, it has been administered to such patients without extrusion of the eye content.

- The *increase in intra-abdominal pressure* is ascribed to fasciculations of abdominal muscles. Although this increase may increase the risk of regurgitation, especially in a patient with an incompetent oesophageal sphincter mechanism, the increase in intragastric pressure is less than the barrier pressure.

- Suxamethonium may *increase cerebral perfusion* and may therefore increase *intracranial pressure*. However, in clinical practice patients with increased intracranial pressure usually receive an induction agent before suxamethonium. The induction agent causes cerebral vasoconstriction. *Therefore, intracranial pressure does not increase significantly with the use of suxamethonium.* Airway stimulation during endotracheal intubation is probably the main cause of increased intracranial pressure.

- *Postoperative myalgia* has been blamed on the fasciculations caused by suxamethonium. Myalgia has been reported in more than 70% of patients who had received suxamethonium, but also in about 20% each of patients who received a NDMR and no relaxant. Myalgia has been *attenuated with a varying degree of success* with a small dose of a NDMR (*taming*, precurarezation), a benzodiazepine, dantrolene, lignocaine, aspirin, or chlorpromazine. It is however now believed that no method has a clinically significant effect on the incidence of fasciculations and myalgia. The *taming principle is not advised* since the NDMR may cause significant NMB, which may predispose to hypoventilation and loss of upper airway integrity and aspiration. Furthermore, the NDMR may antagonize the effect of suxamethonium making it ineffective.

- *Hyperkalaemia* is a well-known side-effect of suxamethonium under certain circumstances. Na^+ enters the muscle cells during depolarisation, which is followed by K^+ leaving the cells (repolarization). At the junctional membrane this happens through activation of mature postjunctional nAChRs. Suxamethonium causes transient increase in plasma potassium concentration of *0.5 mM to 1.0 mM* within 3 min to 5 min lasting 10 min to 15 min. With *immobilization (paraplegia, stroke), denervation (paraplegia), inflammation, abdominal sepsis, and extensive tissue trauma* (crush injury, burns) there is an *upregulation of mature and proliferation* of extrajunctional foetal nAChRs. In *patients with burns* this occurs after the first few days and may persist for months. In paraplegia, suxamethonium should be avoided *24 hours after injury until about six months (or longer) after injury*. As pointed out earlier, foetal receptor channels have a higher affinity for agonists and a two- to ten-fold longer open time. Stimulation of these receptors is consequently followed by much larger and longer ion fluxes, i.e. entry of Na^+ and exit of K^+. *This K^+ flux can more than double plasma K^+* concentrations leading to severe dysrhythmias and cardiac arrest. The hyperkalaemia is aggravated by an acidosis. *Suxamethonium must be avoided in patients with an underlying neuromuscular disease*.

- An increase in *masseter muscle tone* is rather commonly seen after the administration of suxamethonium administration and occurs in children as well as in adults. This is a normal reaction of the tonic muscles of mastication to suxamethonium. When it becomes excessive and prolonged it is referred to as masseter muscle spasm (MMS). In about 7% of cases, MMS is followed by malignant hyperthermia (MH), while the halothane-caffeine contraction test (the gold standard diagnostic test for MH) is positive in about 60% of patients who develop MMS, indicating that they are MH-sensitive (see Chapter 11).

- Allergic reactions

- Suxamethonium apnoea (See pharmacokinetics)

Given the side-effect profile of suxamethonium, the drug should probably be avoided whenever possible and be reserved only for emergency airway management.

Pharmacokinetics of suxamethonium (Table 2)

Suxamethonium is not metabolised by junctional AChE, but by BuChE, which hydrolyses it to the inactive metabolite succinylmonocholine (see Chapter 11). Hydrolysis of suxamethonium starts immediately after it has been administered. Therefore, only about 10% reaches the neuromuscular junction. The average adult has adequate BuChE to metabolise about 80 mg of suxamethonium per minute.

The effect of suxamethonium is terminated by diffusion of the drug out of the junctional cleft. The duration of paralysis is therefore a function of clearance of the drug from the plasma by BuChE. In the absence of normal enzyme or low enzyme levels, the kidneys excrete the drug. This can prolong paralysis to several hours. Decreased levels or activity of BuChE may be inherited, may occur physiologically (dilutional in pregnancy, dilutional and immature liver in neonates), in disease states (burns, liver failure, and kidney failure), cancer (effect of oncotherapeutic agents such as cyclophosphamide), and iatrogenic and toxic (neostigmine, plasmapheresis, hormonal contraception, organophosphates).

Blockade of the postjunctional nAChRs: The non-depolarising neuromuscular blockers
The NDMRs used in this country currently are pancuronium, alcuronium (seldom), vecuronium, atracurium, cisatracurium, mivacurium, and rocuronium.

The interaction of ACh with muscle nAChRs can be blocked by either *competitive antagonists* of ACh or by drugs that do not compete with ACh but change the receptor or plug the entrance to the channel, which will prevent binding of the agonist to the receptor (*channel block*). The latter group include some antibiotics, steroids, anticholinesterases, local anaesthetics, volatile anaesthetics, and intravenous anaesthetics. They are competitive antagonists at the ACh binding sites at the α subunits of the muscle nAChRs.

When the postjunctional nAChRs are blocked, ACh cannot interact with the two α units of the receptor, the Na^+ channels stay closed (resting state), and no nerve-evoked opening (active state) is possible. Whereas two ACh receptors are needed to activate a receptor by interacting with the two α subunits, *a single NDMR molecule can block the receptor*. Therefore, on a molar basis, (number of molecules of ACh and NDMR), blockade is preferred. Blockade is further promoted as ACh is continuously removed by junctional AChE. If AChE is inhibited, the number of ACh molecules at the receptors increases, the NDMR molecules are replaced, and two ACh can bind the α subunits. Due to a large receptor reserve muscle paralysis is only noticed when more than 75% of muscle nAChRs are occupied, while occupation of $\geq$ 95% causes complete paralysis.

A non-depolarising block is characterized by a decreased force of contraction, fade with TOF (Figures 6 and 7) and tetanic stimulation, and posttetanic facilitation. Fading indicates an effect on prejunctional neuronal nAChRs. The *snake venom α-bungarotoxin* is a selective *irreversible postjunctional* (muscle type nAChR) blocker with no prejunctional effect and causes non fade, except under certain conditions.

The doses presented in Table 1 are the ED95s (the doses causing a 95% decrease in the single twitch response) and the intubation dose (usually 1.5 to 2 times the ED95). *A follow-up dose is about 0.5 the ED95* and is given *about every 2.0 times the recovery time, i.e.* the time from the return of first posttetanic response, i.e. the posttetanic count = 1 to first of TOF.[viii] *(You must understand the concepts discussed in foot note[viii])*

[viii] When there is no TOF response after administration of a NDMR (e.g. after an intubation dose of a NDMR), it is called a *deep neuromuscular block*. That means that ACh released from the nerve ending cannot displace the competitive antagonist (NDMR) from the postjunctional nAChRs in response to nerve stimuli. However, if a large number of ACh molecules are released from the prejunctional fibre, they can momentarily displace some of the NDMR molecules from the receptors. This stimulus is a 50 Hz stimulus applied to the nerve for about 5 s and is called a *tetanic stimulation*. After about 3 s, the nerve is stimulated a frequency of 1 Hz (i.e. once per second) and the number of times the muscle contracts is counted. The number of times that the muscle responds after the tetanic stimulation is called the *posttetanic count,* which and depends on the number of NDMR molecules at the postjunctional receptors. Therefore, there is a delay from the appearance of the first posttetanic response to the return of the first TOF response. This time is called the *recovery time*. Once the first TOF stimulus is back, the block is called a *recovering block*.
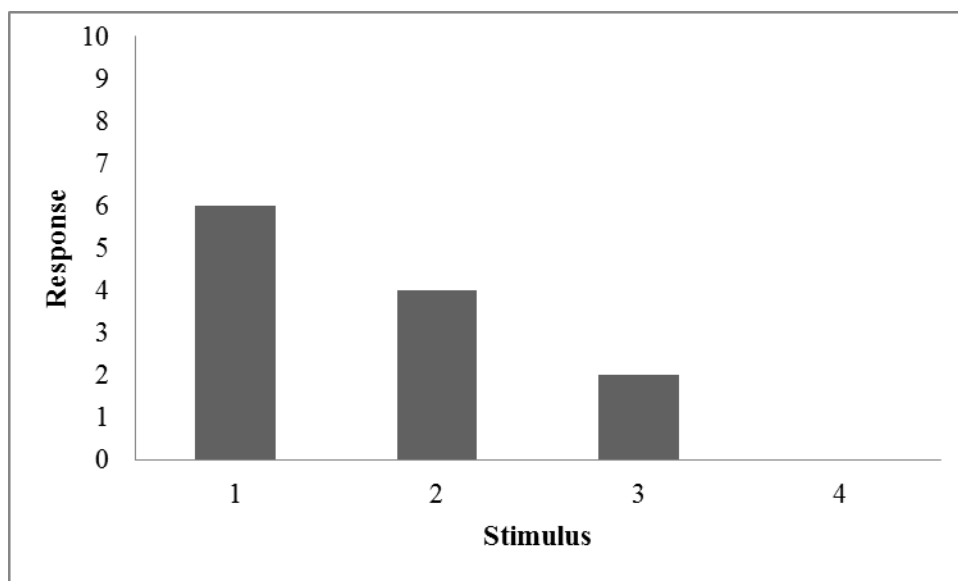
Figure 6 Fade of the train-of-four: The TOF count is 3/4 and the TOF% = 0/6 = 0%
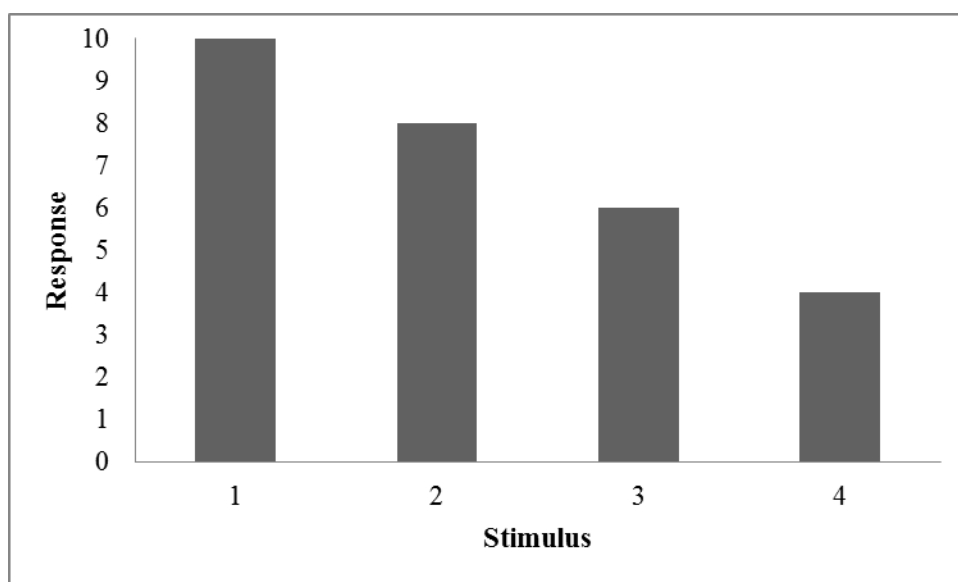
Figure 7 Fade of the train-of-four: The TOF count = 4/4 and the TOF% = 4/10 = 40%

Table 1 Pharmacodynamic profile of NDMR

Relaxant	ED95 (mg kg^{-1})	Intubation (mg kg^{-1})	Maximal block* (min)	Clinical duration † (min)	Recovery time† † (min)
Suxamethonium	0.30	1.0	0.8	7.6	-
Atracurium	0.23	0.4	2.4	38	10
Cisatracurium	0.05	0.1	7.7	46	10
Mivacurium	0.08	0.15	1.8	16	5
Vecuronium	0.05	0.1	2.4	44	10
Rocuronium	0.23	0.6	1.0	43	10
Pancuronium	0.07	0.08	2.9	86	35

*After intubation dose; †Recovery to 25% of T1; †† the time from the return of first posttetanic response to the first TOF response.

The NDMRs are divided into two groups: the benzylisoquinolines and the aminosteroids.

Benzylisoquinolines

This group was developed from the alkaloid extracted from the plant *Chondodendron tomentosum*, which was used by South American Indians in a poison applied to their arrows to immobilize animals. The oldest member of this group is d-tubocurarine. This drug has a very unfavourable pharmacodynamic and kinetic profile and is not in clinical use any more.

Atracurium and cisatracurium

Atracurium is a racemic mixture of 10 stereoisomers, each having a unique pharmacological profile. It does not possess any antimuscarinic or ganglion-blocking properties. It releases histamine when injected over a short time (< 30 s) and at higher doses (three times the ED95). This may cause urticaria, hypotension, tachycardia, and bronchospasm (avoid in asthmatic patients). The hypotensive effect is aggravated in patients treated with the H_2-receptor antagonist cimetidine but is attenuated by simultaneous administration of an H_1 and H_2 receptor antagonist.

Atracurium is cleared by Hoffmann elimination (spontaneous temperature and pH dependent degradation) and non-specific ester hydrolysis. Hoffmann elimination renders, amongst others, laudanosine. It is often put forward as the main clearance mechanism of atracurium. However, the concentration of laudanosine is the highest directly after injection of atracurium, which is incompatible with Hoffman elimination. It may also be that laudanosine is already present in the ampoule. The role of liver and kidney function, and acid-base in the clearance of atracurium is negligible. Ester hydrolysis plays an important role and is probably responsible for the slow production of the metabolite laudanosine.

Laudanosine is eliminated by the liver (80%) but also by the kidney (20%). However, it does not it accumulate in patients with fulminant liver failure, in patients receiving the drug during liver transplant, or anephric patients. Although laudanosine crosses the placenta, atracurium may be used safely during caesarean section. The epileptogenic effect of laudanosine is of no clinical significance.

Cisatracurium is the 1R *cis*-1′R *cis* isomer of atracurium and comprises 15% of the commercial atracurium product. *It is pharmacologically the cleanest muscle relaxant available.* The absence of isomers with short and long $t_{1/2}$s makes cisatracurium pharmacokinetically and -dynamically more predictable than the racemic mixture. It is about *four times more potent* than atracurium but has a much slower onset of action (Table 1). The *slow onset of action* makes it unsuitable when rapid relaxation is required. The compound has a favourable adverse effect profile; the minor increase in plasma histamine is not accompanied by any cardiovascular changes.

The *pharmacokinetics of cisatracurium is similar to that of atracurium*, but Hoffmann elimination is more important (77%), ester hydrolyses less important, and renal excretion responsible for about 16% of elimination. Therefore, clearance is slower in patients with renal impairment.

Mivacurium

Mivacurium is a short-acting relaxant with a *slow onset but a short duration* of action. The *short duration* of action of mivacurium can be ascribed to rapid clearance from the plasma. At clinical doses mivacurium has *no cardiovascular effects*. At high doses mivacurium releases histamine, which may cause some decrease in blood pressure and increase in heart rate.

Mivacurium is metabolised by BuChE at a rate of about 70% that of suxamethonium, into pharmacologically *inactive metabolites*. The metabolites as well as a small fraction of unchanged drug are excreted in urine and bile. As clearance mainly depends on BuChE activity, the duration of effect is *prolonged in patients with low BuChE enzyme activity* (avoid in Scoline apnoea; see Chapter 11). Human cholinesterase can be used to antagonize profound mivacurium-induced neuromuscular blockade in patients with abnormal BuChE activity.

Should a mivacurium block be reversed? If reversal is attempted at a *deep* mivacurium block, neostigmine not only causes

ACh accumulation at the NMJ, but will also inhibit further clearance of mivacurium. Therefore, neostigmine should only be administered once the mivacurium block has recovered to a TOF count of at least three out of four. The same applies to patients with low BuChE activity as they clear mivacurium purely by redistribution and excretion by the liver and kidneys.

The aminosteroid muscle relaxants

As was the case with many useful drugs, the aminosteroids had its origin from a plant. The poison malouetine was extracted from the African plant *Malouetia bequaertiana*. The basic structure of the steroidal NDMRs contains stereo-selective 1,2-diamino alcohol forming two ACh-like moieties, which interact with nAChRs. The one ACh-like moiety renders affinity for the *muscular nAChR* while the other is responsible for affinity at *muscarinic AChRs*.

Pancuronium

Pancuronium is the longest acting NDMR. About 75% of pancuronium is excreted *unchanged*; about 60% in the urine and about 15% in the bile. The remainder is deacetylated in the liver to the 3-OH, 17-OH, and 3,17-di-OH metabolites, which are excreted by the kidneys. The *main metabolite is 3-OH-pancuronium; it represents about 25% of the dose injected. This metabolite has a potency of about 50% but duration of action similar to that of the parent drug. Liver and kidney impairment* lead to significant *prolongation* of relaxation.

Pancuronium blocks M_2 *receptors*. This may explain the adverse effects of pancuronium, namely an increase in heart rate and increased peripheral and pulmonary vascular resistance. The increased blood pressure causes suppression of the baroreceptors, and subsequently a reduced sympathetic outflow and catecholamine levels. Pancuronium does *not release histamine. Pancuronium inhibits BuChE at clinical doses*, but the dose-response relationship is not linear and BuChE activity *remains within the normal range*.

Vecuronium

Vecuronium is a NDMR with an *intermediate duration* of action. It is a pharmacologically clean drug as it does *not release histamine*, does *not inhibit M_2 receptors*, and does *not affect ganglionic transmission*. The bradycardia observed in some patients is rather the effects of concurrently administered induction agents and opioids.

About *30% of vecuronium is excreted unchanged by the kidneys*. The rest is deacetylated in the liver. About 12% of vecuronium is metabolised to the *active metabolite 3-OH-vecuronium*. The *3-desacetyl metabolite has a potency of about 60% of vecuronium and* is mostly excreted by the *kidneys*. Therefore clearance of the *drug and its metabolites (including active metabolites) are decreased in the presence of impaired liver and kidney function*.

Rocuronium

Rocuronium is an aminosteroid with a fast onset (about 1 minute after 2 times the ED95) and an intermediate duration of action. At clinical doses, rocuronium does not cause histamine release or cardiovascular instability. Due to a vagolytic effect, higher doses may cause a tachycardia and an increase in blood pressure.

The metabolism of rocuronium is similar to that of vecuronium but has *no active metabolites*. Rocuronium is *cleared unchanged primarily by the liver* and excreted into the bile. About 33% is excreted unchanged in the urine over twelve to 24 hours. At a dose of 0.6 mg kg^{-1}, patients with end-stage renal failure show changes in both pharmacokinetics (lower clearance) and -dynamics (an increase in the duration of action).

Pharmacodynamic and pharmacokinetic spectrum of NDMRs: Potency, onset, duration, and recovery

The duration of neuromuscular blockade is dependent on drug physico-chemical characteristics (affinity) as well as on drug concentration in the junctional cleft (biophase). Biophase concentration is dependent on concentration in the plasma. *The degree of relaxation* depends on the fraction of

receptors blocked, which is dependent on affinity of the drug for the receptors and the concentration of the drug at the receptors. The limiting factor is affinity; on a molar base, a drug with low affinity (low potency) will block a smaller fraction of receptors. Effect size is therefore proportional to plasma concentration. Onset time, effect size, and offset time are, consequently also dependent on $t_{1/2}\alpha$, while recovery is influenced by $t_{1/2}\beta$ and all the factors that affect them. These factors include the presence of other anaesthetic drugs (intravenous and inhalational), depth of anaesthesia, age, co-existing disease, and treatment. These factors give rise to both pharmacodynamic and -kinetic interactions.

The pharmacokinetic spectrum of NDMRs (see Tables 1, 2, and 3)

- *The data regarding pharmacokinetics of NDMR reported in the literature are highly variable*. This may stem from different definitions of relaxation, different pharmacokinetic models used, the experimental circumstances (clinical or animal), and the background anaesthetic technique, i.e. volatile or intravenous agents. There are also age, gender, and ethnic differences, e.g. the duration of vecuronium is shorter in men than in women and that of rocuronium is longer in Chinese than in Caucasian patients. ***Therefore, careful neuromuscular monitoring is always advised***. The data presented in Tables 1, 2, and 3 should therefore be viewed in this light.

- Neuromuscular blockers are *hydrophilic* and are distributed mainly to hydrophilic compartments. Therefore, an *increase in extracellular water* increases the volume of distribution and/or a decrease in biotransformation and excretion (decreased clearance), and *prolongs the $t_{1/2}$ of NDMRs*. (Remember, $t_{1/2}\beta = (0.693 \times VDss)/Clp$.)

- Neuromuscular blockers are distributed mainly to hydrophilic compartments, namely blood and muscle (*small volume of distribution*). Some diseases cause a change in the fraction and distribution of the *body water component*. These include conditions where a large component of body mass is made up of oedema (heart, renal, and liver failure) or transcellular fluid (ascites). In patients with *poorly perfused tissue* (hypovolaemia, ischaemic limb), the volume of distribution is decreased and the doses must be reduced. In *obese patients* the fraction of lean tissue is smaller. Therefore, doses of NDMRs should be calculated according to a *adjusted body mass* and not the total body mass (see Chapter 17).

- *Infants* have a *larger volume of distribution* (larger extracellular fluid compartment) and immature liver *and kidney function*. These factors contribute to *resistance* (larger volume of distribution), *lower clearance* (*longer $t_{1/2}s$*) of muscle relaxants (Table 3). The pharmacokinetics of vecuronium and rocuronium in *children are similar to those in adults*.

- *In geriatric patients, the delayed onset,* as well as the *prolonged duration* of blockade, is completely explained by the *changes in pharmacokinetics*. In elderly patients, there is *more body fat* and a *less muscle*. This *increases the sensitivity* of patients to the effect of the same dose of NDMR *per total body mass*. The elderly have a decrease in *cardiac output and organ perfusion and function, resulting in decreased liver and kidney function* and drug clearance. The *increased circulation time* causes a *delay in the onset* of muscle relaxation (except rocuronium). The clearance of *atracurium is not affected* by age.

- *During pregnancy*, there is an *increase in total body water*, *blood volume*, *cardiac output*, and vital organ perfusion, but a decrease in *plasma protein* concentration. These differences decrease the sensitivity (larger volume of distribution) and *increase the clearance of NDMRs*. BuChE is *decreased* (haemodilution) and remains low during the puerperium, causing a *decreased clearance of suxamethonium*.

- Muscle relaxants are *transferred from the mother to the foetus*. Due to the *low concentrations of muscle relaxants that reach the foetus as well as the resistance of the foetus to relaxants*, clinical doses have *negligible effects* on the foetus when administered.

- *BuChE activity is decreased in the elderly. This causes* an increased *duration of action of suxamethonium and mivacurium*.

- The *onset and duration of action* of a relaxant is determined by perfusion of the neuromuscular cleft, and plasma drug concentration. Therefore, all *hypoperfusion states* delay the onset of effect and prolong $t_{1/2}s$ of NDMRs. The opposite is true for high cardiac output states.

- The *aminosteroids pancuronium and vecuronium have active metabolites*, which explain the high variability in response and reversal observed with these agents – especially with repeated or long-

term administration.

- ***Avoid the administration of combinations of muscle relaxants – especially relaxants from different groups, i.e. an aminosteroid plus a benzylisoquinoline***.
- Several anticonvulsants *induce liver enzymes*, which may contribute to the decreased sensitivity for NDMRs – especially aminosteroids, as they are more dependent on liver function for their clearance.
- **Therefore, careful neuromuscular monitoring is always advised**.

Table 2 Pharmacokinetic profile of muscle relaxants (You must have an idea of *****)

	Releases histamine*	**$t_{1/2}\beta$ (minutes)***	**Duration***	**PPB (%)**
Suxamethonium	**Yes**	**5 for 1 mg kg^{-1}**	**Short (about 5 min)**	20
Mivacurium	**Yes**	**18 (20)**	**Short (about 10 min)**	30
Atracurium	**Yes**	**21 (20)**	**Medium (about 30 min)**	80
Cisatracurium	**No**	**30**	**Medium (about 40 min)**	40
Vecuronium	**No**	**71 (70)**	**Medium (about 30 min)**	70
Rocuronium	**Yes**	**97 (100)**	**Medium (about 30 min)**	50
Pancuronium	**No**	**132 (130)**	**Long (about 60 min)**	90

$t_{1/2}\beta$, Elimination half-life; PPB, Plasma protein binding

Table 3 ED95 (mg kg^{-1}) in infants, children and adults (You must know **the adult ED95s**)*

Relaxant	**Infants**	**Children**	**Adults**
Suxamethonium	1.0	0.50	**0.30**
Atracurium	0.24	0.33	**0.20**
Cisatracurium	0.07	0.08	**0.07**
Mivacurium	0.13	0.14	**0.10**
Pancuronium	0.07	0.09	**0.07**
Vecuronium	0.05	0.08	**0.05**
Rocuronium	0.26	0.40	**0.35**

* ***When a follow-up dose is given, never give an intubation dose, but at the most 0.5 × ED95***.

The pharmacodynamic spectrum of NDMRs

- *Stereoisomerism* plays a role in the dynamics and kinetics of many drugs. The enantiomers have different pharmacological profiles (dynamic and kinetic), e.g. cisatracurium is about three times more potent than the racemic mixture of atracurium.
- *With NDMRs, potency appears to be inversely proportional to onset time*. A high dose of a weak relaxant, e.g. rocuronium, results in a high plasma concentration (many molecules) and therefore in the junctional cleft (*quicker onset*). However, the low affinity results in a higher dissociation constant from the receptor (*quicker recovery*).
- *Onset time to relaxation can be shortened*. As the onset time decreases with increasing numbers of molecules in the biophase, *higher doses* of any relaxant will shorten the onset time. However, high doses cause a much longer and unpredictable duration of relaxation and a higher incidence of side-effects.
- *The priming principle:* Priming the receptors by administering about 30% of the intubation dose about three minutes before and the remainder immediately after induction of anaesthesia shorten onset time. This technique may cause significant relaxation before loss of consciousness resulting in difficult breathing and swallowing and increase the risk of aspiration.
- Onset of effect can be hastened by *combining* NDMRs. Combining the properties of different drugs may lead to very potent (additive or synergistic) combinations. Not only may the onset time be shortened, but the degree and duration of effect are *significantly enhanced and unpredictable*. Therefore, *this technique is mentioned but not advocated.*
- Onset, depth, and recovery of relaxation are affected by *upregulation of muscle nAChRs*. This happens with immobilization, denervation, and burns. Resistance is characterized by slow onset, inadequate relaxation, and fast recovery of relaxation. *In burns patients a dose of rocuronium* 1.2 mg kg^{-1} to 1.5 mg kg^{-1} without priming is recommended for safe and rapid airway management.
- *The plasma concentration-effect relationships of muscle relaxants vary between different muscle*

groups. The sensitivity of the *adductor pollicis* is *similar to that of the muscles of the upper airway. The plasma concentrations of NDMRs to relax the larynx and diaphragm are about 1.7 times higher than that required to relax the adductor pollicis. With incomplete reversal of muscle relaxation coughing, deep breathing, and the ability to maintain an open airway is significantly impaired.* At an *adductor pollicis TOF ratio of < 0.90*, there is a large increase in misdirected swallowing and aspiration. *Therefore, a TOF ratio of 0.7 may be adequate for ventilation but function of the pharynx and upper oesophagus only recovers at an adductor pollicis TOF ratio of ≥ 0.90 (Figure 8).*

- *Hypothermia* effects *pharmacokinetics (slower clearance), and pharmacodynamics (more potent, lower ED95)*. During hypothermia but with central temperatures still > 34°C, mainly pharmacokinetic factors seem to be affected, resulting in an increased duration of action. *A decrease in body temperature from 36.5°C to 34.4°C more than doubles the duration of action*[1]. *Therefore, patients who need complete return of muscle strength postoperatively should have their airway protected and ventilation assisted until central temperature is > 36°C. The delayed reversal of neuromuscular blockade during hypothermia may be explained by the increased plasma concentrations of the relaxant.* During anaesthesia, the *set point* for vasoconstriction decreases to about 34°C. It can be accepted that adductor pollicis temperature reflects central body temperature when this is > 34°C. At lower central temperatures, the adductor pollicis temperature may decrease and monitoring may not represent the function of central warmer muscles. Therefore, *with central temperatures of 34°C to 37°C vasoconstriction does not contribute to a decreased adductor pollicis response and neuromuscular monitoring at adductor pollicis is reliable.* It is advised that *lower doses of relaxants* be administered and neuromuscular monitoring done, *even in mildly hypothermic patients.*

- *Neonates* have *foetal type nAChRs* in the *postjunctional and extrajunctional membranes*, contributing to *resistance to NDMRs*. The sensitivity of *infants* (after the neonatal period) and of adults to muscle relaxants are the same, while *children and young adults* (*larger muscle/fat ratios*) are resistant again. Infants (patients younger than 2 years) need *more suxamethonium* than children and adults because they have more muscular nAChRs. The *neonatal diaphragm is more resistant* than peripheral muscles *to NDMRs*. Despite these differences, the pharmacokinetics of vecuronium and rocuronium in children are similar to those in adults.

- *Pre-eclamptic patients may receive magnesium* and other anticonvulsants. Magnesium potentiates the effect of NDMRs.

- *The pharmacodynamic spectrum illustrates the need for careful neuromuscular monitoring.*
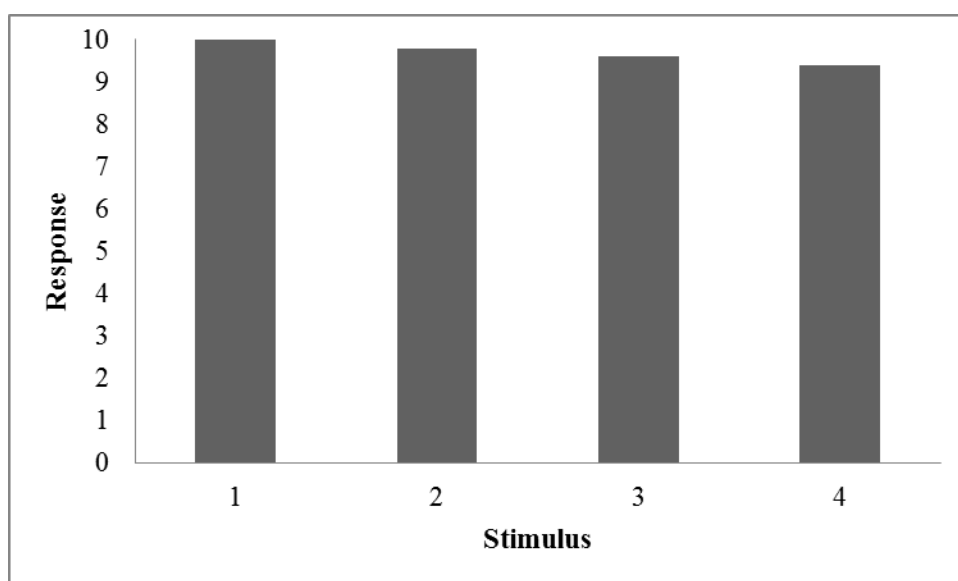
Figure 8 Fade of the train-of-four: The train-of-four ratio (TOF%) = 9.4/10 = 94%

Reversal of non-depolarising neuromuscular block

The effect of NDMRs can come to an end due to at least one of three mechanisms: it may wears off spontaneously, it can be competitively antagonised by increasing the concentration of ACh at the NMJ, or the aminosteroid NDMRs can be bound by sugammadex.

The success (*time* to reverse the block to a *TOF ratio of > 0.9*) of spontaneous recovery depends on the dose and pharmacokinetics of the particular NDMR. The success of competitive antagonism of the drugs depends on the relative concentrations of the drug and ACh in the NMJ. The concentration of ACh can be increased by inhibiting AChE. The dose of AChE inhibitor necessary to reverse a block depends on of the depth of the block; the deeper the block, the more ACh molecules are required to replace (antagonize) the NDMR. Since inhibitors of AChE have a ceiling effect, the success of reversal will depend on the concentration of the NDMR at the NMJ when the AChE inhibitor is administered.

NDMRs are often classified according to their duration of action, namely short-, intermediate- or long-acting. However, this classification must be applied to the individual patient; different pharmacodynamic and -kinetic factors influence duration of action. It has been demonstrated that two hours after a single intubation dose (about $2 \times$ ED95) of the so-called intermediate acting relaxants vecuronium and atracurium, about 10% of patients still had a TOF ratio of < 0.7, while about 30% had a TOF ratio of < 0.9. Therefore, monitored reversal of relaxants is strongly advised.

The cholinesterases

Two acetylcholinesterases (ChE) can hydrolyse ACh, namely the synaptic (AChE) and plasma/pseudo/butyril ChE (BuChE). ChE is a generic term for a family of serine hydrolases that belongs to the esterase family that hydrolyse choline esters. AChE is also known as acetylcholine acetyl-hydrolase, specific, true, genuine or type 1 ChE.

The reversible inhibitors of acetylcholinesterases

Esters of carbamic acid (NH_2-CO-O-R), namely neostigmine and pyridostygmine bind covalently to AChE (the enzyme is *carbamoylated*). The carbamoylated enzyme complex is far more resistant to hydrolysis than the *acetylated enzyme*. The $t_{1/2}$ of the *carbamoylated* enzyme for hydrolyses is not milliseconds, as is the case for the acetylated enzyme. The $t_{1/2}$ of the carbamoylated enzyme is 15 minutes to 30 minutes, which is much *shorter than the plasma $t_{1/2}\beta s$* of neostigmine (77 minutes) and pyridostigmine (112 minutes). Therefore, the carbamoylated enzyme prevents binding of ACh for *about 3 h (about 5×30 min = 150 min)*. The *onset of effect* of neostigmine is 6 minutes to 9 minutes, of pyridostigmine 16 minutes, and of edrophonium about 2 minutes.

It must be appreciated that NDMRs are not inactivated by the inhibitors of AChE (antiChEs) but only indirectly competitively antagonized at the NMJ. The result of competitive antagonism is dependent on the concentrations of the competing agents at the receptors. As is the case with all drugs, the antiChEs are redistributed and cleared from the plasma. During these processes, their concentrations decrease and AChE activity returns.

Carbamates used in clinical practice include the drugs with a *quaternary* amine group, namely *neostigmine* and *pyridostigmine* and those with a *tertiary* amine group, e.g. *physostigmine*. They are all quaternary at physiological pH. *Neostigmine* is mostly used as reversal agent of NDMRs. *Pyridostigmine* is used in the treatment of myasthenia gravis. *Physostigmine* is used in the treatment of toxicity of antimuscarinic drugs that cross the BBB, e.g. atropine. *Neostigmine and pyridostygmine also inhibit BuChE* and therefore *prolong the effect of suxamethonium*.

Fifty present of neostigmine and 80% of pyridostygmine is excreted *unchanged by the kidneys*. The renal excretion occurs by glomerular filtration and tubular secretion. This explains the two- to threefold increased $t_{1/2}\beta s$ of these drugs in patients with *renal failure*. Since the clearances of NDMRs are also decreased in patients with renal impairment, recurarization is unlikely.

Contrary to the compensated interaction of NDMR and reversible antiChEs in patients with renal failure, *liver failure affects reversal of NDMR with antiChEs*. Whereas hepatic failure does not affect the clearance or antiChEs significantly, the metabolism and excretion of NDMRs are often decreased. Therefore, *the $t_{1/2}\beta s$ of NDMRs are prolonged much more than those of the antiChEs*. This makes reversal of NDMRs more difficult.

Changes in the *hydrogen ion concentration* effects the *polarity of NDMRs*: *acidosis* protonates monoquaternary relaxants and thereby *potentiates their effect*, while already bisquaternary relaxants are not affected. A metabolic *alkalosis* and a *hypokalaemia* decrease the reversing effect of neostigmine. Respiratory acid-base derangements do not affect the action of neostigmine.

The initial volume of distribution for neostigmine is larger in *the elderly* than in younger patients. Similar to NDMRs, the effect of neostigmine and pyridostigmine is *prolonged* in the elderly.

Adverse effects of ChE inhibitors
The argument against routine reversal of NMB is motivated by the side-effects of antiChEs. The onset of the side-effects occurs in tandem with the reversal effect of these drugs:
- Anticholinesterases cause an *increase of acetylcholine at nicotinic and muscarinic receptors*. AntiChEs are *potent indirect parasympathomimetics*.
- Reversal of muscle relaxation *increases bronchial* tone. Although co-administration of *anticholinergic drugs may attenuate bronchoconstriction*, their efficacy is *unpredictable*. Several confounding factors, e.g. pain, airway irritation by the tracheal tube or suctioning, may trigger bronchospasm, especially during the time of lightened anaesthesia when muscle relaxation is reversed.
- The antiChEs cause *bradydysrhythmias*. The increase in heart rate after the administration of atropine plus neostigmine is more if the initial heart rate is low than when the initial heart rate is fast. *Ventricular fibrillation* has been reported in patients with *mitral valve prolapse* and patients with *prolonged QT syndrome*. It should however be kept in mind that several anaesthetic drugs, e.g. the vapours and antihistamines, may prolong the QT interval, especially in the presence of electrolyte disturbances, such as hypokalaemia and hypomagnesaemia. Both *atropine and glycopyrrolate* attenuate the cardiovascular effects of antiChEs. Anticholinergic drugs should be given cautiously in patients where a slow heart rate is preferred. Glycopyrrolate increases the heart rate less than atropine and is therefore is preferred in patients with ischaemic heart disease.
- The *gastrointestinal tract muscarinic effects* include increased salivation and motility. Although both *atropine and glycopyrrolate* attenuate the cardiovascular effects of antiChEs *neither prevents the intestinal effects of increased motility*. Neither neostigmine-glycopyrrolate nor neostigmine-atropine *causes postoperative nausea and vomiting*.

Prevention of the muscarinic effects of the antiChEs
Atropine or glycopyrrolate are commonly used. *Atropine* has an *onset* time of about *1 minute* and *duration* of effect of about *1 hour*. It is a *tertiary amine*, crosses the BBB, is anti-emetic, and can cause the central anticholinergic syndrome. *Glycopyrrolate* is a *quaternary amine*, does not cross the BBB, works within about 2 minutes, and also works for about 1 hour.

Foetal bradycardia has been reported when muscle relaxation was reversed with a neostigmine-glycopyrrolate combination, but not with neostigmine-atropine. Although neostigmine and glycopyrrolate are quaternary amines, they may cross the placenta. Neostigmine crosses the placenta more readily than glycopyrrolate. Being a tertiary amine, *atropine is preferred to glycopyrrolate when reversing a muscle relaxant with neostigmine during pregnancy*. Glycopyrrolate is preferred in patients with ischaemic heart disease, since it increases the heart rate less than atropine.

The *dose of atropine* is about 50% of the neostigmine dose and the *dose of glycopyrrolate* about 25% of the neostigmine dose (see below). The *anticholinergics must be given before edrophonium* because

of its short onset time, but can be given *simultaneously with neostigmine or pyridostigmine* because of their longer onset time.

Anticholinesterase-induced neuromuscular blockade
AChE is bound by anticholinesterases, such as neostigmine, pyridostigmine (reversible), and organophosphates (irreversible). The *increased junctional ACh* (agonist) can *displace a NDMR* from the receptors and terminate its action. *However*, if an AntiChE is administered *after spontaneous reversal* of a block, the increased ACh concentration at the NMJ causes a *depolarising, and desensitisation neuromuscular block*: The increased junctional ACh concentration causes a sustained occupation of the nAChRs and inactivation of the Na^+ channels. The receptors are therefore initially *activated (depolarising block) followed by insensitivity* to stimulation by ACh (desensitisation block) and the muscle remains paralysed. A desensitisation block is, like a depolarising block, characterized by absence of fade with TOF and tetanic stimulation.

Since omitting the reversal of residual NMB increases risk of residual paralysis and postoperative morbidity and mortality – even after the use of short-acting relaxants, *reversal of residual NMB is important*. However, *after recovery of neuromuscular function*, neostigmine markedly impairs upper airway dilator, genioglossus muscle (upper airway patency), and diaphragmatic function, which may cause airway obstruction, aspiration, and hypoventilation. Ideally, neuromuscular function should be monitored objectively and reversed only in the presence of demonstrable residual curarization, i.e. TOF ratio < 0.9.

When can a NDMR be reversed?

Since neostigmine (and pyridostigmine) has a plateau effect, reversal of NMB can only be attempted once recovery has started, otherwise the increased concentration of ACh in the NMJ may not be able to replace the still large number of NDMR molecules. Neostigmine can be administered __once the TOF count is at least 4/4__ (TOF% is still = 0).

The dose of antiAChE

The dose necessary to antagonize the neuromuscular block depends on the degree of residual curarization. However, the effect of the antiChE will reach a ceiling once all the enzyme molecules have been inhibited (carbamoylated) and additional doses will render no additional effect, *but can cause muscle weakness in reversed patients*. The ceiling dose of neostigmine is 70 μg kg^{-1}. The recommendations made regarding reversal of NDMRs with neostigmine are based on those by Kopman and Eikermann (Table 4).[11] Note that these recommendations *assume neuromuscular monitoring* – objective (quantitative) or subjective (palpation).

The *dose of neostigmine can be calculated from the TOF%* (see Figure 9). If the TOF% = 0% (i.e. TOF count ≥ 4/4), the dose of neostigmine is 50 μg kg^{-1}; if the TOF% ≥ 90%, no neostigmine is necessary; if the TOF% is, say 30%, the neostigmine dose is read off the graph (Figure 9) and is about 33 μg kg^{-1}, etc. It can also be calculated, e.g. at a TOF% of 30%, the dose is (50 μg kg^{-1})(90% – 30%)/90% = 33.3 μg kg^{-1}. (This graph assumes linearity of the dose-response – which is not necessarily the case.)

Table 4 Neostigmine dose (μg kg^{-1}) according to neuromuscular response

Objective response	Dose	Subjective response	Dose
TOF ratio > 90%	0	Four without fade	15 to 25
TOF ratio 40% to 90%	15 to 25	Four with fade	40
TOF ratio < 40%; count ≥ 4	25 to 50	Two to three	50
No response	Delay reversal	None	Delay reversal

Neutralization of non-depolarising blockers: Sugammadex
The cyclodextrin sugammadex forms a complex with aminosteroid NDMRs.

The irreversible inhibitors of ChE
These substances are the organophosphorus inhibitors. They are very toxic and phosphorylate or phosphonylate AChE and BuChE. These conjugates are extremely stable. BuChE is replaced by the liver within two weeks, while it will take months to re-establish AChE activity at synapses. When patients have been exposed to these agents the effect of suxamethonium is prolonged.
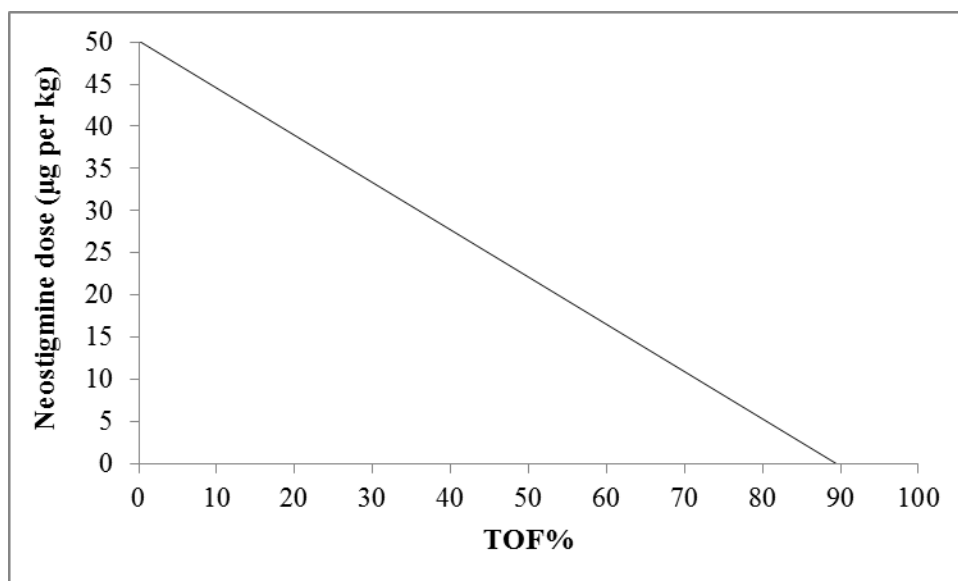
Figure 9 Neostigmine dose and TOF%. If the TOF% is > 90%, reversal is unnecessary.

Allergic reactions and muscle relaxants

Muscle relaxants can cause allergic reactions. In between 27% and 84% of intraoperative allergic reactions, NMBs were found to be the allergens. NMBs (benzylisoquinolines > aminosteroids) are known to cause a non-specific histamine release from mast cells, which can be prevented by slow injection.

Symptoms of *histamine release* are usually limited to flushing over the chest and neck. *Systemic reactions*, including hypotension and bronchospasm occur less commonly and then in patients with a history of atopy. *Severe hypersensitivity reactions* to NMBs are usually IgE-mediated, with *the onium group* as the main allergenic epitope. All NMBs contain at least one onium group and are responsible for *cross-sensitisation between NMBs*. The incidence of cross-sensitisation between NMBs in patients with proven hypersensitivity to a NMB, may be in the order of 60%, depending on testing protocols.

Although muscle relaxants are implicated in allergic drug reactions, several other substances can cause hypersensitivity reactions intraoperatively. These agents include active ingredients (anaesthetic and non-anaesthetic), stabilizers, preservatives, latex, disinfectants, colouring agents for sentinel node mapping, etc.

First-time receivers may also react to NMBs. This can be explained by *cross-sensitivity to onium ion-containing substances*, including chemicals in other medicinal, household, industrial and food substances. This may also explain the differences in the incidence of allergic reactions in *different geographical areas*; chemicals that are not available in one area or country will not expose those populations to cross-sensitisation. There is, for example a *higher incidence of anti-morphine and -suxamethonium antibodies in Norway* than in Sweden. In *Norway* the semis-synthetic morphine derivative *pholcodine* is marketed in cough mixtures. This potent allergen is not registered in Sweden. *Pholcodine is also available in South Africa*.

Effect of neuromuscular blockade on CNS activity

As has been discussed, vapours and intravenous anaesthetics decrease muscle tone. However, the inverse is also true; a neuromuscular block or muscle relaxants may potentiate the CNS activity of centrally active anaesthetic drugs. In addition to immobility, neuromuscular blockers may *contribute to analgesic and hypnotic components of the anaesthetic state*. The non-relaxant effects of neuromuscular blockers has been attributed to, firstly *deafferentation* due to a decreased proprioceptive input during muscle relaxation, and secondly to *effects of neuromuscular blocker in the brain and spinal cord*.

Effects of non-neuromuscular blocker anaesthetics and related agents on nAChRs
Both inhalational and intravenous anaesthetic agents decrease neuromuscular transmission through actions on the muscle nAChR. The mechanism of these inhibitions includes channel block and allosteric inhibition.

Inhalational anaesthetics
At clinical and subclinical concentrations of enflurane, halothane, isoflurane, methoxiflurane, and N_2O *potentiate the effect of NDMRs through an action at the NMJ*.

The mechanisms of this effect include allosteric change of the receptor channels, channel kinetics, prejunctional effects, and CNS effects. Sevoflurane potentiates the effect of rocuronium not only through a postsynaptic mechanism, but also demonstrates a *prejunctional effect* at the NMJ, producing fade to train-of-four stimulation. Clinical concentrations of desflurane attenuate muscle potentials after central stimulation, preferentially through *inhibition at spinal cord level*, namely at transmission from both corticospinal to α motor neurons and at interneuron synapses.

Intravenous anaesthetic agents
Intravenous anaesthetic agents attenuate nAChR channel activity in a way similar to that of inhalants, namely *channel inhibition*.

The effects of these agents also appear to be *related to their potency*. Propofol decreases the open time of the channel. The differences between anaesthetic agents regarding channel block is ascribed to the rate at which the anaesthetics bind to, and then dissociate from the receptor. *Ketamine* interacts with the nAChR of mouse muscle at subanaesthetic concentrations. Experimental data suggest that ketamine reduces neuromuscular transmission by non-competitive inhibition of NMDA receptors at the NMJ. Ketamine also prolongs the phase I and phase II neuromuscular blocks of suxamethonium.

Magnesium
The neuromuscular blockade observed in patients receiving $MgSO_4$ is ascribed to pre- and/or postsynaptic inhibition. Magnesium prevents ACh release from the nerve terminal. The effect of magnesium is utilized clinically; a small non-relaxant dose of NDMRs before the main dose expedites relaxation (*priming principle*). *Magnesium shortens the onset time of vecuronium*. At an ionised whole blood magnesium concentration of 1.2 mM (corresponding to a plasma level of about 1.7 mM), the *duration of action of cisatracurium* is nearly doubled. Similar effects have been demonstrated with vecuronium, mivacurium, and rocuronium. Administration of *$MgSO_4$ after recovery from neuromuscular block* causes recurarization enough to compromise ventilation. Magnesium also *attenuates the fasciculations* following administration of suxamethonium (*taming principle*).

Antibiotics
Several antibiotics have been implicated in potentiating neuromuscular blockade. Although these results were obtained at supratherapeutic concentration of these antibiotics, these side effects may become *clinically relevant when they are co-administered with NDMRs or when the clearance of these drugs are decreased*, e.g. in patients with hepatic failure, renal failure, myasthenia gravis or the myasthenic syndrome, and hypocalcaemia.

Conflicting mechanisms have been put forward for these effects, which probably point to different mechanisms for different groups of antibiotics, members of the same group of antibiotic do not demonstrate a uniform effect, and many of these findings are from *in vitro* studies where supraclinical concentrations were used.

Gentamycin blocks prejunctional nAChRs, reducing calcium-dependent ACh release from the motor nerve terminals, which potentiates a non-depolarising block. This effect is antagonized by neostigmine, which increases ACh concentrations in the neuromuscular cleft, and by calcium, which stimulates ACh release from the nerve terminal vesicles. The block caused by gentamycin is sometimes reversed by neostigmine and usually by calcium.

Clindamycin blocks prejunctional release of ACh, but also *enters open channels at the postjunctional nAChRs* (*channel block*), which *enhances non-depolarising block*. Since ACh and calcium open the postjunctional channels, *clindamycin-induced block is enhanced by neostigmine and calcium.*

Lithium and neuromuscular block
Being an alkali metal, lithium chemically *resembles sodium and potassium*. However, its smaller ionic radius, large sphere of hydration, and high charge density, makes it functionally *closer to calcium and magnesium*. Lithium *may potentiate the effect of NDMRs*.

Anticonvulsants
Anticonvulsant therapy is often complicated by muscle weakness. This may be ascribed to *prejunctional inhibition* of release of ACh or postjunctional NDMR-like nAChR blockade. The weak neuromuscular blocking properties of anticonvulsants may induce up-regulation of postjunctional nAChRs. Patients on *long-term phenytoin therapy clear vecuronium at twice the rate* found in normal patients. They also need four- to fivefold vecuronium concentrations to maintain neuromuscular block than controls. Patients on phenytoin therapy also *recover about 30% faster* from a rocuronium block than controls.

On the other hand, patients on chronic anticonvulsant therapy may have an *increased sensitivity to suxamethonium*. The effect of anticonvulsants on depolarising and non-depolarising block may partly be explained by *up-regulation of postjunctional muscle nAChRs*.

If a muscle relaxant shows an unusually prolonged effect, drug interactions must be considered. In circumstances where the precise drug or mechanism of interaction is unclear, it is safer to ventilate the patient until the block has reversed spontaneously, than to attempt reversal with more neostigmine or calcium.

Intracellular calcium and muscle tone (See Chapter 11)
Dantrolene decreases muscle strength by decreasing intracellular availability of calcium. (See masseter muscle spasm, malignant hyperthermia, and dantrolene, Chapter 11.)

The ideal muscle relaxant
After the discussion about anaesthetic drugs that effect muscle tone, it should be clear that the ideal muscle relaxant will have the following characteristics:
1. Non-depolarising
2. Predictable and small variability in effect
3. Ability to block muscle groups selectively
4. Rapid onset and recovery
5. Appropriate duration
6. No cardiovascular side-effects
7. No histamine release
8. No drug interaction
9. Non-cumulative: no organ- and enzyme-independent clearance, no active metabolites
10. No nervous system effects (ICU use)
11. No direct muscular effects (ICU use)
12. Ready-for-use solution stable at room temperature

The compound that fulfils these requirements will probably be a highly hydrophilic inhaled agent, which is minimally metabolised.

CHAPTER 9

LOCAL ANAESTHETICS AND AN INTRODUCTION TO REGIONAL ANAESTHESIA

Key points
- Classification of local anaesthetics
- Uses of local anaesthetics
- Pharmacokinetics
- Potency of local anaesthetics
- Toxicity of local anaesthetics

In contrast to general anaesthetic agents that anaesthetise the whole body, local anaesthetics are applied to a selected area, and thereby anaesthetise a limited part of the body.

Classification of local anaesthetics
Local anaesthetics are classified into two groups, namely the amides and the esters (Table 1).

Table 1 Classification of local anaesthetics

Amides	Esters
Lignocaine (Xylocaine, Xylotox)*	**Cocaine***
Bupivacaine (Marcaine)*	Chloroprocaine
L-bupivacaine (Chirocaine)	Procaine
Ropivacaine (Naropin)*	
Prilocaine (with lignocaine in EMLA, Topla cream)*	
Mepivacaine (Carbocaine)	
Tetracaine	
Etidocaine	

 *Frequently used

Pharmacokinetics of local anaesthetics
Absorption into the circulation depends on:
- *Site of injection*: A site with close association between nerve and blood vessel are more likely to absorb more local anaesthetic. In descending order of absorption, the following site will yield higher plasma level of local anaesthetic drug: Intercostal > caudal > epidural > brachial plexus > spinal.
- *Physico-chemical properties*: Plasma levels are lower when the local anaesthetic drug is more lipid soluble, more highly protein bound i.e. more potent, e.g. bupivacaine is more tissue-bound than lignocaine.
- *Addition of vasoconstrictors* such as adrenaline or noradrenaline slows absorption of local anaesthetics into the circulation. This lowers the drug concentrations in the plasma and, therefore the risk of toxicity. It also prolongs the duration of the block. Vasoconstrictors have a much larger effect on less tissue-bound local anaesthetics, such as lignocaine, as opposed to bupivacaine, which is not much influenced by addition of a vasoconstrictor. ___Remember, never inject a vasoconstrictor-containing solution into organs with end-arteries, i.e. the digits (fingers and toes) and the penis.___

Lignocaine works for about 60 minutes, while bupivacaine works for 3 h to 4 h.

Metabolism
Amides are metabolized in the liver by *amidases*, whereas the *esters* are hydrolysed by *pseudo-cholinesterase. The metabolites are eliminated by the kidneys.*

Structure-activity relationship
The chemical and physical make up of individual drugs have profound influence on the potency, onset, and duration of action of each drug (Table 2).
- *Lipid solubility* (the ability of the drug to penetrate lipid membranes). The higher the lipid solubility, the more potent the drug, the longer the duration of action, but the slower the onset of action.
- *pKa* (the pH where 50% of the drug is ionised). The local anaesthetics are bases. The higher the pKa, the slower the

onset of action.
- *Protein binding* (the ability to bind to tissue protein, including the receptors). The higher the protein binding, the longer the duration of action.
- *Isomerism* (the spatial structure of the molecule existing in more than one form). L isomers are more potent than, and less cardio toxic than R isomers

Table 2 Physico-chemical properties of local anaesthetics (You must have an idea of *)

	Lipid solubility	pK$_a$	% Protein binding	Potency*
Esters				
Cocaine	0.6	8.7	5.8	**1**
Procaine	0.6	8.9	5.8	**1**
Tetracaine	80	8.6	75	**6**
Amides				
Lignocaine	2.9	7.7	64	**4**
Ropivacaine	6.1	8.1	94	**3.5**
Bupivacaine	27	8.1	95	**16**
L-bupivacaine	27	8.1	95	**16**
Etidocaine	141	7.1	94	**16**

From Table 2 it can be seen that
- *Bupivacaine* is a *long-acting potent drug* with a slow onset, and is preferred for regional anaesthesia and analgesia that must last for hours.
- *Lignocaine* is *shorter-acting less potent drug* with a rapid onset, and is preferred for procedures of shorter duration.

Nerve anatomy and effect of local anaesthetics
- *Diameter*: large diameter nerves are more difficult to block.
- *Myelination*: non-myelinated nerves are easier to block than myelinated nerves.
- *Activity*: nerves with high impulse traffic are blocked easier than low activity nerves.
  Therefore:
  o Aδ (myelinated) conduct fast (sharp) pain and temperature sensation.
  o C fibres (non-myelinated) conduct slow (visceral) pain (drC fibres) and autonomic impulses (sC fibres). These fibres are very sensitive to local anaesthetics and the area blocked is often larger than the area blocked for fast pain. Pain and temperature are conducted along the same tracts. These tracts are the spinothalamic tract.
  o *Sensation of vibration, pressure, and proprioception* are conducted in thicker myelinated Aβ fibres and are the last sensations to disappear. Proprioception, pressure, and touch are conducted in the dorsal columns of the spinal cord.
  o Motor fibres are myelinated Aα fibres and may stay intact with low concentration of local anaesthetics last.

Pharmacodynamics of local anaesthetics
Mechanism of action
- Normal impulse conduction rely on the depolarisation of nerve tissue by means of Na$^+$ influx through ion specific channels (Figure 1).
- The *non-ionised fraction* (N) of the local anaesthetic drug crosses the cell membrane of the nerve (Figure 2).
- Since intracellular pH (6.9) is less than plasma pH (7.4), the local anaesthetic will become ionized again (N-H$^+$). The protonated drug enters the inside of the Na$^+$ channel preventing the influx of sodium ions, and thus depolarisation and impulse propagation (Figure 3).
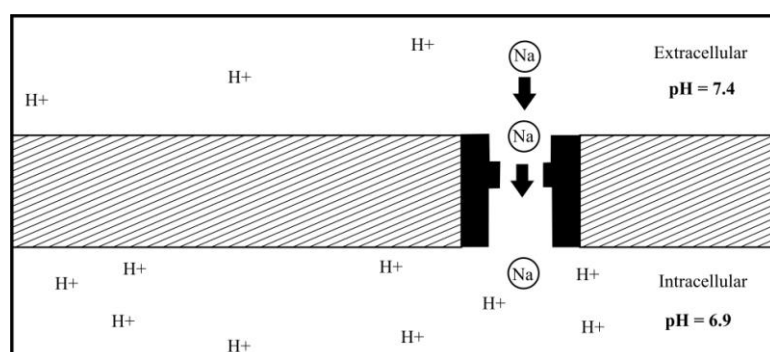
Figure 1 Depolarization of neuronal membrane
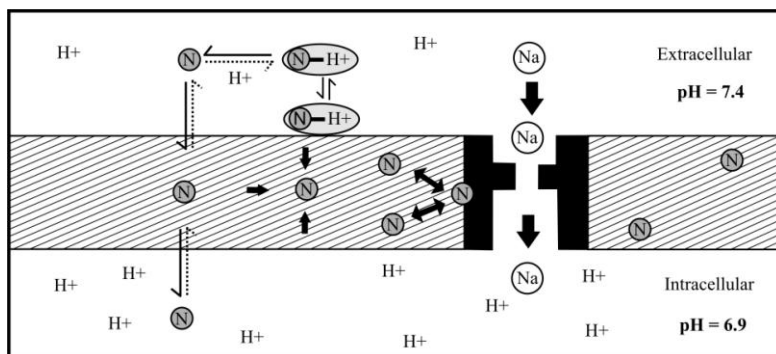
Figure 2 The non-ionised local anaesthetic crosses the membrane
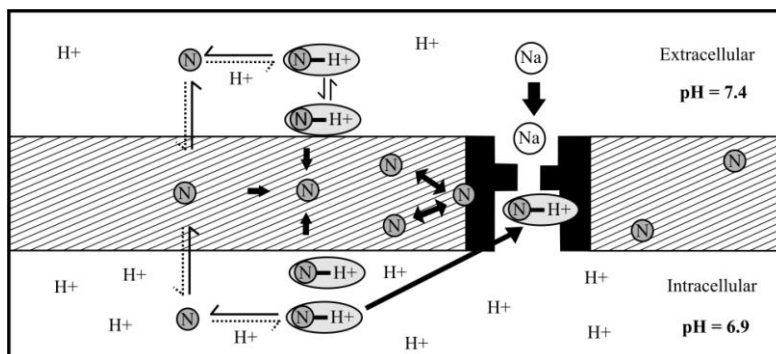
Figure 3 Protonated drug enters the inside of the Na$^+$ channel preventing the influx of sodium ions

Toxicity of local anaesthetics
NOTE: The concentrations of local anaesthetic drugs are often expressed as %. To convert % to mg per ml, you multiply by 10 to get mg per ml:
Example:
A 2% lignocaine solution contains 2 g per 100 ml = 2 000 mg per 100 ml = 20 mg per ml
A 0.5 % bupivacaine solution contains 0.5 g per 100 ml = 500 mg per 100 ml = 5 mg per ml

Local anaesthetics drugs can cause *three classes of toxicity*:
- *Local nerve toxicity*, which may present with:
  o   Direct neurotoxicity
  o   Transient neurological symptoms
- *Myotoxicity* with direct muscle damage in the area of infiltration, e.g. the extraocular muscles in eye blocks.
- *Local anaesthetic systemic toxicity (LAST)*
  o   Central nervous system
  o   Cardiovascular system

Guidelines regarding local anaesthetic systemic toxicity (LAST) have been reviewed and recommendations have been made by the American Society of Regional Anesthesia and Pain Medicine and are summarised here.[12]

Systemic toxicity can present acutely or after some time following administration of the local anaesthetic. An acute rise in blood concentration happens with intravenous injection and the signs of toxicity are observe within seconds of injection. Gradually increasing blood levels occur after injection of drug for regional anaesthesia. In those cases, toxicity presents after a longer time (20 minutes to 30 minutes).

Classic LAST usually presents as a progression of subjective symptoms of *CNS excitement* (agitation, auditory changes, and metallic taste) or abrupt onset of psychiatric symptoms, followed by seizures.

This is *followed by CNS depression* (drowsiness, coma, or respiratory arrest). Near the end of this continuum, *initial signs of cardiac toxicity* (hypertension, tachycardia, or ventricular arrhythmias) are *followed by cardiac depression* (bradycardia, conduction block, asystole, decreased contractility) (Table 3).

Bupivacaine overdose may present with refractory ventricular fibrillation or asystole. Ropivacaine and levo-bupivacaine are less cardiotoxic than bupivacaine. Although the more potent local anaesthetics are more cardiotoxic than less potent anaesthetics at the same blood concentrations, *once high concentrations are reached, local anaesthetics of all potencies can cause severe myocardial depression. It should also be remembered that local anaesthetics are not only capable of causing cardiac arrest before seizures or even in the absence of seizures.*

Diagnosing LAST
There is an *overall variability of LAST signs and symptoms, timing of onset, and association with various disease states.* Therefore, the anaesthetist must maintain a low threshold for diagnosing LAST in patients with atypical or unexpected presentation of CNS or cardiac signs and symptoms after receiving more than a small dose of local anaesthetic. The following atypical or unexpected presentation of LAST can be expected:

- *Simultaneous* presentation of CNS and cardiac toxicity.
- Cardiac toxicity *without prodromal* signs and symptoms of CNS toxicity.
- *The timing* of LAST presentation is variable: Immediate (< 60 s) presentation suggests intravascular injection of local anaesthetic with direct access to the brain, whereas presentation that is delayed for 1 minute to 5 minutes suggests intermittent intravascular injection, lower extremity injection (longer circulation time), or delayed tissue absorption. Since LAST can present > 15 minutes after injection, patients that have received potentially toxic doses of local anaesthetic should be closely monitored for at least 30 minutes after injection.
- Variation in the presentation of LAST may occur more frequently in patients with cardiac, neurologic, pulmonary, renal, hepatic, or metabolic disease. Heightened vigilance is also warranted in the very young and the elderly.

Table 3 Symptoms and signs local anaesthetic toxicity

Central nervous system	Cardiovascular
Initial phase	*Initial phase*
Circumoral paraesthesia	Hypertension
Tinnitus	Tachycardia
Confusion	
Excitatory phase	*Intermediary phase*
Convulsions	Myocardial depression, decreased cardiac output, hypotension
Depressive phase	*Terminal phase*
Decreased consciousness followed by coma	Peripheral vasodilatation, severe hypotension
Respiratory arrest	Sinus bradycardia, conduction defects, ventricular dysrhythmias, asystole

LAST depends on:
- *The dose* (dose = concentration × volume), i.e. using a large *volume* of a diluted solution, or a smaller dose of a *concentrated* solution. The recommended dose must never be exceeded. Mixtures of local anaesthetics have additive toxic effects. Therefore, if the maximum dose of one anaesthetic has been reached, it does not mean that you can switch to another anaesthetic.
- In adults, *body mass and body mass index* correlates poorly with plasma levels of local anaesthetics. In children, the correlation is better. Block site, intrinsic vasoactivity of the local anaesthetic, use of vasoconstrictors, and patient co-morbidity are more important predictors of plasma levels than body mass or body mass index. *Therefore, the doses of local anaesthetics must always be calculated according to lean body mass.*

- *Area of injection*: The more vascular the area into which the drug is injected, the better the systemic absorption will be, e.g. intercostal > caudal > epidural > brachial plexus > spinal.
- *Vasoconstrictor*: If a vasoconstrictor is added to the local anaesthetic, the absorption of *less lipophilic* local anaesthetics is delayed. Therefore, the maximum dose of lignocaine (hydrophilic) with adrenaline is about 7 mg kg^{-1}, while the maximum dose of lignocaine without adrenaline is about 4 mg kg^{-1}. On the other hand, the dose of the *lipophilic drug* bupivacaine is the same with and without vasoconstrictor, namely 2 mg kg^{-1}. The vasoconstrictor most commonly used is adrenaline 1:200 000 (5 µg ml^{-1}). Remember, *vasoconstrictors are often absorbed into the circulation* causing tachycardia and hypertension.
- *Type of drug*: The more potent the drug, the more toxic, e.g. lignocaine (less potent) vs. bupivacaine (very potent). The more potent the drug, the sooner cardiovascular collapse follows neurological signs, e.g. the neurological:cardiovascular ratio for lignocaine is about 1:7, but about 1:3 for bupivacaine.
- S*imultaneous use of anticonvulsant sedatives*: The neurological signs are clouded or suppressed by sedatives with anticonvulsant properties, e.g. benzodiazepines and propofol. Therefore, neurological signs, e.g. convulsions will be absent in a patient who has received midazolam. In this patient, the first sign of toxicity may be cardiovascular collapse.
- *Dose reductions are even more important in frail patients*, i.e. malnutrition and patients with abnormal vital organ function (ischaemic, heart disease, cardiac failure, abnormal cardiac conduction abnormalities, lung disease, renal failure, liver failure, metabolic disease, epileptics), the elderly (> 70 years), and the young (< 4 months).

*Toxicity of local anaesthetics **can be prevented** by limiting high peak plasma levels*:
- There is *no single measure* that can prevent LAST.
- Do not exceed the *recommended maximum dose*. Use the lowest effective dose of local anaesthetic (dose = volume × concentration).
- Use a *vasoconstrictor* (but not in toes, fingers, penis, and intravenous blocks).
- Inject local anaesthetics slowly, attend to needle movement, and aspirate repeatedly during the injection of large volumes. Remember that aspiration through needles and catheters may fail to identify intravascular injection in at least 2%
- Use a *test dose* for epidural anaesthesia: The test dose consists of 50 mg of lignocaine plus adrenaline 15 µg. This solution is injected ***after an epidural catheter has been placed***. It is supposed to exclude subarachnoid and intravascular placement or migration of the epidural catheter. If the tip of the catheter is in the subarachnoid space, a dense block with loss of motor function will develop in the blocked area within 5 minutes. If the tip of the catheter is in an epidural vein, the adrenaline in the solution causes an increase in heart rate of at least 10 per min or an increase in blood pressure of at least 15 mm Hg within 15 s.
- When injecting potentially toxic doses of local anaesthetic, use of an *intravascular marker* is recommended. Although adrenaline is an imperfect marker and its use is open to physician judgement, its benefits likely outweigh its risks in the majority of patients:
  o Intravascular injection of adrenaline 10 µg to 15 µg in adults produces a heart rate increase of 10 per min to 15 per min and/or an increase in systolic blood pressure of about 15mm Hg systolic blood pressure increase in the absence of β blockade, active labour, advanced age, or general/neuraxial anaesthesia. Fentanyl 100 µg produces sedation if injected intravascularly in labouring patients.
  o Appropriate subtoxic doses of local anaesthetic can produce subjective symptoms of mild systemic toxicity (auditory changes, excitation, metallic taste, etc.) in unpremedicated patients.
- *Administer the local anaesthetic in incremental doses of 3 ml to 5 ml* with the time between increments not less than one circulation time (about 45 s, but longer with lower extremity blocks). When using a fixed needle approach, e.g. landmark, paraesthesia-seeking, or electrical stimulation, the time between aliquots should be one circulation time (30 s to 45 s).
- *Ultrasound guidance* of regional anaesthesia (UGRA) may reduce the frequency of intravascular injection, but actual reduction of LAST remains unproven in humans. Individual reports describe LAST despite the use of UGRA.

- *Monitor the patient* for at least 30 minutes after the local anaesthetic has been administered.

*Recommendations for **treatment** of LAST*12

- All necessary equipment and drugs for resuscitation must be available before the regional anaesthetic is administered.
- Toxicity must always be anticipated, and the patient must be constantly monitored for symptoms. Keep verbal contact with the patient (small talk). If signs and symptoms of LAST occur, prompt and effective airway management is crucial to preventing hypoxia and acidosis, which are known to potentiate LAST.
- Maintain ventilation and oxygenation. (Hypoxia is the biggest danger.)
- *Convulsions* that continue for longer than 15s to 20 s should be terminated by administering intravenous thiopentone 2 mg kg^{-1} to 3 mg kg^{-1}, *midazolam* 0.2 mg kg^{-1}, or diazepam 0.1 mg kg^{-1}. Although propofol can stop seizures, it can cause further cardiovascular compromise. Early use of lipid emulsion for treating seizures may be considered.
- If seizures persist despite benzodiazepines, small doses of succinylcholine or similar neuromuscular blocker should be considered to minimize acidosis and hypoxemia. *Suxamethonium also facilitate intubation*. Remember, muscle relaxation does not stop seizure activity, and once this has been given the patient has to be intubated and ventilated.
- *If cardiac arrest occurs*, we recommend standard Advanced Cardiac Life Support with the following modifications:
  o If adrenaline is used, small initial doses (10 μg to 100 μg boluses in an adult) are preferred.
  o Vasopressin is not recommended.
  o Avoid calcium channel blockers and β-adrenergic receptor blockers.
  o If ventricular arrhythmias develop, amiodarone is preferred; treatment with local anaesthetics (lignocaine or procainamide) is not recommended. *Ventricular fibrillation* is extremely resistant to resuscitation.
- *The local anaesthetics are lipophilic drugs and can be bound by an intravenous lipid emulsion such as Intralipid.*^{ix} Lipid emulsion (LE) therapy consist of the following:
  o Administer a *20% LE* at the *first signs of LAST*, after airway management. The dose is *1.5 mL/kg bolus*, followed by an *infusion of 0.25 ml kg^{-1}min^{-1}*, continued for at least *10 minutes after circulatory stability has been re-established*. If circulatory stability is not reached, the *bolus must be repeated* and the *infusion increased* to 0.5 ml kg^{-1} min^{-1}. Approximately 10 ml kg^{-1} over 30 minutes is recommended as the upper limit for initial dosing.
  o *Propofol emulsions are not substitutes* for lipid emulsion.
- *If lipid emulsion and vasopressor therapy fail*, institution of *cardiopulmonary bypass* (CPB) should be considered. Since there can be considerable delay in beginning CPB, it is reasonable to notify the closest facility capable of providing it when cardiovascular compromise is first identified during an episode of LAST.^{x}

Other dose-dependent and dose-independent systemic side effects of local anaesthetics

- Neurological injury occurs in about 7/10 000 neuraxial (epidural and intrathecal; see below) blocks. It causes *transient paraesthesiae* and mild motor weakness. Hyperbaric lignocaine 5% has been removed from the market since it was implicated in *cauda equina* syndrome after *continued intrathecal anaesthesia*.
- Although *anaphylaxis following administration of local anaesthetics* is rare (see Chapter 12), this complication must be kept in mind. However, patients may be allergic to the metabolites of the ester local anaesthetics, namely para-amino-benzoic acid (PABA). Preservative are added to multidose preparations of local anaesthetics. These preservative are hydroxybenzoates such as

---

^{ix} *Intralipid* is a lipid emulsion consisting of soy oil, egg phospholipids, and glycerol. It is the main component of total parenteral nutrition and is the solvent in propofol injection. Intralipid is an effective antidote for LAST, particularly the potent more lipophilic ones such as bupivacaine. *Intralipid* acts as a lipid sink (reservoir for lipid soluble drugs) by drawing bupivacaine from plasma, which decreases the free fraction. The high lipid concentration *forces FFA into myocytes*, which increases substrate for energy production and improving the susceptibility for resuscitation.
^{x} I think this recommendation is a good idea but highly unpractical.

methyl- and propylparabene, which are structurally similar to PABA. ___Remember, these preservative-containing preparations should not be used for intravenous blocks (Chapter 26), epidurally, or intrathecally___.

- Prilocaine is used in combination with lignocaine in EMLA and Topla cream and discs for topical anaesthesia. The metabolites of *prilocaine and benzocaine* can cause *methaemoglobinaemia.* Therefore, the maximum recommended doses of these drugs indicated in the package inserts should not be exceeded. The *treatment of methaemoglobinaemia* is methylene blue 1 mg kg^{-1} intravenously. The *maximum dose of prilocaine* is 6 mg kg^{-1}.

- *Cocaine* is often used intraoperatively during nasal procedures (rhinoplasty, endoscopic sinus surgery). It is used, not as much as a local anaesthetic, but as a vasoconstrictor. These procedures are usually done under general anaesthesia, but some surgeons prefer conscious sedation. *Cocaine is usually supplied as a 10% solution. The maximum dose of topical cocaine is 2 mg kg^{-1}.*

Cocaine is an indirect sympathomimetic in the central and peripheral nervous system by blocking noradrenaline and dopamine re-uptake. The drugs is administered on well-perfused mucous membranes and is therefore absorbed very well. The *toxic effects of cocaine* are initially central nervous system (euphoria, paranoia, involuntary motor activity, mydriasis, and seizures) and cardiovascular stimulation (myocardial ischaemia, tachycardia and hypertension). Since cocaine *can deplete noradrenaline stores in the sympathetic nervous system, cardiovascular collapse with cardiac decompensation and hypotension follows.*

Cocaine has a t$_{1/2}$ of 75 minutes. Therefore, the *most important management of intraoperative toxicity is to stop administration of the drug* (remove cocaine-soaked swabs) once signs suggestive of toxicity is observed. Tachycardia and hypertension can be treated with *short-acting α and β blockers and nitrates*, but only with *close cardiovascular monitoring*, since resistant cardiovascular collapse can occur.

INTRODUCTION TO REGIONAL ANAESTHESIA

___Regarding regional anaesthesia and analgesia, there are some important issues. Before doing a neuraxial block for analgesia or anaesthesia, all the following must be complied with:___
- **You must have been** *trained to perform the procedure* **and to** *manage complications***.**
- **The most important patient factor for neuraxial analgesia and anaesthesia to succeed is an** *informed, motivated, and cooperative patient***.**
- **The** *procedure must be explained to the patient***, including what it entails, other options, and possible complications. This patient must** *sign informed consent* **for the procedure.**
- **It must only be done in a** *well-equipped unit***: immediate availability of equipment for CPR, i.e. oxygen, suction, a bed that can be tilted, defibrillator, airway management, and drugs.** *Minimal monitoring* **requirements include blood pressure (cycling on 1 minute), ECG and pulse oximetry.**
- **Well-trained, motivated and reliable** *staff*
- ___IF NOT ALL OF THESE FACTORS ARE FULFILLED, STAY AWAY FROM IT!___

Definitions
- *Local anaesthesia:* A local anaesthetic is applied to a small area. This is done by direct application with an aerosol, gel or cream to the skin or mucous membrane or by direct injection into skin or mucous membrane.
- *Regional anaesthesia (field block):* Anaesthesia is induced to an area supplied by a specific nerve, nerve group, nerve plexus, or spinal cord segment, or single nerve.
  Examples: Mandibular block, femoral nerve block, psoas compartment block, eye blocks, brachial plexus block, epidural block, and subarachnoid (spinal) block.
- *Topical anaesthesia:* A local anaesthetic is applied to the skin and mucous membranes as creams, gels, or aerosols. Drugs used are lignocaine, benzocaine, prilocaine, and cocaine. This method is often used for endoscopy, e.g. airway management, gastroscopy, colonoscopy, cystoscopy, and

bronchoscopy. These procedures are often done with so-called "conscious sedation" where the patient is given sedation and analgesia to a level where the patient can still co-operate. *A mixture of lignocaine and prilocaine (EMLA, Topla)* is used as a cream or drug-saturated disk to numb the skin for insertion of venous cannulas. This is very useful in children and babies (if they co-operate). EMLA takes about 30 minutes to be effective.

- *Local infiltration*: The anaesthetic is infiltrated directly into lesions or around lesions, e.g. infiltration of the skin or mucus membranes to remove small lesions or to sutures wounds.
- *Peripheral nerve blocks*: The anaesthetic is injected around peripheral nerves to anaesthetise the areas supplied by the nerve(s), e.g. a femoral nerve block, sciatic nerve block, and ankle block. In the latter block the five nerves supplying the foot is blocked around the ankle.
- *Intravenous block* (Bier block; See Chapter 26): This is a special type of peripheral nerve block where a limb (usually the arm) is exsanguinated and the arterial and venous supply to the limb is isolated with a double tourniquet. The local anaesthetic (lignocaine, *not* bupivacaine) is injected into a peripheral vein in the hand. The anaesthetic fills the vasculature and blocks the nerve endings.
- *Plexus block*: The anaesthetic solution is injected into sheaths containing nerve plexuses, e.g. the brachial, cervical, and lumber plexus blocks. The *brachial plexus block* is one of the most useful blocks. It can be blocked where it leaves the neck between the anterior and middle scalene muscles (*interscalene block*), supero-posterior to the clavicle (*supraclavicular block*), inferomedial to the tip of the coracoid process (*infraclavicular*), and around the brachial artery medial to the humerus in the axilla (*axillary block*). Above and below the clavicle, the *subclavian artery and vein* are below the plexus, while the three cords surround the *brachial artery* in the axilla. The closer the injection site to the spinal cord, the higher the incidence of *unintentional epidural or subarachnoid injection* of the local anaesthetic. The supraclavicular approaches is often complicated by blockade of the *cervical sympathetic ganglia*, leading to *Horner syndrome*. Along its course, the plexus is closely related to large blood vessels and direct *intravascular injection and absorption of local anaesthetic* occurs more readily. Interscalene and supraclavicular blocks are fairly commonly complicated by blockade of the *phrenic nerve, and less commonly, by a pneumothorax*. Therefore, *bilateral plexus blocks are contra-indicated*.
- *Neuraxial block (see also Chapter 21)*: The local anaesthetic is injected into the epidural space where it anaesthetises the nerve roots, or into the subarachnoid space into the cerebrospinal fluid (CSF), where the spinal cord is blocked. The former is called an *epidural block* and the latter a *subarachnoid, intrathecal*, or usually, a *spinal block*. Depending on the concentration of the local anaesthetic, the local anaesthetic can cause a dense block when using high concentrations (anaesthesia), or selective block of the thinner fibres (pain and temperature) when using low concentrations (analgesia). Apart from local anaesthetics, several agents can be injected into the epidural and subarachnoid spaces to prolong the analgesic effect. These include opioids and clonidine.
- *Use of several opioid and non-opioid analgesics administered locally, including intra-articular, interpleural (intrapleural) and intra-peritoneal analgesia*:[13] Magnesium sulphate (1 g) and morphine (10 mg) may be added to 20 ml of 0.5% bupivacaine with adrenaline[14] and diluted to about 20 ml. This solution can be injected into a large joint (knee, shoulder) after arthroscopy and into the peritoneal cavity after laparoscopic procedures. These techniques must be avoided in hyperaemic inflamed joints and peritoneum since systemic absorption is facilitated. More studies are however needed to test the usefulness and safety of these techniques (Endnote[13] is an excellent review dealing with several non-conventional routes of administration of analgesics.)

A prerequisite of regional anaesthesia is knowledge of the anatomy.

Correct positioning of the needle can be assisted by the following methods:
- *Knowledge of the anatomy*. You must know the general course and relations of the nerve. This is the most important measure.
- *Identification of tissue plains and loss of resistance* to the exploring needle, e.g. epidural and transversus abdominus plain block. This method relies strongly on the proprioception of the operator to feel the slight changes in resistance as the needle is penetrating through tissue layers through tissue layers of different consistencies. The *use of special block needles* facilitates the identification of tissue plains. These needles have a *short bevel* and are therefore *blunter* than the needles used for intravenous or subcutaneous injections. There is a "pop" when these blunt needles pass through dense tissue layer to a less dense tissue layer, e.g. muscle-fascia-muscle.

- Contact of the exploring needle with the target nerve or plexus elicits *paraesthesiae* in the innervated region. You should never inject anything while the patient experience paraesthesia or pain since it may indicate intraneural position of the needle tip. Always withdraw the needle until the paraesthesia or pain disappears.
- A *nerve stimulator* can be attached to the exploring needle. The initial current is about 1 mA at a frequency of 1 Hz to 2 Hz. Once movement is elicited in the target area, the current is decreased to about 0.5 mA and the motor response should disappear. The needle is advanced deeper until a response reappears. The current is reduced to 0.3 mA and the response should disappear. If the motor response is present at 0.3 mA, the needle should be withdrawn since the tip may be in the nerve. Injection of local anaesthetic at this point should be painless and cause immediate loss of motor response. The whole volume of local anaesthetic solution can be administered in aliquots as mentioned above. Since the *stimulating needle passes through muscle, it must be isolated leaving only the tip exposed*. A further development of these isolated stimulating needles is that a thin *catheter can be threaded through the needle* and left in situ. This allows subsequent infusion of local anaesthetic to *prolong anaesthesia and analgesia*. An example of a continuous block is the interscalene brachial plexus block. This block is employed in shoulder surgery where early mobilisation is necessary but very painful. Topping up of the block through the catheter makes *early painless mobilisation* possible.
- *Ultrasound guided regional anaesthesia* employs ultrasound to identify anatomical structures to be blocked.

Subarachnoid anaesthesia (usually called a "spinal")
- *Preparation, positioning, and surface anatomy to do the spinal*
  - *The theatre and anaesthetic equipment must be complete and tested.* Everything must be prepared for a general anaesthetic, i.e. the anaesthetic machine must have been tested, laryngoscopes, endotracheal tubes, tube stylet, oral laryngeal mask, suction, functioning theatre table.
  - The anaesthetist must have a *competent assistant*.
  - Reliable *venous access* is essential (preferably a 16 G cannula) and *start preloading* with about 10 ml kg^{-1} of Ringer lactate so that a volume of about 10 ml kg^{-1} has been infused by the time the spinal has been done. A vasopressor such as phenylephrine, diluted to 50 μg ml^{-1}, must be immediately available. You can prepare it by adding 10 mg of phenylephrine to 200 ml of saline (10 mg in 200 ml = 10 000 μg in 200 ml = 10 000 μg in 200 per ml = 50 μg ml^{-1}).
  - *All neuraxial procedures involve the spinal cord, results in breaching of the spinal meninges. There, the anaesthetist must follow sterile techniques (mask, scrubbing, sterile gown, gloves).*
  - The patient is placed in the *sitting or lateral* position. The procedure is easier if the patient is sitting and bending forwards. The *spinous processes* are usually palpable over the spine and help to define the *midline*. *A line* between the highest points of both *iliac crests* (Tuffier's line) usually crosses either the *body of L4 or the L4-L5 interspace*. This is the ideal *insertion level* for a spinal and epidural. Remember, the spinal cord stops at about the second lumbar vertebra. Therefore, a spinal (intrathecal/subarachnoid) injection is always done below this level.
  - If the patient is sitting, make a horizontal impression with a thumb nail between the spinous processes between which you plan to insert the needle. Palpate the spinous processes with your left and right thumbs and make a vertical impression on both sides of the horizontal impression. Now, you should see an *H-shaped marking on the skin*. The midpoint of the horizontal bar of the H is the entry point of the needle.
- *Draw up the following drugs:*
  - Draw up 5 ml of *lignocaine 2% injection* and attach a needle no longer than 23 mm (in South Africa, at present this is a 23 G blue needle). The *purpose of this injection is two-fold*: to *anaesthetise the skin* and *identify the direction of the interspinous space* (soeknaald). If you cannot get in with this needle, you will definitely not get in with the spinal (or epidural needle). Once you have identified the interspinous space, inject another 2 ml of lignocaine. Why use such a short needle? Because the distance between the skin and the dura varies between 2 cm and 8 cm (mean about 5 cm); if a longer needle is used to identify the interspinous space and administer the local anaesthetic, you may puncture the dura. The direction of the needle at this level is usually slightly cephalad.
  - *The injections used in the subarachnoid space are either hyperbaric or isobaric.*
    Baricity refers to the density of the injection relative to that of CSF; the same (isobaric) or higher (hyperbaric). Hyperbaric solutions contain glucose and have a density higher than that

of CSF.[xi] Therefore, the solution will gravitate to the lowest point in the CSF column. If the patient is put head down, the block will be more cephalad (usually to the thoracic kyphosis at T4) and if the patient is put head up, the solution will gravitate to the sacral area (*saddle block*, S1 to S5). If the spinal is done with the patient lying on the side, the block will stay unilaterally to a large extent (*unilateral spinal*). If the patient is in the horizontal supine position, the head must be elevated on a pillow to prevent the hyperbaric solution from spreading to the cervical segments. The *density of the block* depends on the concentration of the solution.

An isobaric solution has the same density as CSF. The CSF mixes with the isobaric solution. The local anaesthetic in the SCF *diffuses* from the area of injection and binds to the spinal cord. The number of segments blocked (*block width*) is determined by both the volume and concentration of solution injected, i.e. the dose (mg). Remember, dose = concentration (mg ml^{-1}) × volume (ml). The *density of the block* depends on the concentration of the local anaesthetic in the CSF, and therefore, on *the concentration* of the local anaesthetic in the solution injected. The spread of isobaric solutions is less influenced by position and more by concentration than that of hyperbaric solutions.

If an *isobaric solution* is given at L3/4 or L4/5, the block will usually include segments L2 (upper medial thigh) to L5 (big toe) or lower, if the injection is given at level L3/4 or L4/5. The latter block is useful in procedures involving the knee (L3) and lower. Remember, the lateral side of the foot, back of the leg, and knee are supplied by sacral dermatomes, but are usually blocked by an L4/5 spinal. Regarding body position and spread of isobaric solutions: although these solutions are called isobaric, they are actually slightly hypobaric (less dense than CSF) and may rise to higher segments if the patient is kept in the head-up position, and vice versa if the patient is put head-down. Therefore, patients must preferably be kept in the horizontal position after they have received an isobaric solution.

o *Drugs and doses used for spinal anaesthesia*
Bupivacaine is most often used (Table 4). *Please note that the dose of intrathecal (spinal) local anaesthetics is not calculated according to body mass, but according to the number of segments that are needed to be blocked. An opioid may be added* to the bupivacaine. It facilitates, potentiates, and prolongs the block. Sufentanil 2.5 μg or fentanyl 12.5 μg may be added. *Bupivacaine blocks recover* completely within about 6 hours, starting with recovery of motor function, and lastly pain and temperature.

Table 4 Doses of bupivacaine 0.5%, body position, and block level for spinal anaesthesia*

Upper segment	Hyperbaric solution	Isobaric solution
T 6 and higher	3 ml + head down	Unreliable
T11	2.5 ml + head down	3 ml
L2	2 ml + horizontal	2.5 ml
S1 and lower (saddle block)	1.5 ml + sitting	Unreliable

*Doses for caesarean section is less. See Chapter 21

- *Inserting the spinal needle and injecting the local anaesthetic*
The layers breached to achieve a spinal are as follows: skin, subcutaneous fat, supraspinous ligament, interspinous ligament, ligamentum flavum (first loss of resistance), epidural space, dura and arachnoid mater (second loss of resistance) and then the subarachnoid space is entered (Figure 1). *A spinal needle, 25 G or thinner,* is inserted (usually through a thicker guide needle). The *guide needle* is usually packed with these thin needles. *Insert the guide needle* up to a depth of not more than 2 cm where you have identified the interspinous space. The *spinal needle is passed through the guide needle*. The stylet inside the spinal needle is withdrawn every 3 mm to 5 mm to inspect for backflow of CSF. Once there is *free dropping of fluid*, the syringe containing the local anaesthetic is attached to the spinal needle and the *planned volume is injected.* The needle *stylet is*

[xi] If the ready-made heavy bupivacaine is not available, it is prepared by adding 0.5 ml of a glucose 50% injection to 4.5 ml of a bupivacaine 0.5% injection (plain; without glucose).

reinserted into the spinal needle and the needle is removed. The *needle is inspected* to see if it is complete.

- *At which level should the spinal be done?*
  The *spinal cord ends at about L2 in adults and L3 in infants*. In the elderly, osteoporosis causes shortening op the spinal canal, causing downward movement of the spinal cord. Therefore, a spinal should never be done at a level higher than L3/4 to prevent injury to the spinal cord.
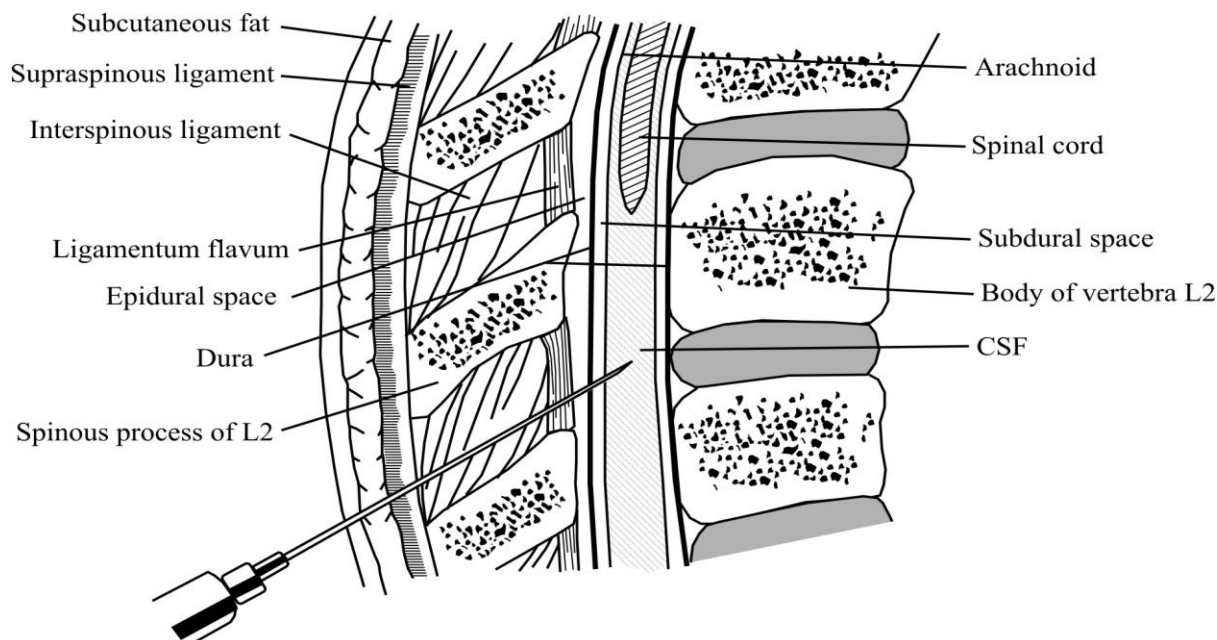
Figure 1 Anatomy of the epidural and subarachnoid spaces

- *Complications of spinal blocks*
  - *High spinal blockade* may occur if excessive doses/volumes of drugs are used or if there is high sensitivity or spread of local anaesthetic. If spinal anaesthesia ascends to the cervical levels severe hypotension, bradycardia and respiratory insufficiency may ensue (high/total spinal). Patients complain of dyspnoea and have numbness and weakness in the upper extremities. If the local anaesthetic spreads to the brain stem, the patient will lose consciousness, develop apnoea, become hypotensive and bradycardic, and have large pupils. Once it is recognized, reassure patient, provide supplemental oxygen, and correct bradycardia and hypotension. The airway must be maintained; intubation and mechanical ventilation may be necessary. Support the circulation with intravenous fluids, vasoconstrictors, and positive inotropes (see above).
  - *Hypotension is the most common adverse effect of spinal anaesthesia.* In morbidly obese patients, the hypotensive response will be much more pronounced if a left lateral tilt is not adequate.
  - *Severe bradycardia and hypotension* may be followed by *cardiac arrest.* This is thought to be caused by a Bezold-Yarisch cardiac reflex.
  - *Urinary retention* is caused by blockade of segments S2 to S4, which decreases urinary bladder tone and inhibits the voiding reflex. Therefore, all patients should have a urinary catheter *in situ*; if a catheter has not been inserted, the patient should be observed postoperatively for bladder distension and voiding.
  - *Inadequate anaesthesia and analgesia* (failed spinal)
  - *Direct neurological injury* can result from spinal cord or nerve root injury. Any sustained paraesthesia should alert the clinician to redirect the needle. Injections should be immediately stopped and the needle withdrawn if they are associated with pain. Direct injection into the spinal cord can cause paraplegia. Apart from direct neurological injury, the spinal cord can also be affected by the tonicity of the injection or direct toxicity of the components of the injection. These complications include *cauda equina syndrome, transient neurological symptoms*

(transient radicular irritation), and anterior spinal cord syndrome.

o *Transient hearing loss* is a common complication of spinal anaesthesia. It occurs more in women and lasts for about 2 days.

o *Spinal haematoma* can occur, particularly in the presence of abnormal coagulation (bleeding disorders, anticoagulant therapy). The pathological insult to the spinal cord and nerves are due to a mass effect compressing neural tissue and causing direct pressure injury and ischaemia. Rapid diagnosis and intervention (surgical decompression within 8 h) is of paramount importance to prevent permanent neurological sequelae.

o *Meningitis and arachnoiditis* can be caused by contaminated equipment or injected solutions, or as a result of organisms tracking in from the skin. Therefore, this procedure should be undertaken in an aseptic manner. *However, do not contaminate block needles the antiseptic agent, e.g. chlorhexidine in alcohol, since it is neurotoxic and cause irreversible nerve damage.*

o *Backache*

o *Post-dural puncture headache (PDPH)* is a common, unfortunate side effect of dural puncture in young patients, especially when *needles thicker than 25 G are used*. Onset is usually within 12 h to 72 h, but may also be seen immediately. *Typically*, PDPH is bilateral, frontal, retro-orbital, occipital and extends into the neck. It may be throbbing or constant and associated with photophobia and nausea. *The hallmark* is that the headache worsens when the patient sits up and improves when lying down. *The pathogenesis* is thought to be due to a leakage of CSF from a dural defect, which causes a decrease in intracranial pressure (ICP). The decreased ICP causes traction on the pain-sensitive basal meninges – especially if the patient sits up. ***PDPH must be distinguished from meningitis***.

Modifications of technique and *new technology needles* have decreased PDPH to acceptable levels. These include: using needles not thicker than *25 G*, penetrating the dura with the *bevel of the needle* parallel to the spinal cord (split rather than cutting the longitudinal dural fibres), and use of *pencil point needles.* (There is still uncertainty about the latter two factors.) *Management of PDPH* consists of clinical exclusion of meningitis, bed rest, simple analgesics, caffeine, and oral (coffee) or intravenous fluids. If the headache persists for more than 24 hours, an epidural blood patch should be done. The epidural blood patch consists of injection of 15 ml of the patient's blood into the epidural space at the level where the spinal was done. This procedure is done in an operating theatre under sterile technique by two doctors. The one performs the epidural. Once the epidural needle is in the epidural space, the second doctor draws blood from the patient. The blood is injected slowly into the epidural space. Typically, this provides instant relief of headache.

Epidural (Extradural) anaesthesia and analgesia

With epidural anaesthesia/analgesia, the local anaesthetic is injected between the two layers of the dura mater; the one covering the ligamentum flavum and vertebral bodies, and the other outside the arachnoid mater.

The epidural space contains the nerve roots, venous plexus (Batson), areolar (loose) connective tissue, and fat. The following method is used to identify the epidural space (the "*loss of resistance method*"): A low resistance syringe is filled with saline or air and attached to an epidural needle (Touhy needle). While advancing the needle through the different layers, constant pressure is being applied on the syringe plunger. Once the tip of the needle reaches the dense ligamentum flavum, the resistance to the needle increases. As soon as the needle enters the epidural space, there is a sudden loss of resistance and the plunger moves forward easily. While keeping the needle steady, the epidural catheter is advanced through the needle into the epidural space and the needle is removed. The catheter is connected to a antimicrobic filter, and local anaesthetic can be injected into the epidural space.

Since the epidural catheter can migrate (penetrate) into the subarachnoid space or a epidural vein, it is possible to inject local anaesthetic inadvertently into the wrong space. Therefore, a test dose is injected through the epidural catheter to exclude subarachnoid and intravenous position of the tip of the catheter. This is done by injecting indicator agents (the *test dose*) into the catheter (see above). If the catheter tip is in the subarachnoid space, it is not wrong to leave it there; you just take note of it and proceed as for a spinal. The dose of an continuous spinal is about 1/10th of the epidural dose.

The level at which the epidural is done, depends on the required level of anaesthesia/analgesia. Since the epidural catheter is situated at a particular level, the local anaesthetic is injected until the correct width of block is acquired, usually about *1 ml to 1.5 ml per segment*. Epidural injections spread about equally upward and downward. For example, if the catheter tip is at say L2 and you want a level of T6, the volume needed is 9 ml for upward spread but also 9 ml for downward spread. Therefore, the total volume is about 18 ml given in fractions of about 5 ml.

Caudal block

A *caudal block* is actually a low epidural block where the needle is inserted through the sacral hiatus into the sacral epidural space. Remember that the *dural sac[xii] ends at the second sacral vertebra*. If a caudal needle is advanced too deeply, the dural sac can be punctured and local anaesthetic can be injected into the CSF causing a spinal block. Since the volumes used for caudal blocks are similar to those used in epidurals, administration of a large volume of local anaesthetic into the dural sac can cause a high spinal.

Spinal and epidural blocks regress toward the place of insertion, i.e. to centre of the block. Motor function returns first, followed by proprioception and lastly pain and temperature.

Contraindications to neuraxial blockade (spinals and epidural analgesia or anaesthesia)

- *Absolute contraindications*
  - *Inexperienced* operator
  - *Patient* refusal, uncooperative patient, inability to communicate with patient (see above)
  - Infection at the site of injection
  - Any *coagulopathy* (bleeding diathesis or anticoagulant therapy) (See Chapter 19)
  - Severe *hypovolaemia*
  - Increased *intracranial pressure*
  - *Fixed cardiac output states*[xiii] (severe aortic stenosis, severe mitral stenosis, constrictive pericarditis, cardiac tamponade)
- *Relative contraindications*
  - Systemic *sepsis*
  - Active *neurological disease*, e.g. demyelinating lesions, motor neuron disease, etc. If you decide to do it, the neurological function must be noted and the benefit risk must be considered.
  - Prior *back surgery* at the site of surgery
  - *Complicated surgery* (prolonged operation, major blood loss anticipated, manoeuvres that compromise respiration, severe foetal abnormalities)

Monitoring during regional anaesthesia

- *Physiological monitoring*

  Look for signs of LAST (see above). The *ECG, oxygen saturation, and blood pressure* must be monitored closely. In the case of neuraxial anaesthesia, do not wait for hypotension and hypoxaemia to develop. Administer oxygen if the saturation decreases below about 98%. The *first indication of a decrease in blood* pressure justifies administration of *phenylephrine* 50 μg. *If the hypotension is accompanied by a bradycardia*, inject *ephedrine* 0.1 mg kg (usually 5 mg), or adrenaline 5 μg to 10 μg. You can prepare this by diluting ephedrine 50 mg to 10 ml; this dilution contains 5 mg ml^{-1}. Alternatively, *adrenaline* 100 ng kg^{-1} is administered (usually 5 μg to 10 μg). You can prepare this by diluting 1 ampoule of adrenaline (1 mg) to 200 ml; this dilution contains 1 mg in 200 ml = 1000 μg in 200 ml = 1000 μg/200 per ml = 5 μg ml^{-1}. If the patient has a body mass of say 80 kg, the dose is 100 ng kg^{-1} × 80 kg = 8 000 ng = 8 μg = 0.5 ml to 1.0 ml of the dilution.

- *Monitor the development of blocks*.

  The closer the local anaesthetic is injected to the nerve and the thinner the nerve, the quicker the onset of the block. A spinal block works within about 5 minutes, a peripheral nerve block, e.g. an eye block between 5 and 10 minutes and a sciatic nerve block 10 to 15 minutes, while a plexus block, e.g. a brachial plexus block may take up to 45 minutes. During this time, you must *keep contact with the patient*; ask him/her to *move the hands* to identify a high spinal and *speak to them* to identify decreased consciousness. *Nausea* may be a sign of hypotension and must not be disregarded.

- *Testing the width and density of blocks:*
  - Pain and temperature: Use ice or needle prick.
  - Proprioception: Light touch with, e.g. cotton wool
  - Motor function: In the case of a field block, you can ask the patient to move the block area. In the case of neuraxial block, motor function is graded using the Bromage scale (Table 5)

[xii] *The dural sac is the membranous* sac that encases the spinal cord and CSF within the vertebral column.
[xiii] Fixed cardiac output means that the cardiac output cannot increase if the demand for an increased output would arise.

Table 5 The Bromage scale

Grade	Criteria	Degree of block
I	Free movement of legs and feet	Nil (0%)
II	Just able to flex knees with free movement of feet	Partial (33%)
III	Unable to flex knees, but with free movement of feet	Almost complete (66%)
IV	Unable to move legs or feet	Complete (100%)

CHAPTER 10

MANAGEMENT OF POST-OPERATIVE PAIN

Main points:
- Pain
- Nociception
- *The pathophysiology* of nociception and pain (how does nociception cause pain?)
- *Modulation of pain:*
- Peripheral, spinal, supraspinal, cognitive modulation
- *Classification of acute pain used for diagnostic and therapeutic purposes***:**
- Superficial, somatic, visceral
- *Patterns of referred pain*
- *Why must pain be treated*?
- *Therapy of acute pain*
- *Drug therapy*

  - o Non-opiates: Aspirin, paracetamol, ibuprofen, diclofenak, ketorolac, paracetamol-codeine combinations
  - o Opiates: Morphine, pethidine, pentazocine, dihydrocodeine, codeine, tilidine, tramadol
  - o The $\propto_2$-agonists: the student must know their names
  - o Ketamine: the place of ketamine in analgesia, its dosages and side-effects.
- *Regional anaesthesia*
- *Multimodal analgesia*
- *Pre-emptive analgesia*
- *Acute pain versus chronic pain*

What is pain?
Pain is not a sensory modality only, but an experience. It is an unpleasant sensory and emotional **experience** associated with existing or potential tissue damage. This definition acknowledges the interplay between **objective** physiological sensory as well as the **subjective** psychological aspects of pain.

The term **nociception** is derived from the Latin word for damage or injury, *noci*. It refers to neural response to injury only. All nociception causes pain, but pain is not always caused by nociception. It is therefore clinically useful to classify pain as **acute pain**, which primarily results from nociception, and **chronic pain** that often result from nociception, but where psycho-behaviouristic factors are involved.

How does nociception cause pain?
Mechanical, thermal, and chemical **tissue injury** stimulate free nerve endings (**nociceptors**). Peripheral nerve afferents (Aδ and C fibres) conduct the stimulus centrally. The Aδ fibres are thick myelinated fast conducting fibres and is responsible for fast pain. C fibres are thin, unmyelinated, slow conducting, responsible for slow pain and modulation of nociception. The peripheral afferents (first order neuron) send axon projections to the dorsal horn and other areas in the spinal cord (relay centres for pain). Axons synapse in the relay areas with second order afferents which cross to the spinothalamic tract on the contralateral side. In the thalamus, axons synapse with projection neurons to the cerebral cortex.

Pain experience can be **modulated** resulting in an experience which is not proportionate to the stimulus; pain may follow harmless stimuli like touch. Modulation of nociception may occur peripherally or centrally.

- **Peripheral modulation** is caused by locally secreted substances (potassium, lactate, serotonin, bradikinin, histamine, and prostaglandin) that sensitise nociceptors. The analgesic effect of the NSAIDs and glucocorticosteroids is ascribed to their inhibitory effect on prostaglandin synthesis. Opioid receptors on the sensory nerve endings are stimulated by endogenous opioids from inflammatory cells. These opioids stimulate the peripheral opioid receptors resulting in hyperpolarization of the nerve ending. This may explain the peripheral analgesic effect of opioids.
- **Spinal modulation** (spinal wind up) is caused by neuron transmitters like glutamate, aspartate and substance P.
- **Supraspinal modulation** occurs by descending inhibitory neurons that synapse in the dorsal horn where neurotransmission from first order to second order neurons is inhibited. These inhibitory tracts are opioidergic and α$_2$-adrenergic. Their cell bodies are situated in the periaqueductal grey matter and the reticulate formation respectively, and secrete endorphin and noradrenaline,

respectively.
- **Cognitive modulation** occurs by e.g. making the environment more pleasant in order to make pain more bearable. The patient's attention can also be distracted in order to fix the attention on something else.

It should now be clear which drugs and other methods can be utilized to treat pain.

From a **diagnostic and therapeutic** point of view, it is useful to know or to predict the origin of nociception. Therefore, acute pain is classified into **three types**:
- **Superficial** – nociception comes from the skin, subcutis or mucosa. The pain is well localized and is described as being sharp, stabbing or throbbing.
- **Somatic** – nociception comes from muscles, tendons, joints or bone. It is less well defined, but depends on the intensity of the stimulus, e.g. only the knee or the whole leg is painful. The pain is dull, aching, and persistent.
- **Visceral** – pathology or dysfunction of a viscus or visceral covering (pleura, peritoneum, pericardium)

There are four types of visceral pain:
- Real localized visceral pain
- Localised parietal pain
- Referred visceral pain (Table 1)
- Referred parietal pain

Real visceral pain is dull, diffuse, in the midline and is often accompanied by autonomic nervous system activity like nausea, vomiting, sweating and disturbances of heart rate and blood pressure.
Parietal pain is sharp, cutting and is localized or referred. The central diaphragmatic parietal pleura and peritoneum refers to the chest and upper abdominal wall. The parietal covering of the peripheral pleura of the diaphragm is referred to the shoulders and neck.

Why must pain be treated?
It is cruel to allow patients to suffer pain. Furthermore, pain is accompanied by unwanted systemic effects (Table 2). It has, however, not been proved beyond any doubt that effective analgesia expedites convalescence. The reason may be that the term "recovery" does not mean the same to the patient and all members of the health team. It is, however, cruel to leave pain untreated. Furthermore, if pain is not treated timeously, it may become chronic. Chronic pain is difficult to treat and has a high morbidity.

Who experiences pain?
Postoperative pain, trauma, burns
Musculoskeletal disease: back pain, arthritis, fractures
Cancer
Childbirth
Myocardial infarction, nephrocolic, sicle cell crisis, pancreatitis, etc.

Table 1 Patterns of referred pain

Organ	Referred to dermatome
Central diaphragm	C4
Lungs	T2-T6
Heart	T1-T4
Aorta	R1-T2
Oesophagus	T3-T8
Pancreas and spleen	T5-T10
Stomach, liver, gall bladder	T6-T9
Adrenal glands	T8-L1
Small intestine	T9-T11
Colon	T10-L1
Kidneys, ovaries, testes	T10-L1
Uterus	T10-T12
Bladder, urethra, prostate, uterus	S2-S4
Rectum	S2-S4

Table 2 Systemic effects of pain

Pulmonary	Hypoventilation, hypoxemia, pneumonia
Cardiovascular	Hypertension, dysrhythmias, myocardial ischaemia, cardiac failure
Gastro-intestinal	Decreased motility
Genito-urinary	Urinary retention
Blood clotting	Decreased mobility that makes the patient prone to thrombo-embolism
Immunological	Immunosuppression
Endocrinological	The stress response with decreased anabolism (insulin, testosterone), increased catabolism (glucagon, somatotropin, adrenaline, thyroxin, cortisol), and sodium and water retention (ADH, cortisol). This response is accompanied by an increase in oxygen consumption and forms the basis for the other systemic effects of injury or pain.

Drug therapy of acute pain

As few types of analgesics as possible should be used in a hospital: all parties involved in the treatment of pain know the drug(s), the side effects, doses and algorhythms. It also contributes to effective analgesia and patient safety. In our hospital the **opioid of choice is morphine**.

- **Non-opiates**
  - The **NSAIDs and paracetamol** are especially useful when prostaglandins contribute to nociception, namely musculo-skeletal, posttraumatic and inflammatory pain. These drugs may impair the inflammatory response necessary for fracture healing and should therefore not be prescribed without the approval of the orthopaedic surgeon.

    NSAIDs can precipitate acute **renal failure** in the presence of kidney disease, loop diuretics, or loss of more than 10% of the blood volume. The NSAIDs should be avoided in patients with a history of **peptic ulceration**. Anti-inflammatory drugs should be used with caution in the elderly. The COX II inhibitors inhibit the production of prostacyclin (vasodilation) by endothelial cells. These drugs have appeared and many have disappeared from the market. They are probably safe in young healthy patients but must be avoided in the elderly, patients with ischaemic heart disease, cerebrovascular disease, or renal impairment. **The NSAIDs are equally effective, whether they are administered parenterally, orally or rectally.** Avoid intramuscular injections as far as possible. ***Remember, COX II inhibitors are contraindicated in patients with sulphonamide allergy.***

    Aspirin
    Each soluble table contains 300 mg. The dose is up to 80 mg kg^{-1} day^{-1} in six doses, usually approximately 10 mg kg^{-1} 4 hourly. Aspirin is not recommended for children, especially in the presence of fever.

Paracetamol

Paracetamol is safe in all age groups, in the presence of peptic ulceration, renal failure, and thrombocytopathy. Each injection contains 1 g, a tablet contains 500 mg and the syrup 24 mg per ml (120 mg per 5 ml). The oral and intravenous dose in adults and children is up to 80 mg kg^{-1} day^{-1} in 4 doses, usually 15 to 20 mg kg^{-1} 6 hourly. Limit the dose to not more than 30 mg^{-1} kg^{-1} day^{-1} in the presence of liver disease. The rectal dose of paracetamol is 30 mg kg^{-1} every 6 hours. The dose in neonates is about 20 mg kg^{-1} twice daily, and in babies, 20 mg kg^{-1} 8 hourly. The intravenous preparation is registered for the first 24 hours postoperatively. The dose is 15 mg kg^{-1} four hourly (maximum 60 mg kg^{-1} day^{-1}), neonates 15 mg kg^{-1} twice daily (maximum 30 mg kg^{-1} day^{-1}), and babies 15 mg kg^{-1} six hourly (maximum 45 mg kg^{-1} day^{-1}). The dose must be decreased in patients taking hepatotoxins, and patients with decreased liver function.

Iboprofen

A tablet contains 200 or 400 mg and the suspension, 20 mg per ml. The daily dose is 24 mg kg^{-1} in 4 doses, thus about 6 mg kg^{-1} 6 hourly.

Diclofenak

There are 25 or 50 mg per table, 12.5 mg, 25 mg or 100 mg per suppository, 75 mg per 3 ml *intramuscular*injection (not recommended) or 15 mg per ml drops. The dose is up to 2 mg kg^{-1} day^{-1} in 3 doses, usually about 0.7 mg kg^{-1} 8 hourly. Avoid in porphyria.

Ketorolac

This NSAID can be given intravenously. The dose is about 1 mg kg^{-1} day^{-1}. A person of 70 kg can receive 30 mg followed by 10 mg 6 hourly intravenously.

Paracetamol-codeine combinations

The 8 mg of codeine combined with 500 mg of paracetamol is possibly of little use. The simultaneous administration of paracetamol 10 mg kg^{-1} and codeine about 1 mg kg^{-1} is effective against moderate to severe pain, and is comparable to ibuprofen 6 mg kg^{-1}. The combination of paracetamol and ibuprofen is effective in the treatment of moderate pain.

o **The α_2 agonists**

These drugs, e.g. clonidine and dexmedetomidine, work via spinal $\alpha_2$receptors. On their own, these drugs are not effective analgesics, but decrease the need for other analgesics.

o **Ketamine**

A single dose of about 0.2 mg kg^{-1} with induction of anaesthesia is opiate-saving for up to 24 hours. This is a versatile drug that can be used as part of sedation in the intensive care unit, patient controlled analgesia and in the prevention and treatment of neurogenic pain (phantom limb pain after amputations).

o **Regional anaesthesia**

Regional analgesia is the only way in which the afferent sympathetic influence can be blunted effectively. In this way, the endocrine stress response is greatly reduced which improves respiratory function, intestinal motility, and a lower incidence of thromboembolism. Regional analgesia is especially useful in the scenario of day case surgery.

Regional analgesia or by simply infiltrating wounds with local anaesthetic can be analgesic for many hours. During this period, NSAIDs, with or without low dose opiate, can be given; in this way a smooth transition from regional to systemic analgesia is made. A good example of this method is the mandibular block with bupivacaine before extraction of wisdom teeth. These patients need less anaesthesia, recover sooner from anaesthesia and is discharged earlier.

The intra-articular administration of 20 ml of bupivacaine plus 10 mg of morphine after arthroscopy gives very effective analgesia. A n. femoralis block gives good analgesia after arthroscopy of the knee.

- **Opiates**

Opiates are the drugs of choice for the treatment of severe pain. Unfortunately, effective doses are withheld due to ignorance and concern about respiratory depression and addiction. Patients suffering from severe pain do not get addicted to opiates; they get tolerant.

Opiates may cause respiratory depression when administered if given in doses that are larger than are required for analgesia. There is *no proof that one opiate is better than* another in an *equi-analgesic dose. Pethidine*, however, has *many side effects*, namely increased peripheral vascular resistance, atropine like side effects, and the accumulation of the epileptogenic metabolite norpethidine in the presence of renal failure.

Morphine and its derivates (diamorphine, codeine, and dihydrocodeine) all have an *active* rather than a toxic *metabolite*, namely *morphine-6-glucorunide*. It is about eight times more potent than morphine and in the presence of renal failure it has a $t_{1/2}$ of more than 20 hours. This is no problem if the dose is titrated to effect.

Besides their analgesic effect, opiates are sedating, suppress ventilation, are antitussive and alleviate dyspnoea. Although these effects may be advantageous, it always causes some degree of *haemoglobin desaturation (hypoxaemia)*. Therefore, if continuous pulse oximetry is not possible, it is safer to *administer oxygen* to all patients receiving potent opiate during the night and for the whole day to those who are obese, older than 70 years.

Other side effects of opiates are nausea, vomiting (especially *pethidine*), constipation, pruritus and urine retention. Opiate also cause a decrease of REM sleep. When the loss of REM sleep is caught up later on, it is accompanied by an increase of sympathetic nervous system activity. This may give rise to cardiovascular activation that can increase postoperative morbidity and mortality in susceptible patients.

The *key to effective and safe opiates analgesia* is the *titration* of the dose until pain disappears with the minimum of side effects. When a *dose is ineffective, a follow up dose* can be given: 5 to 10 minutes after intravenous injection, one hour after intramuscular injection, or 90 minutes after oral administration. If the follow up dose is ineffective, a further follow up dose can be given, and or the dose can be increased with about 25%, or the route of administration can be changed. The need for opiates decrease as healing takes place.

Sedation and hypoventilation may point to an *overdose* in which case the *next dose is delayed* until sedation subsides, without loss of analgesia. Thereafter, the dose is decreased with about 25% while the same dose interval is maintained. It should be clear that the treatment of pain is not merely the prescription of rigid regimens but careful *individualization of doses and monitoring of analgesia and side effects*. The prn (as necessary) prescription of analgesics is therefore not recommended; the opiates are titrated to effect and as soon as the effective dose has been established, this dose serves as guideline for dosing schedules. The sedation and respiratory depression of all µ agonists can be reversed by naloxone 5µg/kg IV or IMI.

Intramuscular and subcutaneous administration of opiates have their disadvantages: it is irritating and painful and results in unpredictable blood levels, especially in obese patients and those with *low peripheral perfusion (hypothermia, vasoconstriction, low cardiac output)*. Intramuscular and subcutaneous injections should be avoided in **children**, as they fear needles. *Transdermal and sustained release preparations* are not suitable for the treatment of acute pain.

Morphine

The bioavailability is 25%, the plasma protein binding (albumin) is 35%, and the $T_{1/2}$ is 3 hours. It is effective within 10 minutes after intravenous and about 20 minutes after intramuscular and subcutaneous injection. It is effective for approximately 4 hours. The injection contains 10 mg or 15

mg per 1 ml. The intravenous dose is 50 to 300 μg/kg/hour; usually about 30μg/kg every 5 to 10 minutes until an effective plasma level has been reached. The total of these doses can serve as guideline for the hourly dose; this can be given as a constant infusion (ONLY IN INTENSIVE CARE UNIT) or as a third every 20 minutes. Constant infusions may cause a gradual rise in morphine blood concentrations that can result in dangerous respiratory depression. The intramuscular and subcutaneous dose is about 200μg/kg 4 hourly. If this is not effective, an additional dose can be given an hour later, and again an hour later if necessary.

Morphine syrup contains 0.2, 1.0, or 2.0 mg per ml. Start with morphine 0.15 to 0.5 mg kg^{-1} hourly to four hourly. Oral morphine is effective for approximately 3 hours. As soon as the total daily dose has been determined, it is divided by two, and given as two doses of Morphine MST Continus. As tolerance occurs, the daily dose can be increased with 25%.

Morphine tablets (MST Continus sustained release) contain 10 or 30 mg. The dose is about 0.5 mg kg^{-1} 12 hourly. Morphine syrup at a dose of 25% of the present daily dose is given for brake through pain and the MST Continus dose is adjusted according to the new daily dose, i.e. the morphine in the syrup plus the tablet. Morphine syrup and tablets are reserved for the treatment of cancer pain.

Pethidine
Pethidine is not a drug of choice because it causes severe nausea and vomiting, myocardial suppression, increased peripheral vascular resistance and tachycardia. The bioavailability is 50% and the $T_{1/2}$ is 3 hours. Analgesia takes effect 1 minute after intravenous and 10 minutes after intramuscular injection. It is effective for 4 hours. Ampoules contain 25 mg per 1 ml, 50 mg per 1 ml or 100 mg per 2 ml. The dose is 1.0 to 1.5 mg kg^{-1} intramuscularly 4 hourly.

Pentazocine
This agonistic dualist can cause dysphoria, hallucinations, and systemic and pulmonary hypertension. The injection contains 30 mg per 1 ml or 45 mg per 1.5 ml. The dose is 0.5 mg kg^{-1} to 1.0 mg kg^{-1} intramuscularly or subcutaneously 4 hourly. The maximum dose is 5.0 mg kg^{-1} day^{-1}. Avoid this drug in porphyria patients and the elderly.

Dihydrocodeine
The table contains 30 mg and the injection 50 mg per ml. The dose is 0.5 mg kg^{-1} to 1.0 mg kg^{-1}; usually 0.4 mg kg^{-1} orally or 0.8 mg kg^{-1} intramuscularly or subcutaneously 4 hourly. The injections are *not for intravenous use*.

Codeine
Tablets contain 15 mg or 30 mg and the syrup 5 mg per ml. The dose is 0.5 to 1 mg kg^{-1} 4 hourly. *Note*: *It is doubted if codeine is of any value, as only about 10% is metabolised to the active metabolite morphine. Furthermore, this reaction stands under genetic polymorphism and is unpredictable. Codeine administration may thus be regarded as a complicated and unpredictable way of giving small doses of morphine.*

Tilidine
This drug is metabolised in the liver to the active metabolite, nortilidine. It is an agonistic dualist. The capsule contains 50 mg and the drops 2.5 mg per drop. The dose is 0.5 to 1.5 mg kg^{-1} 4 hourly; usually 0.8 mg kg^{-1}. The drug forms an effective combination with paracetamol. Avoid in porphyria.

Tramadol
This drug works as an opioid but also inhibits noradrenaline and serotonin reuptake, which produces analgesia. The serotoninergic cation contributes to the nausea and vomiting observed with this drug. It is contraindicated in pregnancy, lactation, and epilepsy. The dose is about 1.5 mg kg^{-1} orally 6 hourly.

- **Multimodal analgesia**

This is the application of several modalities to alleviate pain. NSAIDs and α_2-agonists decrease the need for opiates. These drugs can also be combined with regional analgesia. Although these combinations are theoretically advantageous as far as the crease of side effects are concerned, it is seldom possible to achieve complete post-operative analgesia during movement and coughing.

- **Pre-emptive analgesia**

Pre-emptive analgesia means the administration of analgesia before surgery. It has been found in animals to prevent spinal wind up and the resulting sensitisation for painful stimuli. In man, pre-emptive analgesia has not been very effective, because of the ongoing nociceptive output. On-going postoperative analgesia is therefore necessary for analgesia and to prevent sensitisation.

- **High technology methods**

These include nerve blocks, with or without local anaesthetic infusions, neuraxis blocks and patient controlled analgesia. These methods are very effective, but are expensive and labour intensive.

Acute versus chronic pain

Acute pain is caused by nociception that results from *injury, a disease process or abnormal function* of muscles or viscera. It serves to localize and limit the pathological process and is always accompanied by a *neuro-endocrine response*, the severity of which is proportional to the tissue trauma (see later). Acute pain usually subsides when treated or as healing takes place.

Whenever *pain persists* due to *inadequate treatment* or due to *abnormal healing*, acute pain becomes *chronic*. Chronic pain is often neurogenic (results from some nerve pathology like injury, tumour infiltration, etc.). *Chronic pain* is influenced strongly by psychological, behavioural and environmental factors. It is also disproportionate to the nature (grade, type) of the stimulus. Patients experience dysaesthesia, hyperaesthesia, allodynia, or paraesthesia. Chronic pain often persists. In order to prevent a chronic pain cycle, acute pathology should be treated adequately from the outset, both as far as nociception and healing is concerned. Furthermore, it follows from the pathogenesis of chronic pain, that its management lies at a different level as far as the approach and means are concerned. Chronic pain is treated with the anticonvulsants carbamazepine, gabapentin and pregabalin, the anti-depressants that inhibit both NA and serotonin re-uptake, e.g. amitriptyline, the membrane stabilizers lignocaine and mexilitine, and the inhibitors and the NMDA antagonists ketamine and dextromethorphan.

CHAPTER 11

ANESTHETIC CONSIDERATIONS AND PHARMACOGENETIC CONDITIONS: PORPHYRIA, SUXAMETHONIUM APNOEA, AND MALIGNANT HYPERTHERMIA

Key points
- *Porphyria*
  - Acute intermittent porphyria, variegate porphyria
  - Epidemiology
  - Porphyric crisis
  - General principles
  - Anaesthetic management
- *Inherited causes of abnormal butyrylcholinesterase (Scoline apnoea)*
  - The various variants of BuChE: EU normal enzyme, Ea atypical enzyme, Ef fluoride sensitive, Es silent
  - Dibucaine and fluoride number
- *Malignant hyperthermia (MH)*
  - Pathophysiology
  - Diagnosis
  - Differential diagnosis of and increased PETCO$_2$, tachycardia, and increased temperature
  - Management of malignant hyperthermia
  - Anaesthetic management in proven MH or a patient presenting for muscle biopsy for diagnosis
  - Masseter muscle spasm

Porphyria

The porphyrias are a group of diseases in which there is an *enzyme defect* in the synthesis of haem leading to *accumulation of the precursors* that are oxidized to porphyrins. The accumulation of products before the abnormal enzyme is aggravated by the *lack of negative feedback* by the end product (haem) on the enzyme δ-aminolaevulinic acid synthase. There are hepatic and erythropoietic varieties, but only the two common hepatic forms in South Africa, inherited in an autosomal dominant manner with variable expression, affect administration of anaesthesia:

- *Acute intermittent porphyria (AIP)*: Increased porphobilinogen and δ-aminolaevulinic acid (δALA) in the urine
- *Variegate Porphyria (VP)*: Increased copro- and proto-porphyrin in the stools

Epidemiology

In South Africa, porphyria can be traced back to a single marriage in 1688 of one of the free burghers of the Dutch Cape Colony. His name was Gerrit Jansz van Deventer who married an orphan from Holland, Adriaantjie Adriaanse. Common surnames such as Nel, Potgieter, Van Niekerk, Van Rooyen, Barnard, and Van Deventer should alert the anaesthetist to enquire about family members having porphyria. The prevalence in the South African population is 3 in 1000, but in the Eastern Cape it is 3 in 100.

Porphyric crisis

An acute porphyric crisis may be precipitated by drugs, infection, stress, alcohol, starvation and dehydration; that induce the rate-limiting enzyme δALA-synthetase. Symptoms include acute abdominal pain, vomiting, motor, and sensory peripheral neuropathy, cranial nerve palsies, autonomic dysfunction, mental disturbances, coma, and convulsions. Treatment consist of withdrawing possible precipitating drugs, reversing factors which increase δALA-synthetase such as treating infection, dehydration, giving glucose and haem arginate, which causes negative feedback of ALA synthetase. Treat all symptoms with 'safe' drugs.

General principles

Patients with a positive family history must be taken seriously and are potentially at risk. Latent carriers may exhibit no signs, may give only a positive history of skin sensitivity and still be at risk from acute attacks.

Anaesthetic management

Avoiding drugs that have the potential to trigger a porphyric crisis and potential precipitants such as infection and stress is essential. A table of drugs considered definitely unsafe, probably safe, and controversial can be found in the SAMF. Also, see the following web site: http://www.porphyria.uct.ac.za/professional/prof-blank.htm

Pre-medication is important to minimize stress as well as limiting fasting and administering a dextrose

drip during the fasting period. Definitely unsafe drugs often used during anaesthesia that needs to be avoided include barbiturates (such as sodium thiopental), etomidate, enflurane, alcuronium, analgesics such as diclofenac, tilidine, pentazocine, as well as metoclopramide and aminophylline.

When regional anaesthesia is considered, in the context of the peripheral neuropathy, a detailed preoperative examination and documentation before performing the regional is essential. In an acute porphyric crisis, regional anaesthesia should be avoided, as neuropathy may be rapid in onset and progressive.

With general anaesthesia, propofol is the induction agent of choice and can be used for maintenance. For neuromuscular blockade suxamethonium and atracurium, and for analgesia morphine, fentanyl and pethidine are considered safe. Neostigmine and atropine are safe reversal agents. *During the anaesthetic,* care should be taken with positioning due to a fragile sensitive skin and the delicate facial area should be protected from mask-induced trauma. Monitoring should be individualized, but hypovolaemia and the autonomic neuropathy may contribute to unstable intra-operative hypertension and tachycardia.

Post-operative management include adequate analgesia, hydration, maintaining a high caloric intake with intravenous glucose and/or TPN. Infection must be avoided and prophylactic antibiotics given appropriately.

Newly diagnosed porphyric patients need to wear a Medic Alert bracelet and follow-up testing, biochemical and/ or genetic, of relatives arranged.

Inherited causes of abnormal butyrylcholinesterase (Scoline apnoea)
Suxamethonium (succinyldicholine) is not metabolised by acetylcholinesterase (AChE) occurring in the neuromuscular junction, but by plasma butyrylcholinesterase (BuChE, PsChE), which hydrolyses it to form the inactive metabolite succynilmonocholine. Hydrolysis of suxamethonium starts immediately after it has been administered. Therefore, only a small fraction (about 10%) reaches the neuromuscular junction. The average adult has enough BuChE to metabolise about 1 mg kg^{-1} of suxamethonium per minute. Succynilmonocholine is a weak non-depolarising muscle relaxant.

BuChE also hydrolyses non-choline esters, including procaine, amethocaine, mivacurium, esmolol, cocaine, pancuronium, cyclophosphamide, and aspirin. Exogenously administered BuChE may be useful in the treatment of cocaine toxicity. BuChE is, like AChE, inhibited by carbamates and organophosphates.

The *effect of suxamethonium is terminated* by diffusion of the drug out of the junctional cleft. The duration of paralysis is therefore a function of clearance of the drug from the plasma by BuChE. Prolonged presence of suxamethonium in the neuromuscular junction causes a *Phase II block* (see Chapter 8). In the absence of normal enzyme or low levels, the drug is excreted by the kidneys. This can prolong paralysis to several hours. This is called suxamethonium apnoea or "Scoline apnoea".

The normal activity of BuChE is 600 IU L^{-1} to 1600 IUL^{-1}. At an activity < 400 IU L^{-1}, there is a steep increase in the recovery rate from suxamethonium-induced paralysis. *Decreased quantity or activity of BuChE* occur physiologically (pregnancy, neonates); in disease states such as burns, liver failure, kidney failure, cancer (effect of oncotherapeutic agents such as cyclophosphamide); iatrogenic, toxic (neostigmine, plasmapheresis, hormonal contraception, organophosphates), and genetic abnormal or absent enzyme.

Suppressed or abnormal BuChE (heterozygotes) causes muscle relaxation following suxamethonium lasting about 30 minutes, and is usually of no clinically important consequence. Even with a BuChE level of only 20% of normal, the effect of suxamethonium is prolonged from 3 minutes to about 9 minutes. In patients receiving echothiopate (an organophosphate) eye drops for glaucoma, BuChE

activity is decreased to about 50% and the duration of muscle relaxation following suxamethonium administration is between about 8 minutes. Administration of suxamethonium following reversal of a nondepolarising muscle relaxant prolongs the effect of suxamethonium to about 30 min.

It is not only the effect of suxamethonium that is prolonged with low BuChE activity, but also the drugs mentioned above, including the *nondepolarising relaxant mivacurium*. Therefore, do not administer this drug to patients lacking BuChE.

In patients with an *inherited abnormal or absent BuChE*, there is a change on this locus (Gene E) in the gene responsible for the production of BuChE. These variants of BuChE hydrolyse suxamethonium at different rates. Heterozygotes hydrolyse suxamethonium and mivacurium at a slower rate, whereas the homozygotes do not metabolise the drug at all.

The various variants have been described:
- EU normal enzyme
- Ea atypical enzyme
- Effluoride sensitive
- Es silent

Dibucaine is a local anaesthetic that has an affinity for BuChE and is used to detect atypical enzymes for which it has no affinity. Dibucaine inhibits the activity of normal plasma cholinesterase by approximately 80% (dibucaine number is 80). Dibucaine will inhibit only 20% of the atypical enzyme (dibucaine number is 20) (see Table 1). The sensitivity of BuChE to fluoride is used to identify the Ef genotype and is called the *fluoride number*.

Table 1 Dibucaine number and response to suxamethonium and mivacurium

Type of BuChE	Genotype	Dibucaine number	Response to SM and MVC
Homozygous typical	UU	70 to 80	Normal
Heterozygous	UA	50 to 60	Prolonged by 50% to 100%
Homozygous atypical	AA	20 to 30	Prolonged by 4 h to 8 h

SM, Suxamethonium; MVC; Mivacurium

Patients that appear to have "Scoline apnoea" should have a blood test done to determine butyrylcholinesterase levels, as well as the dibucaine and fluoride numbers. If these tests indicate absent or decreased BuChE activity, a "Medic Alert" bracelet is indicated to prevent the future administration of suxamethonium.

Clinical presentation of "Scoline apnoea"
This condition must be suspected if a patient fails to "wake up" and to breath after an anaesthetic technique, which included suxamethonium. In such cases all causes of prolonged emergence must be excluded. Neuromuscular monitoring will reveal abnormal neuromuscular function – usually a phase II block, which resembles a non-depolarising block. If the patient received a non-polarising muscle relaxant after the suxamethonium, and has subsequently been reversed by neostigmine, *pharmacological chaos* will leave you one option: ventilate the patient until all the drugs have worked out. Remember, neostigmine also blocks the breakdown of suxamethonium.

Management of "Scoline apnoea"
Sedate the patient since it is very unpleasant to be awake and paralysed. Ventilate the patient until muscle relaxation has been reversed. This may take several hours. Although the administration of BuChE (purified or in fresh-frozen plasma) has been advocated to manage prolonged apnoea, it is probably safer to ventilate the patient until muscle strength has returned to normal.

The C_5 *variant* of BuChE causes more rapid hydrolysis of suxamethonium.

Malignant hyperthermia (MH)

A pharmacogenetic syndrome described by Denborough and Lovell in 1960. It occurs in sensitive patients that are *exposed to trigger drugs, namely suxamethonium and al the anaesthetic vapours, but nitrous oxide is safe*. Before the availability of dantrolene, the mortality was about 80%; presently it is about 10%.

This condition is autosomal dominant with varying penetrance and decreased expression. That means that the full clinical syndrome does not develop in all patients. A patient may be exposed to triggering agents without any consequences, but may develop MH with subsequent exposure. Many of these undiagnosed patients complain of muscle cramps. The only condition shown to be connected to MH is *central core disease*. However, several musculoskeletal syndromes and myopathies have been associated with MH. On the other hand, many patients who have developed MH appear normal and lack features that could point to an underlying myopathy.

Pathophysiology

The sarcoplasmic reticulum (SR) stores Ca^{2+} bound to calciquestrin. During depolarization, Ca^{2+} is released from the terminal cisternae of the SR into the myoplasma to initiate interaction of the contractile proteins. The ryanodine receptor (RyR1) is the major Ca^{2+}-releasing channel in the SR membrane and is the defective channel in MH.

At the end of the action potential, the interaction of Ca^{2+} with the contractile proteins ends and calcium is pumped back into the SR against a ten thousand-fold concentration difference by the ATP utilizing SERCA1 Ca^{2+} pump, which is followed by muscle relaxation. Due to the high concentration difference, Ca^{2+} constantly seeps out into the myoplasma. This Ca^{2+} is also returned to the SR by the SERCA1 pump. ATP utilization causes heat production. This recycling of Ca^{2+} contributes to basal energy expenditure and heat production.

During an episode of MH, the myoplasma Ca^{2+} overload increases muscle tone. The massive release of Ca^{2+} from the SR by the RyR1 receptors overwhelms the capacity of the SERCA1 pumps to return the Ca^{2+} to the SR. The concomitant ATP consumption increases oxygen consumption five-fold. *Dantrolene* and the newer azumolene (not on the South African market) produce skeletal muscle relaxation by blocking calcium release from the SR and are the only drugs that terminate MH.

Diagnosis

The syndrome may have an insidious onset or may present with a florid presentation of the whole picture. It usually presents intraoperatively but may *rarely present postoperatively*. Genetically susceptible patients must be admitted to a high care unit postoperatively, since *MH may be retriggered.*

Following the administration of trigger agents, the first signs of MH are nonspecific and the result of increased metabolism, namely tachycardia, *rapid increasing end-tidal PCO_2 ($PETCO_2$)* – often > 80 mm Hg. Increased muscle tone (which may start out as increased masseter muscle tone) may occur early. This is characterised by inability to open the mouth for airway management and increased peak ventilator pressures. Increased temperature may be a late sign; once the temperature starts to increase, the rise is rapid and reaches 40°C or higher quickly. The patient becomes hypotensive and the skin becomes mottled. Death is caused by acidosis, hyperkalaemia, hyperthermia, haemostatic failure, and renal failure.

The first special investigations done are blood acid-base state and electrolytes. These usually show respiratory (elevated $PaCO_2$) and metabolic acidoses, as well as a hyperkalaemia. Once rhabdomyolysis starts, myoglobinaemia and myoglobinuria becomes evident (pink-brown urine) followed by renal failure. Creatine kinase (CK) increases.

The Larach clinical grading scale indicates the likelihood that the observed clinical picture was MH (Table 2). Do not memorise this scale, but you may need to use is in future.

Differential diagnosis of and increased PETCO$_2$, tachycardia, and increased temperature
- The most common cause of an increased intraoperative temperature is surgical drapes that cover the entire patient and overzealous heating.
- Hypoventilation (though, no increased temperature)
- Sepsis
- Blood transfusion reactions
- Thyrotoxicosis or thyroid storm
- Neuroleptic malignant syndrome
- Atropine toxicity
- Serotoninergic syndrome

Table 2 The Larach raw score[†] for clinical grading scale for MH

Process*	Indicator**	Points
Rigidity	Generalised muscular rigidity. (see 1 below)	15
	Masseter spasm shortly following succinylcholine administration.	15
Muscle breakdown	Serum myoglobin>17 µg L^{-1}	5
	K$^+$> 6 mM (see 2 below)	3
	Urine myoglobin > 60 µg L^{-1}	5
	Cola coloured urine in perioperative period.	10
	Elevated CK > 20 000 IU L^{-1} after succinylcholine.	15
	Elevated CK > 10 000 IU L^{-1} after anaesthetic without succinylcholine.	15
Respiratory acidosis	PETCO$_2$ > 55 mm Hg with appropriately controlled ventilation.	15
	PaCO$_2$ > 60 mm Hg with appropriately controlled ventilation.	15
	PET CO$_2$ > 60 mm Hg with spontaneous ventilation.	15
	PaCO$_2$> 65 mm Hg with spontaneous ventilation.	15
	Inappropriate hypercapnia (see 3 below)	15
	Inappropriate tachypnoea.	10
Temperature	Inappropriate rapid increase.	15
	Inappropriately increased > 38.8°C in the perioperative period. (see 3 below)	10
Cardiac involvement	Inappropriate sinus tachycardia.	3
	Ventricular tachycardia or ventricular fibrillation.	3
Other	Arterial base excess more negative than -8mmol/L.	10
	Arterial pH < 7.25.	10
	Rapid reversal of metabolic and/or respiratory acidosis with dantrolene.	5

1. In absence of shivering due to hypothermia, or immediately following emergence from inhalational general anaesthesia.
2. In absence of renal failure.
3. In anaesthesiologist's judgement.
The process refers to the system affected;
**The *indicators* point to the abnormality in the system;
[†] *Scoring.* Review the list of clinical indicators. If any indicator is present, add the points for each indicator while observing the double-counting rule below, which applies to multiple indicators representing a *single process*. If no indicator is present, the patient's MH score is zero.
Double counting: If more than one indicator represents a single process, only the indicator with the highest score is counted.
Exception: The score for any of the indicators mentioned under "other indicators" should be added to the total score disregarding the double-counting rule.
Interpretation:

Raw Score	MH rank	Description of Likelihood
0	1	Almost never
3-9	2	Unlikely
10-19	3	Somewhat less than likely
20-34	4	somewhat greater than likely
35-49	5	Very likely
50+	6	Almost certain

The clinical *diagnosis is confirmed with the in vitro contraction test* (IVCT) using halothane and caffeine as triggering agents. These tests consists of a muscle biopsy (muscle strip) that is exposed to trigger drugs and the degree of contraction is noted. Genetic studies include determination of the gene

coding the ryanodine receptor on chromosome 19.

Management of malignant hyperthermia
- Call for assistance and immediately order *dantrolene*; enough for at least 3 mg kg^{-1}.
- Immediately *terminate the vapour*, disconnect the *vaporisers* from the anaesthetic machine, increase the *fresh gas flow* to at least 10 L min^{-1}, and *hyperventilate* the patient to decrease the $PaCO_2$ and to wash out the vapour. Use a clean anaesthetic circuit and soda lime.
- Switch to an *intravenous anaesthetic* technique.
- Remove excessive drapes, blankets, and warming devices. Perform gastric lavage with cold Transfuse cold intravenous fluid and place ice packs over the large arteries (axilla, groin).
- The *metabolic acidosis and hyperkalaemia* usually improve once hyperventilation, fluid resuscitation, cooling and dantrolene take effect.
- *The specific antidote is dantrolene*. The dose is 2.5 mg kg rapidly intravenously every 10 minutes until a dose of 10 mg/kg has been given.
- Admit the patient to a *high care unit postoperatively* for at least 36 hours and administer dantrolene 1 mg kg^{-1} every 6 hours for at least 24 hours postoperatively.
- Treat myoglobinaemia if necessary (see Chapter 23)

All units where anaesthesia is administered must have at least 720 mg (36 × 20 mg) of dantrolene available.

Anaesthetic management in proven MH or a patient presenting for muscle biopsy for diagnosis
- *Avoid trigger drugs*, and use an intravenous or regional anaesthetic technique.
- All vaporisers should be removed from the anaesthetic machine. *Flush the machine* with oxygen 10 L min^{-1} for 20 minutes.
- Use new face masks and anaesthetic breathing circuits.
- *Dantrolene can also be used prophylactically* for patients with known sensitivity, but remember, dantrolene causes muscle weakness.

Masseter muscle spasm
An increase in *masseter muscle tone* is rather commonly observed after the administration of suxamethonium. It occurs in children as well as in adults. This is a normal reaction of the tonic muscles of mastication to suxamethonium. When it becomes excessive and prolonged, it is referred to as masseter muscle spasm (MMS). In about 7% of cases, MMS is followed by malignant hyperthermia (MH), while the halothane-caffeine contraction test is positive in about 60% of patients who develop MMS, indicating that they are MH-sensitive.

If a patient develops MSS after receiving suxamethonium, the procedure can be abandoned until the MH susceptibility has been excluded using an IVCT. Alternatively, manage the patient as for MH, except the administration of dantrolene. However, dantrolene should be available should MH follow MSS.
Remember that all patients who react abnormally to any drug must WEAR A medic alert bracelet.

CHAPTER 12

ANAESTHETIC APPROACH TO THE CARDIOVASCULAR SYSTEM

Key points
- In this lecture, the focus will fall on principles of cardiovascular physiology as they relate to anaesthesia. *Remember: The biggest enemy of the anaesthetist is hypoxia. One of the most important causes of hypoxia is ischaemia (lack of perfusion). All cardiovascular abnormalities will at some stage progress to ischaemia, and therefore hypoxia, i.e. lack of oxygen at cellular level.*
- *Preoperative assessment* of the cardiovascular system
- *Anatomical considerations in* vascular disease and cardiac disease
- *Physiological (functional) components* of cardiovascular disease
- *Determinants of cardiac output*: Preload, afterload, inotropy, pulse rate, rhythm, and impulse conduction, coronary perfusion, boundaries of the heart, intrinsic and extrinsic control of the cardiovascular system.
- *Perfusion, autoregulation, ischaemia, reperfusion injury, and oedema*
- *Pharmacological aspects of cardiovascular disease*
- *The cardiovascular system and anaesthesia*: Preload, afterload, inotropy, pulse rate, rhythm, and impulse conduction, coronary perfusion, boundaries of the heart, intrinsic and extrinsic control of the cardiovascular system
- *Intraoperative approach to the patient with cardiovascular abnormalities*:
  o Preload (hypovolaemia) and afterload (hyper- and hypotension)
  o Anaphylaxis
  o Inotropy
  o Intraoperative rhythm disturbances: Sinus bradycardia, **s**upraventricular bradycardia without P waves (nodal or junctional bradycardia), **s**upraventricular tachycardia with P waves, **s**upraventricular tachycardia without P waves (AV junctional or nodal tachycardia), **p**remature ventricular beats (PVC)
  o Intraoperative management of the patient with myocardial ischaemia
  o The boundaries of the heart: Pathology of the pericardium, mitral stenosis and regurgitation, aortic stenosis and regurgitation, prophylactic antibiotics, and anticoagulation
  o Control of the cardiovascular system: Intraoperative management of a patient with suspected autonomic neuropathy

In this lecture, the focus will fall on principles of cardiovascular physiology as they relate to anaesthesia. *Remember: The biggest enemy of the anaesthetist is hypoxia. One of the most important causes of hypoxia is ischaemia (lack of perfusion). All cardiovascular abnormalities will at some stage progress to ischaemia, and therefore hypoxia, i.e. lack of oxygen at cellular level.* If hypoxia is caused by a low cardiac output, it is called *stagnation or ischaemic hypoxia*. If the tissues do not receive oxygen, they cannot consume it. Therefore, a low cardiac output will decrease oxygen consumption (VO_2) (See Chapter 14).

Patients work hard during and after surgical procedures; they need substrate (oxygen, nutrients) to repair traumatized tissue. Where does the *extra substrate* come from? It is supplied from the *patient's reserves*, i.e. *nutritional state* from where nutrients can be mobilized, and by the *cardio-vascular-respiratory reserves*, which increase the *oxygen supply* during the period of tissue injury and repair. This response to injury is called the *stress response* (see Chapter 17).

If the patient is unable to supply substrate during the stress response and tissue repair, a state of *homeostatic failure* with *multiorgan failure* ensues. Therefore, patients who are unable to supply substrate to survive the stress response and to repair injured tissue will need *perioperative (pre-, intra, and postoperative) homeostatic support to survive*. This *homeostatic support includes* preoperative optimisation, intraoperative support, and additional postoperative physiological support. *Without this reserve and support, the morbidity and mortality is high. How much reserve does the patient need?* This topic is very important and is addressed in Chapter 14.

The preoperative evaluation of the patient with cardiac disease presenting for elective non-cardiac procedures is based on their:
1. Cardiac reserve: history of ischaemic heart disease, i.e. symptoms, previous infarction, angioplasty, bypass surgery)
2. Metabolic reserve: functional capacity (METs)[xiv] and
3. Oxygen demand in the perioperative period: type of surgery.

After the preoperative assessment of all the components mentioned above, you must *consider the outcome* of the patients presenting for a procedure (therapeutic of diagnostic); is the patient going to be discharged from hospital alive and well? What are the risks and the benefits? Will the patient be able to recover (heal) from the procedure?

Preoperative assessment of the cardiovascular system
The aim of evaluation of the cardiovascular system is to assess the reserve to survive the procedure. In this regard, emergency surgery is easier since the anaesthetist receives the patient with cardiovascular compromise in theatre. There is little time for special investigations or optimization. The assessment is often limited to a history (often scant) and a clinical examination. The anaesthetist must work with what is presented to him/her.

What should be assessed? Now remember, the function of the cardiovascular system is tissue perfusion. For elective procedures, all the components determining perfusion must be optimized. The components must be stratified (what is the degree of pathology) and optimized (treated). Cardiovascular (cardiac and vascular) diseases have the following components: *Anatomical, physiological, pharmacological, monitoring. These four components interact with one another, always*. It is the *cardiac and vascular* systems. All these components must *be considered together*. You must consider the *distribution* of disease (cardiac or vascular) and the *aetiology*. If you find one component, look for the others. If a patient suffers from *any systemic disease, congenital defects, or chromosomal defects, you must consider the co-existence of cardiac and vascular lesions, e.g. congenital heart disease, coarctation of the aorta, dextrocardia, etc.* Furthermore, you must consider these aspects *preoperatively, intraoperatively, and postoperatively*.

ANATOMICAL COMPONENTS OF CARDIOVASCULAR DISEASE

- The cardiovascular system consists of the pulmonary and systemic circulations. These systems are arranged in series, and consist of the systemic and pulmonary circulations. Each of these components consists of two systems in series: pump $\rightarrow$ arterial (efferent) network $\rightarrow$ capillary bed $\rightarrow$ venous (afferent) network $\rightarrow$ pump.
- Although it is customary to speak of the left heart and systemic circulation and the right heart and the pulmonary circulation, these systems function in tandem: malfunction of the one usually adversely affect the other. The up- and downstream pressures or beginning and end of the systemic circulation are the left ventricle and the right atrium, while the up- and downstream pressures of the pulmonary circulation are the right ventricle and the left atrium.
- These right (pulmonary) and left sided (systemic) systems do not function in isolation, but interact (in parallel) via humoral (hormones) and mechanical factors (interatrial and –ventricular septae and atrio-ventricular valves). Malfunction of these humoral factors and mechanical borders adversely affect the other systems.
- *Anatomical considerations in vascular disease*
  - May involve arteries and/or veins (e.g. venous thrombosis)
  - May be localized or diffuse.
  - Is often caused by systemic metabolic (e.g. diabetes mellitus, hypercholesterolaemia, thyroid disease) or immune-mediated disease (SLE, HIV, Takayasu arteritis).
  - Is often associated or complicated by other vital organ dysfunction, e.g. renal failure,

---

[xiv] A MET refers to a *metabolic unit* and is the amount of oxygen used per minute by a person during rest. In an adult it is about 3.5 ml kg^{-1} min^{-1}. See also Chapter 15

cerebrovascular disease, coronary artery disease, abnormal clotting, etc.
- o Is often aggravated by hypertension (arteriosclerosis, aneurismal changes, rupture).
- o Is often caused by other organ failures, e.g. respiratory failure (right heart hypertrophy, failure) and renal failure (hypertensive changes, remodelling).
- *Anatomical considerations in cardiac disease*
  - o Is often caused by *systemic*, e.g. hypertension and rheumatic fever, or *primary cardiac* disease, e.g. cardiomyopathy.
  - o May involve one or more, but often all the *cardiac components*, i.e. epi- and *pericardium* (effusions, fibrosis, and tamponade), *myocardium* (hypertrophy, dilatation, ischaemia, infarction, cardiomyopathy, myocarditis), *endocardium and valves* (endocarditis, stenosis, regurgitation, mural thrombosis), *boundaries of the heart* (valves, septae, free walls of the heart, epi- and pericardium), *coronary arteries* (stenosis or occlusion caused by atheroma, inflammation, thrombosis), and the *pacemakers and conductive tissue* (atrial, atrioventricular, ventricular, accessory). The disease may involve mainly the *left side or the right side* but eventually both sides.
  - o Is often found in *systemic metabolic* (e.g. diabetes mellitus, hypercholesterolaemia, thyroid disease, phaeochromocytoma), *immune-mediated* disease (SLE, HIV), vascular disease (hypertension, ischaemic heart disease), or pulmonary disease (COPD, fibrosis, infection). The heart is often the target of *systemic inflammation*, e.g. sepsis.

PHYSIOLOGICAL (FUNCTIONAL) COMPONENTS OF CARDIOVASCULAR DISEASE

You must consider the following statement very carefully. If you do not appreciate the importance thereof, you are going to harm patients: *The function of the cardiac and vascular systems is to transport oxygenated blood to all tissues.* The physiology of the heart is *influenced by anatomical and pharmacological factors*. Determinants of cardiac output, perfusion and ischaemia, autoregulation, and oedema are summarized in Table 2.

Determinants of cardiac output
Stroke volume (SV) refers to the amount of blood ejected by the heart into the pulmonary and systemic circulations during one heart cycle. Cardiac output (Q) is the SV × heart rate (HR). *The functional components underlying cardiac output are* preload (right and left hearts), afterload (of right and left hearts), inotropy (contractility), pulse rate, rhythm, and conduction, myocardial perfusion, and control of the heart (intrinsic and extrinsic).

Now listen carefully: You must always be aware of the close interaction between these functional components of the cardiac function. A change in one of the components always affects all the others and cardiac output to some extent. A change in cardiac output will also have an effect on all these components to some extent. The more these components are subject to disease, the more prominent these changes and interactions are. The examples given in the following section occur very commonly, and you will come across them often – as GP anaesthetist and specialist anaesthetist.

Preload is the left and right ventricular end-diastolic diameter or volume (EDV) and is responsible for the Starling law of the heart: Within physiological limits, the stroke volume and contractility is proportional to the preload. However, when this characteristic is exhausted, the heart dilates (fails) and the heart contains a large amount of blood at the end of systole (ESV). On the other hand, if the heart does not receive blood, the contractility and the stroke volume is low. If the heart is over-stretched, the heart cannot eject all the blood and the stroke volume decreases (Staring's law of the heart). See Figure 1.

Preload is influenced by venous return (intravascular volume), and the ability of the heart to receive blood. The ability of the heart to receive blood is called the *diastolic function* of the heart. The diastolic function of the heart is decreased by *anatomical factors* (e.g. mitral stenosis, myocardial remodelling, pericardial disease, including fibrosis, effusion, and tamponade), *physiological factors*

where the heart does not relax completely during diastole (lusitropic failure) (e.g. myocardial ischaemia (NB)), or *pharmacological* (sympatholytics).
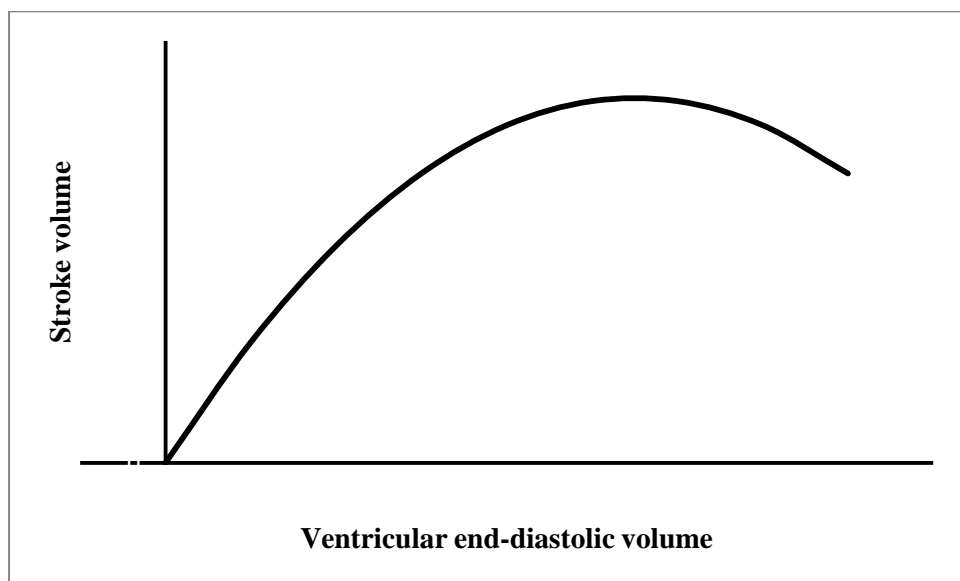
Figure 1 Effect of preload on stroke volume (Starling curve)

Afterload is the tension that develops in the ventricular walls during systole. It gives an indication of the work the ventricle must perform to eject the SV.

During systole, the shortening myocardium develops force, which increases intraventricular pressure. This pressure (P) must overcome the pressure in the aorta to eject the stroke volume and represents the transmural pressure (pressure inside – pressure outside). The force, or wall tension or stress (T) that develops in the wall of a ventricle with a cavity radius r, and wall thickness h, is described by the law of Laplace for a sphere:

$$T = Pr/2h$$

Laplace's law states that wall stress increases if intraventricular pressure (P) and/or radius (r) increase, but decreases if the wall (h) of the ventricle thickens (a thick ventricular wall protects against increased pressure, while a thin dilated ventricle is vulnerable to increased pressure). In other words, a higher pressure and a larger ventricle cause a greater oxygen demand.

The causes of an increased afterload include:
- *Anatomical*: aortic stenosis, pulmonary stenosis, and coarctation of the aorta
- *Physiological*: pulmonary hypertension, essential hypertension, secondary hypertension (phaeochromocytoma, hyperthyroidism, hypothyroidism, diabetes mellitus, Cushing syndrome, renal failure, etc.), and hypothermia (vasoconstriction).
- *Pharmacological*: all vasoconstrictors, including recreational drugs such as the amphetamine derivatives and cocaine.

Blood pressure is the pressure that exists in the vascular system, namely pulmonary and systemic arterial, arteriolar, capillary, and venous. The arterial pressures are determined by the cardiac output (Q = SV × HR), the pressure at which the SV is ejected into the arterial system (pulmonary and systemic) and the resistance (R) exerted by the arterial system:

$$\text{Blood pressure} = Q \times R = SV \times HR \times R$$

Therefore, you must interpret a blood pressure in the clinical context (Table 1 gives some common examples). If you do not have access to monitors to assess the sufficiency of Q, you can in general regard blood pressure as normal (or at least not life threatening) if:
- It is "normal" for the patient (the blood pressure which the patient is used to, within the autoregulatory limits (see later),

- There are *no clinical signs of hypoperfusion*, i.e. clinical signs of shock (hypovolaemic, anaphylactic, neurogenic, septic, and cardiogenic),
- *Normovolaemia* – neither hypovolaemia (absolute or relative) nor hypervolaemia (cardiac failure, renal failure),
- *There is adequate end-organ function*. This includes all of the following: hydration state, colour (not anaemic or cyanotic), normal temperature of the extremities (not cold and clammy, or warm and dry, or warm and clammy), consciousness (in presence of a normal and awake brain), respiratory function (tidal volume, respiratory rate), adequate urinary output (although not a very reliable sign of kidney function, oliguria is still a useful marker of a low cardiac output).
- A *normal homeostatic state*, i.e. acceptable blood chemistry (electrolytes and acid-base state) and acceptable haematocrit. *If you do not have access to these investigations, and you must resuscitate a patient, the above mentioned clinical signs are crude but still reliable signs to assess your attempts and that you may safely transfer the patient to another centre.*

Table 1 Blood pressure (BP), cardiac output (Q), and systemic vascular resistance (SVR)

BP	Q	SVR	Example
Normal	Normal	Normal	Normal
	↑	↓	Hyperthyroidism, SIRS, β_2 stimulants
	↓	↑	Hypovolaemia, cardiac failure, aortic cross-clamping, hypothyroidism
↑	normal	↑	The hypertensive patient
	↑↑	↓	Hyperthyroidism, physical exercise
	↑↑	↑↑	Phaeochromocytoma, α stimulants, aortic cross-clamping, spinal AN
	↑	normal	Hypervolaemia with a normal heart
	↓↓	↑	Hypertensive cardiac failure, pre-eclampsia
↓	normal	↓	Relative hypovolaemia with vasodilatation
	↑	↓↓	Septic shock, neuraxis block + adequate intravascular volume
	↓↓	↑	Absolute hypovolaemia, cardiogenic shock, abdominal compartment syndrome
	↓↓	↓↓	Severe relative hypovolaemia, vagal reflexes

AN autonomic neuropathy

Hypertension is a multisystem disease. Patients with hypertension often suffer from cerebrovascular disease, ischaemic heart disease, cardiac diastolic dysfunction, renal impairment, etc. Patients with a systolic blood pressure > 180 mm Hg and/or a diastolic blood pressure > 110 mm Hg must be postponed. *Although this statement may be contentious, hypertension of this degree is most probably associated with significant morbidity, which may only benefit from a lower perioperative blood pressure.* End-organ involvement must be evaluated with special investigations, e.g. ECG, chest X ray, serum urea, creatinine and electrolytes, etc. Patient must receive their routine medication throughout the perioperative period (perhaps, excluding ACE inhibitors and angiotensin receptor blockers). Do not forget to give the antihypertensive drugs postoperatively!

Any condition (anatomical, physiological, or pharmacological) that increases the afterload also increases the myocardial *oxygen demand* and decreases the coronary oxygen (flow) reserve. *If chronic*, the heart undergoes anatomical changes. These changes are mediated by *neurohumoral* activation involving the *kidney*. The physiological changes result in *hypertrophy*, interstitial fibrosis, and eventually *dilatation*. This process is mediated by aldosterone, and is called *remodelling*. Remodelling affects *both diastolic and systolic function*.

Cardiac remodelling is an important concept, which is present in virtually all diseased hearts. This process is reversible to some extent by ACE inhibitors, angiotensin inhibitors, aldosterone receptor inhibitors such as spironolactone and eplerenone, and β blockers such as carvedilol. This concept illustrates the close *interaction between the heart and kidneys (cardiorenal interaction)*. Therefore, if you diagnose a cardiac problem in your patient preoperatively, you must also consider renal pathology and *vice versa*.

All patients with heart problems activate a neuro-endocrine/humoral response involving the kidneys, and virtually all patients (except some diabetics) with renal pathology have increased renin-angiotensin-aldosterone system (RAAS) activity, which promotes cardiac remodelling.

All remodelled hearts are non-compliant (stiff) and are filled at higher pressures. This is called *diastolic dysfunction*. Can you see the interaction between preload and afterload? Therefore, if you identify any factor that increases afterload, or when you see an enlarged heart on a chest X-ray, you must suspect that the heart:

1. requires more oxygen than normal hearts,
2. has a lower oxygen reserve (lower METs – see Chapter 14),
3. is stiff and dependant on adequate filling pressures (very sensitive to hypovolaemia),
4. is very dependent on adequate myocardial perfusion (becomes ischaemic easily),
5. is very sensitive to an increased afterload (increased oxygen demand), and
6. that the perioperative morbidity and mortality may be increased.

Causes of a decreased afterload include:
Conditions (anatomical, physiological, or pharmacological) that decrease the afterload (vasoplegia), are often accompanied by a hyperdynamic circulation (hyperthyroidism, sepsis), or hypotension (septic shock, neurogenic vasodilatation):

- *Anatomical*: Arterio-venous fistulae (blood is shunted directly from an artery to the veins and back to the heart). This increases the venous return to the heart and may cause high-output cardiac failure.
- *Physiological*: Any arteriolar vasodilatation causes a decreased afterload. The causes may be vasovagal, autonomic neuropathy (diabetes mellitus, uraemia), hyperthermia, hypermetabolism (hyperthyroidism), hypercapnia, sepsis (including *septic shock*), anaphylaxis, spinal shock of spinal cord injury, etc.
- *Pharmacological*: All arterial vasodilators, including nitrates, calcium channel blockers, α blockers, ACE inhibitors, sympathetic block.

Vasodilated patients:
- may have a *low cardiac output* due to a decreased preload (spinal shock, vasovagal shock, anaphylaxis, venodilators such as nitrates).
- may have a *hyperdynamic circulation* (hyperthyroidism, sepsis, hyperthermia)
- may have a *lower myocardial oxygen demand* and increased oxygen reserve, but hypotension *decreases coronary perfusion*.
- may be hypotensive due to vasodilatation and must, if possible, be *stabilized before induction of anaesthesia* (general or regional) since all anaesthetic agents (except ketamine) are *vasodilators*, *mechanical ventilation* aggravates the hypotensive effect of vasodilatation, and *intraoperative volume loss* compromises vital organ perfusion.

Inotropy
Inotropy refers to the ability of the myocardium to contract. Any factor that influences myocardial physiology, affects contractility. These factors include anatomical, physiological, and pharmacological:
Anatomical: congenital heart disease, all remodelled hearts, infection, degenerative (all cardiomyopathies), etc.
Physiological: Preload (Starling mechanism; an empty heart does not contract; an over-filled heart fails), ischaemia, sympathetic stimulation or suppression, hypertrophy, sepsis, inflammation, malnutrition, electrolyte disturbances, etc.
Pharmacological: All drugs that influence the sympathetic nervous system directly or indirectly, all drugs that affect intracellular calcium (digoxin, drugs acting on α or β adrenergic receptors, calcium blockers, magnesium, *anaesthetic vapours and induction agents*), cardiotoxic agents (ethanol, oncotherapy), etc.

The percentage of the preload that is ejected by the ventricle is called the *ejection fraction (EF)*. The EF gives an indication of myocardial contractility. The normal EF of the left ventricle is between 50% and 75%. If your patient had an EF of < 50%, it is low; if it is < 40%, it is critically low. The normal right ventricular EF is about 30%.

$$EF = \frac{\text{End-diastolic volume} - \text{End-systolic volume}}{\text{End-diastolic volume}}$$

Although the EF is low, the stroke volume may still be maintained. How does that work? Look at the concentric circles (read spheres) in Figure 2:

A: Normal heart and EF

B: Dilated heart with low EF
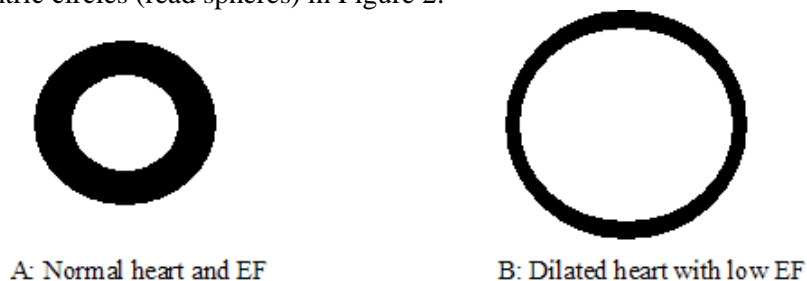
Figure 2 The normal and dilated heart

The areas (volume) between the outer and the inner circles represent the EF or stroke volume. This area (volume) in the dilated heart (B) is about the same as that of the normal heart (A). *Therefore, if you read on a cardiac sonar report that the EF is low, you must realize that this heart is more dependent on contractility, low afterload, and an adequate preload (not too little, not too much).*

Patient in decompensating *cardiac failure* must *not be exposed to elective non-cardiac surgery*. Preoperative function must be optimised. Special investigations that will point to complicated cardiac failure include a chest radiograph, echocardiography, serum urea, creatinine and electrolytes, etc.

Patients with myocardial failure are very sensitive to the effects of surgery and anaesthesia on the circulatory system (ability to provide oxygen for the increased VO_2). They must continue taking their medication. Due to its borderline cardiac function, the cardiovascular system must be monitored more closely perioperatively. Therefore, the patient must be admitted to a *high care facility postoperatively*.

Pulse rate, rhythm, and impulse conduction
Pulse rate, rhythm, and impulse conduction determines cardiac synchrony. The heart rate determines the duration of diastole; the shorter the diastole, the shorter the time for the ventricles to fill and for coronary perfusion. Therefore, *tachycardia* causes passive diastolic dysfunction (too little time) and active diastolic dysfunction (inability of the myocardium to relax due to a lack of ATP). In young normal hearts, this point is reached at high heart rates of about 180 min^{-1}, however in hearts that are preload dependant or ischaemic, this point is reached at far lower rates (< 100 min^{-1}). On the other hand, during a *bradycardia*, the filling time may increase to such an extent that the ventricles overfill (increased radius). This increases wall tension (increased oxygen demand) and causes the ventricle to dilate (fail – remember the knee of the Starling curve).
Therefore, you must take cognisance of an abnormal electrophysiological state in the heart preoperatively and control heart rate, rhythm, and conduction preoperatively:
- An abnormal pulse rate, rhythm, and impulse conduction (dysrhythmias), *affect the determinants* of cardiac output (preload, afterload, contractility, and myocardial perfusion).
- The effect of abnormal heart rates is very often reflected by signs of myocardial ischaemia on the ECG, and *vice versa*.
- Dysrhythmias do not come from nowhere; they are very *often an indication of significant cardiac disease* of whatever cause.
- Elective surgery must be postponed until the cause and treatment of the dysrhythmia has been addressed. In adults, a preoperative heart rate > 90 min^{-1} is associated with an adverse outcome. Bradydysrhythmias (< 50 min^{-1}) must also be attended to.
- Dysrhythmias are often caused by *homeostatic factors*, including abnormal *electrolytes, especially potassium, calcium, and acid-base state. Potassium levels outside the normal range (more than*

about 5.3 mM or lower than about 3.5mM) are associated with an increased morbidity and mortality. Low potassium must be corrected, especially in patients taking digoxin and in patients with ischaemic heart disease. Total *serum calcium* of > 3.2 mM or ionised *calcium* < 0.5 mM must be treated urgently. The causes of the electrolyte abnormalities must be attended to and the electrolytes (both high and low) must be corrected to as close to normal as possible.

- Patients suffering from dysrhythmias often receive treatment. These include *anticoagulants*, e.g. warfarin and antidysrhythmic drugs, e.g. amiodarone, β blockers, and digoxin. Circumstances will determine change to heparin or stopping anticoagulation altogether (eye, brain, and liver surgery). Take note of the *treatment of dysrhythmias*: *rate* control (β blockers, calcium blockers, digoxin), *rhythm* control (Class I and III drugs), *pace maker and conduction* control (implanted pace makers).
- The stress response of surgery is dysrhythmogenic.

Coronary perfusion

This component of the circulation cannot be over-emphasized. It also starts in an artery (coronary ostiae in the root of the aorta) and eventually drains to coronary sinus in the right atrium and the ventricular cavities. The coronary circulation bridges the systemic and pulmonary circulation (left and right heart). Malfunction in any part of the coronary circulation (from the aortic valve to the right atrium) or of the rest of the systemic circulation (from the left ventricle to the right atrium), will affect the coronary circulation. The reverse is also true.

The most common cause of myocardial ischaemia is coronary artery disease (CAD). However, myocardial hypoxia may occur in the absence of CAD. Any factor (anatomical or physiological) that increases myocardial oxygen demand without a congruent increase in supply, e.g. severe hypotension and severe hypoxaemia (very low haemoglobin concentration or PaO_2), causes myocardial hypoxia, which is very often observed on the ECG of such patients.

No patient with unstable myocardial perfusion should be allowed to undergo elective surgery.

Boundaries of the heart

The boundaries of the heart divide the cardiovascular system into functional components and from the other organs in the thorax. They are the interatrial and -ventricular septae, valves, the free walls of the atria and ventricles, and pericardium. Any factor that displaces, removes, or closes the boundaries of the heart has a large impact on cardiac function (al the functional components). These include:

- *Pressure from the outside*: tension pneumothorax, mediastinal tumours, pericardial disease, and interventricular septal shift.
- *Absent boundaries*: valve regurgitations, atrial septal defects, ventricular septal defects, perforating cardiac trauma.
- *Closed boundaries*: valve stenoses, outflow obstruction (congenial, cardiomyopathy).

Control of the cardiovascular system

The heart is controlled by intrinsic and extrinsic mechanisms. The **extrinsic** mechanisms include the autonomic nervous system and several hormones.

The **intrinsic** mechanisms include the Starling mechanism, Anrep effect, Treppe effect, Bainbridge reflex, and Bezoldt-Jarrish reflex, and the secretion of atrial natriuretic polypeptide. *In the healthy heart*, inotropic function increases with an increased afterload (Anrep effect) or increased heart rate (Treppe effect). An increase in preload causes an increase in heart rate (Bainbridge reflex), while a decreased preload (empty heart) causes a bradycardia (Bezold-Jarisch reflex). The latter is observed during spinal anaesthesia when vasodilatation causes under-filling of the heart, or when a patient is put in a beach chair position with legs down .

To illustrate the interactions between the components, look at the following examples:
Hypovolaemia (decrease preload)
↓preload →↓inotropy (Starling) + ↓stroke volume →↓cardiac output →↓blood pressure → global ischaemia →↑sympathetic nervous system (SNS) + ↑RAAS →↑afterload (which may initially maintain blood pressure – remember, BP = vascular resistance × cardiac output)
↓blood pressure →↓coronary perfusion →↓inotropy
↑SNS + ↑RAAS →↑tachycardia →↓coronary perfusion → abnormal wall movement →↓stroke volume

Aortic stenosis (AS):
- ↑afterload→ concentric hypertrophy → ↓coronary perfusion + ↓ventricular volume → ↓preload → ↓cardiac output + ↓hypotension
- ↓cardiac output + ↓hypotension → ↑sympathetic nervous system (SNS) and rennin-angiotensin-aldosterone stimulation (RAAS)
- ↑SNS + ↑RAAS →↑adrenaline → ↑afterload + tachycardia + ↑inotropy → ischaemia, etc, etc
- ↓blood pressure in coronary sinuses → ↓coronary perfusion
- hypertrophy + myocardial ischaemia → (usually) tachydysrhythmias
- tachydysrhythmias → ↓diastolic time → ↓coronary perfusion + ↓preload

Mitral stenosis (MS)
- MS →↑ left atrial after load + ↓left ventricular (LV) filling →↓LV preload → ↓ inotropy + ↓ stroke volume →↓ cardiac output →↓ blood pressure
  ↑left atrial (LA) after load →↑pulmonary venous pressure + pulmonary oedema →↑pulmonary arterial pressure →↑right ventricular (RV) afterload → RV enlargement → shift of interventricular septum →↓LV preload →↓ stroke volume →↓ cardiac output →↓ blood pressure
- ↓blood pressure →↑SNS → tachycardia
  ↑ LA volume → atrial fibrillation → tachycardia
- Tachycardia + ↓ blood pressure → myocardial ischaemia, etc.

Explain the following examples:
- Systemic hypotension → myocardial ischaemia
- Systemic hypertension → myocardial ischaemia
- Myocardial ischaemia → systemic hypotension
- Pulmonary hypertension → myocardial ischaemia
- Myocardial ischaemia→ pulmonary hypertension
- Myocardial ischaemia → right or left ventricular failure
- Right or left ventricular failure → myocardial ischaemia
- Cardiac failure →↓ serum sodium
- Cardiac failure →↑ systemic vascular resistance

- ↑Catecholamines → myocardial ischaemia
- Hypo- and hyperkalaemia → cardiac failure
- Cardiac failure → hypokalaemia
- Left ventricular failure → pulmonary oedema
- Ventricular septal defect→pulmonary hypertension
- Pulmonary hypertension → systemic (peripheral) oedema
- Pulmonary hypertension → left ventricular failure
- Systemic hypertension → left ventricular failure
- Pulmonary hypertension→ RV failure

ISCHAEMIA AND REPERFUSION

Ischaemia
Perfusion is blood flow, while *ischaemia* is decreased blood flow (perfusion). Blood flow is dependent on perfusion pressure and systemic or local vascular resistance (VR) in an organ. Perfusion pressure (PP) = inflow pressure (Pi) – outflow pressure (Po). Therefore,

$$Blood\ flow = PP/VR.$$

You must appreciate the concept of ischaemia. It occurs very commonly and has a very high morbidity (e.g. myocardial infarction, cognitive impairment, prolonged hospitalisation) and mortality. Whenever a patient becomes hypotensive, you must consider the development of ischaemia. The larger the part of the body that is ischaemic, the wider is the systemic impact of ischaemia. ***Ischaemia does not only occur in training hospitals; it occurs everywhere***; in all trauma victim depending on the injuries sustained; it occurs in the brains of foetuses of severely hypotensive parturients; it occurs in the brains and myocardia of all hypertensive elderly patients you anaesthetise for a fractured hip.

Perfusion ensures transport of substrate to organs, i.e. all substances that supports metabolism. These substance include nutrients and oxygen to tissue. The products of metabolism depend on the function of the perfused organ, e.g. glucose from liver gluconeogenesis and glycogenolysis, but lactate and CO_2 from skeletal muscle. Perfusion is also responsible for *the removal* of the products of metabolism.

Ischaemia is the lack of perfusion and may be local or systemic:
Local ischaemia is caused by occlusion of arteries (e.g. tourniquet, peripheral vascular disease,

thrombo-embolism), rupture of arteries (e.g. aortic aneurysm, cerebral aneurysm) or venous occlusion (e.g. thrombosis).

Systemic ischaemia is always the result of a low cardiac output or maldistribution of cardiac output, in spite of a normal or high cardiac output. *The complications of ischaemia* depend on the following factors:

- *Duration*: initially only temporary physiological failure, e.g. myocardial failure; prolonged ischaemia results in tissue necrosis with permanent loss of function. The brain is irreversibly damaged within a total ischaemic time of about 5 min at normothermia.
- *Perfusion reserve*: the less the reserve, the more vulnerable the organ, e.g. an ischaemic myocardium does not tolerate additional ischaemia.
- *Distribution of ischaemia*: cross clamping of an abdominal aorta to repair an aneurysm with ischaemia of the legs and gut vs. a tourniquet on a arm for hand surgery.
- The *function of the ischaemic organ*:
  o *Cerebral ischaemia* results in failure of higher functions (consciousness), vegetative functions (autonomic nervous system, neuro-endocrine function)
  o *Myocardial ischaemia* results in pump failure;
  o *Lung ischaemia* causes abnormal gas exchange (hypoxia and hypercapnia);
  o *Kidney ischaemia* causes fluid and electrolyte abnormalities;
  o *Liver ischaemia* is characterized by hypoglycaemia, lactic acidosis, and decreased detoxification of metabolites (lactate, citrate in bank blood, haemoglobin), toxins (alcohols), drugs (paracetamol, etc., etc., etc.);
  o *Intestinal ischaemia* is followed by breakdown of the epithelial barrier with malabsoption, abnormal intestinal flora, and translocation of endotoxin to the circulation;
  o *Placental ischaemia* results in foetal hypoxia.

Ischaemia does not only affect the particular end organ, but gives rise to *a post-ischaemic syndrome*. Several intracellular substances are released into the circulation. These include K^+, phosphate, myoglobin (nephrotoxic), lactate, etc. Translocation of intestinal endotoxin incites a *systemic inflammatory response syndrome (SIRS)* and eventually homeostatic failure culminating in *multiple organ failure*. Ischaemia of vital organs may result in a SIRS-like syndrome, e.g. in patients with ischaemic and traumatic brain injuries. Hypoperfusion states are always complicated by a *lactic acidosis*. The SIRS following protracted systemic ischaemia is often accompanied by *haemostatic failure* (hypercoagulability followed by a bleeding diathesis).

SIRS is a systemic inflammatory response following any severe insult. The cardiac (myocardial suppression) and vascular (vasodilatation) of SIRS is mediated by cytokines, including interleukins and nitrogen monoxide (NO). You make the diagnosis when two or more of the following exist:
- Core temperature > 38°C or < 36°C
- Heart rate > 90 min^{-1}
- If a patient is breathing spontaneously, a respiratory rate > 20 min^{-1} or PaCO$_2$< 32 m Hg
- White blood cell count > 12×10^9 L^{-1} or < 4×10^9 L^{-1}

Multiple organ failure is the presence of abnormal functions of several organs in the acutely ill patient to such an extent that homeostasis cannot be sustained without intervention (support of the failing organs).

Sepsis is SIRS with infection. If sepsis as accompanied by organ dysfunction, e.g. lactic acidosis, oliguria, or an acute decrease in mental state, the condition is called *severe sepsis*.

Sepsis with hypotension, i.e. systolic blood pressure < 90 mm Hg or a decrease of > 40 mm Hg from the patient's premorbid (before the disease) blood pressure, despite adequate fluid resuscitation, is called *septic shock*.

Reperfusion and reperfusion injury
Reperfusion occurs when blood flow to an organ is restored, e.g. after the deflation of a tourniquet. During the ischaemic time, anaerobic metabolism increases tissue lactate production, membrane pumps fail with the release of K^+, ischaemic membranes initiate the production of prostaglandins, CO_2 accumulates, etc. When the tissue is reperfused, all these metabolites are released into the circulation. The reperfused tissue, e.g. leg vasodilates and steals blood from the rest of the vascular bed, while the

metabolites that are released into the systemic circulation cause systemic vasodilatation. Therefore, reperfusion of large vascular beds is complicated by hypotension and a transient hypercapnia, lactic acidosis, and hyperkalaemia. The hypotension is also transient, but may necessitate the administration of fluid and/or vasoconstrictors such as phenylephrine (0.5 μg kg^{-1} to 1.0 μg kg^{-1}). This phenomenon is called the *reperfusion syndrome.* (Please note that the increase blood pressure following phenylephrine administration gives a false sense of improvement since the pure vasoconstrictive effect is accompanied by a *decreased (not an increased) cardiac output*. Therefore, indirect α + β agonist such as ephedrine, adrenaline and noradrenaline are better choices.)

Reperfusion injury is the increase in damage observed when ischaemia is corrected by restoring oxygen supply to an organ, the so-called "oxygen paradox". Reperfusion injury is often seen after reperfusion of ischaemic tissue, e.g. thrombolysis of coronary thrombosis, unclamping of the aorta after repair of an aorta aneurysm, and fasciotomies in the presence of a tibia fracture. The longer the ischaemic time, the greater the reperfused vascular bed, the greater is the reperfusion injury and its systemic and organ effects. In the heart, the reperfusion injury is characterized by dysrhythmias, stunning (mechanical dysfunction), microvascular damage and accelerated cell death. Reperfusion injury is caused by free radicals, especially reactive oxygen free radicals (OFR). Reperfusion injury is prevented by early resuscitation (reperfusion), prevention of hyperoxia (high PaO$_2$) in the scenario of ischaemia-reperfusion, the administration of agents that may prevent the production of free radicals, e.g. superoxide dismutase and allopurinol, or the administration of free radical scavengers, e.g. N-acetyl-cysteine and allopurinol.

How does reperfusion injury work? Xanthine oxidase (XO) is an important enzyme in the production of ORF. Another source of free radicals is leucocytes. These have been shown to accumulate in the border areas of ischemic tissue and following reperfusion, throughout the ischaemic zone. Complement and leukotrienes may be responsible for attracting white cells and activating them. Several mediators including leukotrienes, chemotactic mediators and mechanical disturbances of cell membranes can stimulate neutrophils to produce superoxide (O$_2^{\cdot-}$). Damage caused by O$_2^{\cdot-}$ activates surrounding granulocytes, which now adhere to endothelium and accumulate in the extravascular space. Evidence exists of radical generation in the intra- and extravascular spaces. Adhesion of leucocytes to capillary endothelium may contribute to the progressive accumulation and activation of neutrophils resulting in microvascular injury and plugging and perhaps the no-reflow phenomenon. Oxidation of the burst of catecholamines released from the heart during reperfusion may be another source of free radicals contributing to reperfusion injury.

Synthesis of prostaglandins and leukotrienes are stimulated by ischaemia and reperfusion. Conversion of prostaglandin G$_2$ to prostaglandin H$_2$ results in superoxide production.
The extent of RPI is determined by the amount of OFR produced during reperfusion and by the capability of cellular mechanisms to neutralize the radicals. These mechanisms are first line enzymatic and second line non-enzymatic substances.

The enzymes scavenging OFR are superoxide dismutase (SOD), catalase and glutathione peroxidase. They remove O$_2^{\cdot-}$ and H$_2$O$_2$ before they react to form the more active hydroxyl radical (OH$^{\cdot}$).

Poly-unsaturated fatty acids are particularly vulnerable to attack by these radicals. A chain reaction is initiated by reaction of a radical with the carbon chain (LH) of fatty acids generating a carbon-centred alkyl radical (L$^{\cdot}$). Oxygen is then rapidly taken up at this centre forming a lipid peroxyl radical (LOO$^{\cdot}$), which extract hydrogen from other fatty acids thus starting a chain of lipid peroxidation:

$$\text{Initiation: } LH + OH^{\cdot} \rightarrow L^{\cdot} + H_2O \text{ and } L^{\cdot} + O_2 \rightarrow LOO^{\cdot}$$
$$\text{Propagation: } LOO^{\cdot} + LH \rightarrow LOOH + L^{\cdot}$$
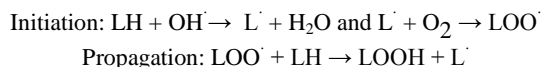
This chain is terminated by depletion of substrate LH, by reaction of lipid radicals with free radical scavengers (non-enzymatic mechanisms) or by self-annihilation of radicals forming non-reactive species (L - L):

$$L^{\cdot} + L^{\cdot} \rightarrow L - L$$
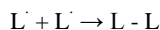
Reactive oxygen species are capable of reversibly or irreversibly damaging compounds of all biochemical classes, including nucleic acids, proteins and free amino acids, lipids and lipoproteins, carbohydrates and connective tissue molecules. OFR have been implicated in ischaemia-reperfusion injury (IRI) in many tissues, including the heart.

During the period of ischaemia, little change in radical composition is observed. When reperfusion starts, a surge of free radical production or stable products reacting with these radicals is measured, where after radical production decreases rapidly. It has been shown that OFR production by reperfused dog myocardium is related to the severity of ischaemia and is maximal two to four minutes after restoration of perfusion. During this period OFR production is 90 fold higher than during ischaemia. Although there is a burst of radical production during the early moments of reperfusion, radical production can be detected for several hours into the reperfusion process. There is evidence for secondary unfavourable events ("slow no-reflow" and delayed contractile impairment) late into the reperfusion period.

Questions:
Considering the four factors that determine the effect of ischaemia, what is the impact of:
A tourniquet on the leg of diabetic patient?
Systemic hypotension in a patient with cerebrovascular disease?
Severe blood loss in a patient with renal failure?
Severe hypotension after a spinal block for a caesarean section in a pre-eclamptic patient?
Age on your paracetamol dosage?
The effect of blood transfusion on serum calcium in the hypovolaemic patient?
A laparotomy in a patient with severe abdominal distension?

AUTOREGULATION

This characteristic of arterial vascular beds protects normal organs from ischaemia, oedema, and haemorrhage. All the vital organs (except the lung and liver; see Chapters 13 and 16) are subject to autoregulation. Of particular interest are the brain, heart, and kidneys (Chapter 16).

Autoregulation causes the organ arterioles to dilate or constrict when perfusion pressure decreases or increases, respectively. The change in organ vascular resistance maintains blood flow during changes in pressure. (Remember, Perfusion pressure (PP) = inflow pressure (Pi) − outflow pressure (Po). Therefore, Blood flow = PP/VR.)

The limits of mean arterial pressure (MAP) between which blood flows will not change is the premorbid MAP ± 20% to 30 %. A MAP below the autoregulation limit (< 70 %) causes ischaemia, while a MAP above the autoregulation limit (> 130 %) causes oedema and vascular rupture (Figure 3). Example:
Preoperative BP = 130/100 mm Hg
Mean arterial pressure = (SBP + 2DBP)/3 = (130 + 200)/3 mm Hg = 110 mm Hg
70 % of 110 mm Hg = 77 mm Hg; 130 % of 110 mm Hg = 143 mm Hg

Long-term changes in blood pressure cause autoregulation limits to readjust. Readjustment probably takes place over several weeks. Lowering blood pressure to below the autoregulatory limit may cause organ ischaemia, while increasing blood pressure above the limit, may cause organ oedema and haemorrhage.
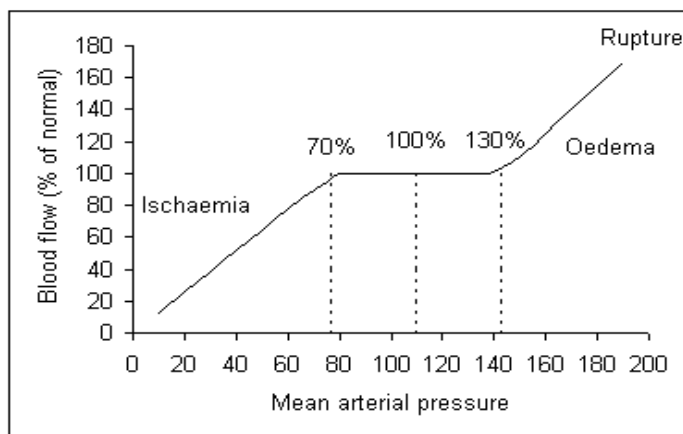
Figure 3 The arterial autoregulation curve

Ischaemia, oedema and cardiovascular derangements (Table 2).
When you must anaesthetize an oedematous patient, you must think of perfusion; particularly the factors that determine microcirculatory function and intercompartmental fluid shifts, i.e. intracellular, interstitial, and intravascular (see Chapter 18).

A close link exists between the pressure inside the capillary (forcing fluid out of the capillary) and pressure outside the capillary (function of lymphatic system), plasma oncotic pressure (crystalloid and colloid oncotic pressure keeping the fluid inside the capillary), and capillary wall characteristics (tight junctions) and integrity (capillary leak). This is *Starling law of the capillary*. Malfunction of the one is often accompanied by malfunction of the others.

Oedema is generalized or regional (e.g. arm oedema after mastectomy and lymph node dissection). Remember that *generalized oedema is always:*
- a sign of significant systemic (affecting several organs) disease
- accompanied by tissue hypoxia and homeostatic derangements (plasma proteins, fluid and electrolytes, and acid-base), and
- complicated by physiological and pharmacokinetic effects (plasma protein binding and drug free/active fractions).

Generalized oedema is caused by:
- cardiac failure (pressure effect, fluid and electrolyte disturbances),
- renal failure (fluid and electrolyte disturbances),
- liver failure (fluid and electrolyte disturbances), and
- malnutrition (multiple organ dysfunction, fluid and electrolytes)
- inflammation (capillary leak).

Oedema causes ischaemia and ischaemia causes oedema. Interstitial oedema increases interstitial pressure →↓ transmural capillary pressure (inside – outside pressure) →↓ vascular diameter →↑ VR →↓ blood flow → ischaemia. The larger interstitial space will also increase the *distance* between the capillaries and the cells, which will impair oxygen diffusion. Unabated ischaemia will always jeopardize capillary integrity and cellular membrane function, causing vasogenic (interstitial) and cytotoxic (intracellular) oedema.

Table 2 Organ ischaemia, oedema, and cardiovascular derangements

Pi (MAP)	Po (CVP)	VR	Capillary integrity	Osmotic pressure	Result	Example
↓	↓	↑	N	N	I	Hypovolaemia (a)
↓	↑	↑	N	N	I + O	Cardiac failure (b)
↓	↑	↓	↓	↓	I + O	Inflammation, septic shock (c)
↑↑	N or ↑	↑	↓↓	N	I + O	Severe hypertension (d)
↓	↓	↓	↓↓	N	I + O	Inflammatory response (e)
N / ↓	N / ↑ / ↓	N / ↓ / ↑	↓	N	I + O	Compartment syndrome (f)

Pi = pressure inside capillary; Po = pressure outside capillary; MAP = mean arterial pressure; CVP = central venous pressure; Osmotic pressure = crystalloid osmotic pressure + colloid osmotic pressure; I = ischaemia; O = oedema
(a) Ischaemia may occur locally, e.g. *peripheral arterial occlusion*, or globally due to *hypovolaemia*.
(b) Ischaemia is global and is caused by *cardiac failure* of any aetiology.
(c) *Septic shock* is characterized by global ischaemia (in spite of an often-high cardiac output), a low vascular resistance (hyperdynamic circulation) and often myocardial failure. Capillary leak and severe hypoalbuminaemia is responsible for generalized oedema. Cardiac failure may cause an increase in Po (central venous pressure), which may aggravate peripheral and pulmonary oedema.
(d) *In severe hypertension,* MAP is > the upper autoregulatory pressure limit causing rupture of junctions between capillary endothelial cells. This results in vasogenic oedema, and even rupture of blood vessels, e.g. blood brain barrier in the brain [(brain oedema or stroke (ischaemia)] and in the glomerulus (renal oedema, ischaemia, and haematuria).
(e) *Inflammatory reactions* cause capillary leak and interstitial oedema, e.g. sepsis, anaphylaxis.
(f) *Compartment syndrome (CS)* . The normal interstitial pressure is about zero mm Hg. If this pressure increases > 30 mm Hg, small vessels in the tissue are compressed, which leads to ischaemia. The difference between pressure in the compartment (fascial compartment, intracranial compartment, intra-abdominal cavity) and diastolic blood pressure affects perfusion; when compartment pressure exceeds 30 mm Hg, it is an emergency. Oedema in a confined space causes CS. The most common CSs are the anterior and posterior compartment syndrome after tibial fractures and intra-abdominal compartment syndrome. *Normal intra-abdominal pressure* (IAP) is < 12 mm Hg. When IAP increases > 15 mm Hg, *intra-abdominal hypertension* is present, and at IAP > 25 mm Hg *abdominal CS* is diagnosed. This causes pressure around arteries, arterioles, capillaries, and veins. This will impede perfusion of all intra-abdominal organs. Increased intra-abdominal pressure also increases the *work of breathing*.

PHARMACOLOGICAL ASPECTS OF CARDIOVASCULAR DISEASE

In general, patients with compromised cardiovascular function (from any of the components) receive treatment for the particular defect, e.g. volume expanders for decreased preload, ACE inhibitors for cardiac failure or hypertension, etc. Patients must receive their treatment throughout the perioperative period; it may be dangerous to stop them, e.g. β-blockers and statins. It may also be necessary to initiate β-blockers and statins preoperatively. The specific indications for β-blockers during the perioperative period are however still debated. Nonetheless, if patients already receive them, they should usually not be stopped. Regarding ACE inhibitors: These drugs cause a pharmacological sympathectomy and may cause protracted hypotension in the intra- and postoperative period – especially in conjunction with other vasodilators (anaesthetic drugs) and hypovolaemia. I usually stop ACE inhibitors preoperatively before major surgery.

THE CARDIOVASCULAR SYSTEM AND ANAESTHESIA

The student must apply the principles outlined above to understand the effect of therapeutic and diagnostic interventions on cardiovascular function. Cardiovascular diseases and their treatment, the effect of interventions on the cardiovascular disease (blood loss, perioperative stress response), the effect of anaesthetic drugs, diagnostic agents (e.g. radiological contrast media) on cardiovascular performance, and interactions between disease and anaesthesia (anaesthetics and ventilation) may compromise cardiovascular function. The focus of the section is the general effects of anaesthesia on the different components of cardiovascular function.

Preload
All anaesthetic drugs (except ketamine) are venodilators and cause distributive hypovolaemia (see Chapters 5, 6, 7, and 9). Preoperative fasting, blood loss, vomiting, the use of preoperative diuretic drugs, bowel preparation, etc. aggravate this relative hypovolaemia. Neuraxis anaesthesia (intrathecal, epidural) blocks the sympathetic nervous system (SNS) function, which leads to distributive hypovolaemia. Mechanical ventilation increases intrathoracic pressure, which decreases venous return to the heart (preload). The decreased preload decrease decreases cardiac wall tension, which may help the enlarged failing heart.

Afterload
All anaesthetic agents (except ketamine) and neuraxial block cause arterial *vasodilatation* (see Chapters 5, 6, 7, and 9). This decreases the afterload and therefore blood pressure. *Ventilation* affects cardiac output; large tidal volumes, high PEEP, and hypoventilation (hypercapnia and hypoxaemia) increase pulmonary vascular resistance and right ventricular wall tension and failure. An increased right ventricular pressure may cause shifting of the interventricular septum, which decreases left ventricular filling (preload). All these factors may cause pulmonary hypertension but systemic hypotension.

Inotropy
All the volatile anaesthetic drugs and induction agents (except ketamine) are negative inotropic; directly (they are Ca^{2+} blockers), or indirectly through their effect on the autonomic nervous system. A patient suffering from cardiac failure may sustain severe myocardial suppression, loss of cardiac output, and hypotension. Preoperative negative inotropes may interact with the anaesthetic drugs, which makes patients receiving these drugs extremely vulnerable to the effects of these cardio-depressors (see Chapters 5, 6, 7, and 9).

Rhythm
The ideal anaesthetic drug is pharmacologically clean. Unfortunately, such a drug does not exist yet. Most of the induction and inhalational agents affect cardiac rhythm. Opioids are sympatholytic and often cause a bradycardia. Ketamine is an indirect sympathomimetic and often cause a tachycardia.

The other intravenous induction agents affect Ca^{2+} channels, often causing a decrease in heart rate, especially in combination with opioids. All the anaesthetic vapours are calcium blockers and affect the electrophysiological function of the heart. A supraventricular tachycardia is often observed when administering these drugs. Halothane is renowned for its dysrhythmogenicity (see Chapters 5, 6, 7, and 9).

Coronary perfusion

All the induction agents (except ketamine) and vapours (especially the ethers) are coronary vasodilators (see Chapters 5, 6, 7, and 9). They dilate normal coronary arteries to non-ischaemic myocardium but do not affect the arteries perfusing ischaemic myocardium, which are already maximally dilated. The blood flow in the dilating arteries will steal blood from the ischaemic areas. This is called *coronary steal*. Isoflurane has been strongly implicated in coronary steal. The importance of this phenomenon is still unresolved. Nevertheless, coronary perfusion is definitely affected by changes in blood pressure, heart rate and rhythm, preload, etc.

Control of the heart

All induction and inhalational agents have direct electrophysiological effects on the heart. These agents also affect the autonomic nervous system. Opioids are potent indirect sympatholytics and parasympathomimetics. The muscle relaxants (except cis-atracurium) are pharmacologically very dirty drugs;[xv] they may be parasympatholytic (pancuronium) causing a tachycardia or sympatholytic (probably via ganglion blocking properties) causing a bradycardia (vecuronium). Neuraxis anaesthesia causes decreased SNS outflow (distributive hypovolaemia with hypotension). A high neuraxial block decreases sympathetic control of the heart (T1 to T4). This is often complicated by a bradycardia (treated with a catecholamine – not with atropine) and hypotension (see Chapters 5, 6, 7, and 9).

The boundaries of the heart

Anaesthetic drugs do not affect the borders of the heart directly, but may indirectly affect structures via their effects on preload, afterload, etc. Mechanical ventilation, however have a profound effect on intrathoracic pressure and therefore on preload and afterload. These effects are detrimental or advantageous. For example, in the presence of cardiac tamponade these changes may cause further cardiovascular compromise, while mechanical ventilation support the failing heart by decreasing preload, afterload, and work of breathing.

INTRAOPERATIVE APPROACH TO THE PATIENT WITH CARDIOVASCULAR ABNORMALITIES

Preload

Most patients are hypovolaemic preoperatively. Hypovolaemia is caused by loss of intracellular of extracellular fluid (*absolute hypovolaemia*) or increase in vascular capacity (*relative hypovolaemia*). *Absolute hypovolaemia* is caused by blood loss, vomiting, diarrhoea, fasting, diuretics, ACE inhibitors, bowl preparation, etc. *Relative hypovolaemia* is caused by vasodilatation. Vasodilatation is caused by spinal block, spinal shock, anaphylaxis, septic shock, and all anaesthetics (except ketamine). Absolute hypovolaemia is treated with transfusion of fluid with a composition similar to the fluid lost (see Chapter 18). Relative hypovolaemia is treated with vasoconstrictors. No *hypovolaemic* patient is fit for elective surgery.

The preload is monitored intraoperatively with central venous pressure, pulmonary artery wedge pressure, and pulse pressure variation (see Chapter 18).

Afterload

Perioperatively the MAP must be kept within the autoregulatory limits; never try to "normalize" a chronic abnormal blood pressure. *An increased intraoperative afterload causes hypertension.* It is

---

[xv] *Dirty drugs* have several effects, e.g. phenothiazines, which are multi-potent blockers, of dopamine-, ACh-, and α-receptors. This is in contrast to clean drugs that work at one site only, e.g. $β_1$ selective blockers.

caused by:
- preoperative hypertension
- SNS activation, e.g. **pain** (remember tourniquet pain and a full bladder), increased intracranial pressure, awareness, myocardial ischaemia, release of catecholamines (phaeochromocytoma, hypercapnia, hypoxia, ketamine, etc.), and increased sensitivity to catecholamines (hyperthyroidism).
- administration of direct or indirect sympathomimetics (recreational drugs such as the amphetamine-like drugs, cocaine)
- occlusion of a large artery, e.g. clamping of the aorta and tourniquet on the thigh.
- The hypertension associated with a *tourniquet* is caused by an exsanguination of a whole leg (increased preload), increased afterload (usually only transiently), and tourniquet pain.

Treatment of intraoperative hypertension:
- Ensure an adequate level of anaesthesia.
- If possible, blood pressure must be treated before it reaches the upper autoregulatory limits.
- Acceptable limits depend on the *preoperative blood pressure* and the intraoperative *cause*.
- Blood pressure is usually lowered by deepening of the *anaesthetic plane* and/or by
- Administer *vasodilators*, e.g. glyceryl trinitrate (TNT) 0.5 µg kg min^{-1} to 1 µg kg min^{-1} or magnesium sulphate 50 mg kg^{-1} followed by 15 mg kg^{-1} h^{-1}.

A decreased intraoperative afterload causes hypotension and is usually caused by the intravenous and inhalational anaesthetic agents, neuraxis block, anaphylaxis, or after the release of vascular clamps or a leg tourniquet (reperfusion syndrome). A decreased intraoperative afterload is aggravated by absolute hypovolaemia and preoperative antihypertensive agents.

Intraoperative vasodilatation is treated with intravenous vasoconstrictor boluses – if possible before the blood pressure decreases below the lower level of autoregulation. Remember, if the heart rate and blood pressure is low, a pure α agonist such as phenylephrine will increase the blood pressure, but the increased blood pressure may stimulate the carotid pressure receptors. This may decrease the heart rate further. This may happen with a high neuraxial block (spinal or epidural). The heart receives its sympathetic innervation from T1 to T4. Stimulation of these nerves (acceleratory fibres) increases heart rate. If these fibres are blocked, the heart is under vagal control only and the heart rate decreases. Therefore, the bradycardia-associated hypotension accompanying a high neuraxial block is treated with drugs that cause both vasoconstriction (α$_1$ effect) as well as an increase in heart rate (β$_1$ effect). These include adrenaline (direct α$_1$ and β$_1$ agonist) or ephedrine (direct α$_1$ and β$_1$ agonist as well as indirect by stimulating the release of noradrenaline from the prejunctional fibre of the postganglionic nerve (Table 3).

Table 3 Treatment of intraoperative hypotension in patients with a sinus rhythm (P-QRS-T)

HR (±)	Drug	Receptors	Bolus per kg*	70 kg*	Dilution
> 60	Phenylephrine	α	0.5 - 1 **µg kg**$^{-1}$	70 µg	10 mg/200 ml = 10 000 µg/200 ml = 50 µg/1 ml
≤ 60	Ephedrine	α + β	0.1 **mg kg**$^{-1}$	7 mg	50 mg/10 ml = 5 mg/1 ml
≤ 60	Adrenaline	α + β	150 **ng kg**$^{-1}$	10 000 ng = 10 µg	1 mg/200 ml = 1000 µg/200 ml = 5 µg/1 ml = 10 µg/2 ml

 * According to **lean body mass**; for calculation of lean body mass, see Chapter 17.

Please note that the increase blood pressure following phenylephrine administration gives a false sense of improvement since the pure vasoconstrictive effect is accompanied by a *decreased (not an increased) cardiac output*. Therefore, indirect α + β agonist such as ephedrine, adrenaline and noradrenaline are better choices. The only indications for pure α agonists such as phenylephrine are:[15] [16]

- Hypotension following vasodilatation in the patient with aortic stenosis
- Hypertrophic subaortic stenosis (left ventricular outflow obstruction)

- Cyanotic spells in the hypotensive patient with tetralogy of Fallot
- Hypotension following neuraxial block (controversial in obstetrics; ephedrine may as safe)
- Portal hypertension with maldistribution of central blood volume to the dilated splangnic veins

Although a decreased preload and afterload may occur separately (mechanically, pharmacologically), *many vasodilators decrease both pre- and afterload*, i.e. they are arterio- and venodilators, e.g. *anaesthetic agents (except ketamine), magnesium, and α adrenergic blockers*.

Inflammatory mediators also are veno- and arteriodilators. A specific phenomenon where large amounts of such agents are released acutely in response to the administration a foreign agent (antibiotics, protamine, heparin, muscle relaxants, blood components, colloid, radiocontrast, latex, drug preservative in local anaesthetic preparations, etc.) is called ***anaphylaxis***.

Latex is a common allergen in the perioperative period. Latex allergy occurs in patients (spina bifida), rubber factory workers, and health workers that have been sensitised to latex occurring in latex powder, dust, gloves, urinary catheters, etc. Latex occurs in several medical products, including catheters, syringes, infusion sets, anaesthetic circuits, etc. These latex-containing products are being phased out. Latex cross-reacts with allergy to kiwi fruit, mangoes, bananas, avocados, pine apple, and stone fruit (peaches, cherries, plums, apricots, and nectarines).

Histamine plays a large role in anaphylaxis (IgE-mediated mast cell and basophil degranulation in sensitised patients or direct histamine release from mast cells). However, other mechanisms such as complement activation give rise to the release of other substances, including slow reacting substance of anaphylaxis (SRSA). Mast cells do not only release histamine but also lipid-derived substances (leukotrienes, prostaglandins), proteases (tryptase), etc.

Anaphylaxis is accompanied by a multisystem clinical picture characterized by:
- Cardiovascular reaction: retrosternal discomfort, vasodilatation with severe hypotension (anaphylactic shock, which is an example of distributive shock), capillary leak with oedema (systemic, pulmonary), tachycardia due to the hypotension, or bradycardia due to direct effect of histamine on the heart, and H_1-mediated coronary vasoconstriction
- Pulmonary: Bronchoconstriction, increased secretions, and pulmonary oedema
- Muco-cutaneous eruptions such as erythema, urticaria, rash, and angio-oedema
- Although anaphylaxis usually occur immediately or shortly after exposure to the allergen, it may follow hours later.

The clinical picture of anaphylaxis depends on how densely the different organs are populated by mediator-releasing cells, namely cutaneous, pulmonary, and mucosal. Drugs that release histamine often cause only an urticarial rash without any vasodilatation or bronchoconstriction, e.g. *atracurium and morphine*. The clinical picture of histamine release is associated with the rate of administration. Such patients must not be labelled to be allergic to these drugs. If an acute drug occurred and uncertainty exists about whether it was an allergic reaction, a blood sample must be sent blood for tryptase, a drug-specific RAST, and complement.

Management of anaphylaxis with cardiovascular collapse
- Immediately stop contact of the suspect agent (drug, gloves, etc).
- Administer 100% oxygen
- Maintain airway
- *Administer adrenaline* IVI: Immediately dilute1 mg (1000 µg) to 20 ml. This gives a dilution of 50 µ ml^{-1}. Give about 50 µg (about 1 µg kg^{-1}) followed by about 1 µg kg^{-1} min^{-1} until blood pressure and bronchospasm improves.
- Alternatively give 0.5 mg (that is 0.5 ml of the 1:1000 or 1 mg per ml ampoule) IMI (not subcutaneously).
- If not done yet, put up intravenous infusion and administer Ringer lactate as necessary.
- Give *cortisol* about 2 mg kg^{-1} IVI
- Give β_2-agonist inhalants if necessary

- Promethazine 0.5 mg kg^{-1} IVI or IMI (not subcutaneously)

Inotropy

Intraoperative inotropic failure is treated with catecholamines:

Adrenaline: 100 ng kg min^{-1} (mainly β effects) to 200 or more ng kg min^{-1} (also α effects)

Noradrenaline (especially in the presence of vasoplegia such as septic shock): 100 ng kg min^{-1} to 200 or more ng kg min^{-1} (α > β effects)

Dobutamine: 5 μg kg min^{-1} to 10 or more μg kg min^{-1} (β$_1$effects; some β$_2$ vasodilatory effects)

Dopamine: 1 μg kg min^{-1} to 5 μg kg min^{-1} (dopaminergic of "renal" effects); 5 μg kg min^{-1} to 10 μg kg min^{-1} (also β effects); >10 μg kg min^{-1} (also α effects)

If the cardiovascular system is very sensitive to the negative inotropic affects of anaesthetics, an opioid- or ketamine-based technique is preferred.

Rhythm

In this section, only the most common dysrhythmias are discussed. For a more detailed discussion of life-threatening dysrhythmias, see Chapter 15. In general:

- If you count the heart beat clinically, the normal heart rate is 60 min^{-1} to 100 min^{-1}. A tachycardia is a heart rate > 100 min^{-1}, and a bradycardia < 60 min^{-1}.
- First, treat the *cause* if possible, e.g. absolute or relative hypovolaemia with a reflex tachycardia, hyperthyroidism, phaeochromocytoma, etc.
- *Look at the preoperative ECG*. If the ECG is stable preoperatively, that ECG is the "normal" ECG. You should *compare the intraoperative ECG* to the normal (for the patient) ECG. If the ECG is unstable (changing) intraoperatively, it is abnormal and you must compare the intraoperative ECG to the preoperative one; it may improve or deteriorate.
- **Anything that affects the *electrophysiology of the heart* is dysrhythmogenic, namely excitability (threshold), automaticity, re-entry, and abnormal repolarisation. The causes of *abnormal electrophysiology* include:**
  - *Homeostatic*: **electrolytes (See Chapter 18), acid-base, temperature, ischaemia, reperfusion**
  - *Pharmacological*: **all anaesthetic drugs, cardiovascular drugs**
  - *Mechanical*: **irritation of the right atrium or ventricle (central venous catheter)**
  - *Heart rate control*: **intrinsic, extrinsic (autonomic reflexes, i.e. parasympathetic and sympathetic)**
  - *Degenerative*: **fibrosis, remodelling, cardiomyopathies.**
  - **<u>Therefore, if you notice an abnormal ECG rhythm or configuration, consider all the possibilities mentioned above. Patients with cardiovascular disease commonly receive medication. Both the disease (cardiac failure, diuretics) and the medication affect electrolytes, especially potassium. Cardiac failure as well as several diuretics cause hyponatraemia and hypokalaemia; the former causes secondary hyperaldosteronism and the latter hyponatraemia → hypokalaemia (distal tubule), or hypochloraemia → hyponatraemia → hypokalaemia, as well as secondary hyperaldosteronism. If the ECG shows changes suggestive of ischaemia, it may be present, but look for a hypokalaemia. Thus, ischaemia, digoxin, a hypokalaemia are a malicious gang with similar ECG changes. Do not miss it.</u>** (Figures 4 and 5)
- Treat dysrhythmias if they cause haemodynamic *instability or predispose* to the development of more *malignant dysrhythmias*.
- Inspect the P wave: absent (junctional rhythm, atrial fibrillation), peaked (**hypokalaemia**, ectopic pacemaker) or inverted or changing or saw tooth (supraventricular or wandering pace maker, atrial flutter)
- Inspect the PR time: it may be normal, prolonged or shortened (wandering pacemaker), or very short with the delta-wave QRS taking off from the P wave (Wolf Parkinson White).
- Inspect the ST segments: elevation (transmural ischaemia, hypothermia), depression (**hypokalaemia**, drugs, hypertrophy, ischaemia, abnormal conduction, intracranial pathology).
- Inspect the T wave: peaked (**hyperkalaemia**, ischaemia, intracranial pathology, P wave in T

wave), distorted (P wave in T wave), flattened (**hypokalaemia, ischaemia**), inverted (**ischaemia, infarction, hypokalaemia**).
- Look for U waves: **Hypokalaemia**, **ischaemia**, **digoxin**.
- Look for a prolonged QT interval: Congenital, antidysrhythmic drugs, anaesthetic vapours, antihistamines, hypokalaemia, hypomagnesaemia, etc.

Hypokalaemia (See also Chapter 18)

Figure 4 Hypokalaemia. Note the prominent P waves, prolonged PR interval, ST segment depression, T wave inversion, and prominent U waves.

Hyperkalaemia (See also Chapter 18)

Figure 5 Hyperkalaemia. Note the flattened P waves, broadened QTS complex, ST segment elevation (may be depressed in some leads). With increasing potassium levels, the P disappears, atrio-ventricular block develops, the QRS complex broadens (bundle branch block), and eventually, ventricular tachycardia, ventricular fibrillation, and asystole.

Sinus bradycardia
A sinus bradycardia occurs with a relative increase in vagal *tone (decreased sympathetic tone) (Table 4a and 4b)*. A sinus (or junctional) bradycardia is common in fit young patients. A new sinus bradycardia may occur intraoperatively and may be caused by:
- *reflex stimulation of the vagal nerve by mechanical stimulation* (stretch) of structures with afferent innervation that relay in the parasympathetic nervous system (vagal nerve, sacral nerves), or
- *physiologically,* or
- *pharmacologically.*
The ECG of a reflex sinus bradycardia is characterized by a normal P wave, PR time, QRS complex, ST segment, T wave, and U wave (Figure 6).
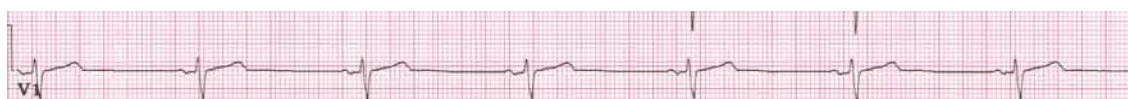
Figure 6 Sinus bradycardia of about 42 min^{-1}

Mechanical stimulation of the vagal nerve include:
o extra-ocular muscles during squint surgery,
o nasal structures during nasal surgery
o pharynx during intubation
o traction on gastrointestinal organs, cervix, anal dilatation
o carotid sinus during neck surgery, severe hypertension

The treatment of mechanical-mediated stimulation of the vagal nerve (reflex bradycardia):
o Stop the stimulus.
o If the bradycardia persists or reoccurs with stimulation, administer an anticholinergic agent such as atropine 20 µg kg^{-1} or glycopyrrolate 10 µ kg^{-1}.
o If the bradycardia is caused by severe hypertension, the treatment is glyceryl trinitrate 1 µg kg^{-1} min^{-1}.

Remember, a Cushing reflex is a terminal phenomenon in patients with severe intracranial hypertension. The treatment of this bradycardia is to decrease intracranial pressure to improve cerebral perfusion, including elevation of the head, hyperventilation, and the removal of the space-occupying lesion – if possible.

Pharmacologically and physiologically induced sinus bradycardia is caused by:
o *Indirect sympatholytics*: Central sympatholytics, i.e. all the *potent opioids* (fentanyl, sufentanil, alfentanil, remifentanil), α_2 *agonists* (sedative analgesics clonidine and dexmedetomidine), pure α_1 agonist phenylephrine given to treat hypotension in patients with an existing bradycardia.
o *Direct sympatholytics*: The β blockers, e.g. propranolol, atenolol, and esmolol.
o *High neuraxis block (T1 – T4)*: Blocks cardiac sympathetic innervation.
o *Autonomic ganglion stimulation (vagotonic)*: suxamethonium
o *Autonomic ganglion block (sympatholytic)*: nondepolarising relaxants (vecuronium, atracurium.
o *Parasympathomimetics*: Acetylcholine esterase inhibitors (AChE): neostigmine.
o *Myocardial ischaemia*
o *Hypothyroidism*
o *Hypothermia*
o *In infants, hypoxia* often causes a bradycardia, which probably is a component of the *diving reflex*. This may contribute to the bradycardia if the time of *laryngoscopy* is prolonged.
The treatment of physiological and pharmacological induced sinus bradycardias is to stop the drug and/or to administer its competitive or indirect antagonist.

Supraventricular bradycardia without P waves (nodal or junctional bradycardia)
When the sino-atrial node (SA node) rate decreases to less than about 60 min^{-1}, the atrio-ventricular node (AV node) may escape from the impulses from the SA node and will pace the ventricles. The QRS complex, ST segment, and T waves are "normal" or may show the cause of the dysrhythmia, e.g. ischaemia. The P wave may still be present and regular, but occur inside the other parts of the ECG. For example, it may be visible at the beginning of the QRS complex or inside the T wave. The causes and management are similar to those of a sinus bradycardia (Figure 7).

Figure 7 Nodal rhythm with a heart rate of about 40 min^{-1} (note the P waves sneaking around)

Table 4a Treatment of a sinus bradycardia

Reflex bradycardia		
Stimulus	**Afferent**	**Drug and dose according to lean mass**
Fit young patients	N X	Atropine 20 μg kg^{-1} or glycopyrrolate 10 μg kg^{-1}. If severe, use atropine since the onset of effect is faster.
Ocular	N III, N VI	
Nasal	N V	
Pharyngeal, Carotid sinus	N IX	
Upper gastrointestinal tract	N X	
Lower gastrointestinal tract Cervix, bladder	S 3, 4, 5	
Hypoxia in infants	Cerebral hypoxia	Ventilate, O_2

Table 4b Treatment of physiological and pharmacological sinus bradycardia

Drug, pathophysiologic	Mechanism	Drug	Dose (about)*
Opioids	Central sympatholysis	Ephedrine	0.1 mg kg^{-1}
		Atropine	20 μg kg^{-1}
		Glycopyrrolate	10 μg kg^{-1}
Central α_2 agonist	Central sympatholysis	Glycopyrrolate	10 μg kg^{-1}
		Atropine	20 μg kg^{-1}
Phenylephrine	↑ BP → Carotid sinus	Glycopyrrolate	10 μg kg^{-1}
		Atropine	20 μg kg^{-1}
β blockers	Negative chronotropic	Adrenaline	100 ng kg^{-1} min^{-1}
		Dobutamine	5 μg kg^{-1} min^{-1}
		Isoprenaline	50 ng kg^{-1} min^{-1}
		Atropine	20 μg kg^{-1}
High neuraxis block	Sympatholysis	Ephedrine	0.1 mg kg^{-1}
		Adrenaline	150 ng kg^{-1} min^{-1}
Suxamethonium	Vagal ganglion stimulation	Atropine	20 μg kg^{-1}
		Glycopyrrolate	10 μg kg^{-1}
Non-depolarising relaxants	Sympathetic ganglion inhibition	Glycopyrrolate	10 μg kg^{-1}
Neostigmine	AChE inhibition → vagotonic	Atropine	20 μg kg^{-1}
		Glycopyrrolate	10 μg kg^{-1}
Myocardial ischaemia	SA node ischaemia, adenosine	Treat cause	Enough
Hypothyroidism	↓ β receptor activity	T_3 or T_4	100 μg per os
Hypothermia	↓ SA node automaticity	Warm up	Slowly

*Approximate according to lean body mass.

Supraventricular tachycardia with P waves
This occurs *very commonly* intraoperatively. The heart is paced by the SA node or by *any focus* in the atria (wandering pace maker). These non-SA node pacemakers outpace the SA node. If the tachycardia has its origin in the SA node, *the P waves* look the same as preoperatively (look at lead II). If the pacemaker is outside the SA node, the P waves look differently; they are tented, smaller, or inverted. With a SA nodal tachycardia, the *PR intervals* are the same as preoperatively; with an extra-SA nodal tachycardia, the PR interval may be shorter if the pacemaker is closer to the AV node, or it may be longer if it is further from the AV node. The P wave and PR interval may also change if the site of pacemaker changes. Depending on the heart rate, the *QRS complexes* may be slightly prolonged (aberrant intraventricular conduction resembling a RBBB), and the ST segments may be depressed if the tachycardia decreases coronary perfusion time (Figure 8).

Figure 8 Sinus tachycardia 110 min^{-1}. QRS complexes prolonged and ST segments depressed.

This dysrhythmia is *caused by dir*ect (sympathetic nervous system) or *indirect* (vagolytic, ketamine) *stimulation of the SA node*, or *increased automaticity* of the SA node or any other area in the atria, or *re-entry circuits* in the atria. These changes are often caused by *increased sympathetic* nervous system activity (light plane of anaesthesia, hypovolaemia, hypercapnia, hypoxia, sympathomimetics, vagolytics), or *re-entry* dysrhythmias. *Re-entry dysrhythmias occur very commonly*. Any factor that affects conduction velocity and duration of the refractory period can trigger a re-entry tachycardia. These factors include *ischaemia, anaesthetic vapours, induction agents, and neostigmine*, but are often obscure.

You must be very cautious when treating patients taking recreational drugs. These substances include the amphetamine-like drugs and cocaine. They *exhaust the NA stores* of the sympathetic nerves. These patients are extremely *sensitive to the suppressant effects of β blockers*. These agents are relatively *short actin*g and the *focus in the intraoperative management of these patients is on maintenance of homeostasis* (fluid, electrolytes, acid-base, glucose, temperature).

The treatment of a supraventricular dysrhythmia with P waves depends on the cause and the haemodynamic consequences (Table 5):
o If the anaesthetic plane is too light, deepen the anaesthetic by increasing the vapour concentration or by administrating opioids.
o If the cause is *transient, and of little haemodynamic significance*, no treatment is necessary.
o You can administer a β blocker or an opioid to prevent a tachycardia, e.g. during *tracheal intubation*.
o If the patient is hypovolaemic, administer a volume expander.
o If the patient is vasodilated, give a vasoconstrictor such as phenylephrine.
o If the patient is hyperthermic (infection, sepsis, hyperthyroidism, malignant hyperthermia), treat the cause and cool the patient.
o Treat *myocardial ischaemia* by increasing coronary perfusion by increasing the diastolic blood pressure (volume expansion or vasoconstrictors) or dilate coronary arteries with TNT.
o The tachycardia of *phaeochromocytoma* is treated with esmolol or magnesium sulphate.
o The tachycardia of *hyperthyroidism* is treated with a β blocker.

If you cannot find a cause, and the tachycardia is not desirable, try the following:
o In the patient with ischemic heart disease, you may administer a *β blocker*.
o If you need *short-lived β blockade*, or if you want to assess the effect of β blockade before administering a long-acting agent, use *esmolol* boluses of 0.5 mg kg^{-1} to 1.0 mg kg^{-1} IVI.
o If esmolol is effective and you need *prolonged β blockade*, used intravenous *atenolol* 0.1 mg kg^{-1} to 0.2 mg kg^{-1}, or intravenous *propranolol* about 30 μg kg^{-1}.

Supraventricular tachycardia without P waves (AV junctional or nodal tachycardia)
If the automaticity of the AV node increases, or if re-entry circuits develop in the area between the right atrium and the ventricles around the AV node (the junctional area), these foci may outpace the AV node. The ventricles are now stimulated without prior contraction of the atria. Since the inherent rate of the AV node is 40 min^{-1} to 60 min^{-1}; a nodal rate of > 60 min^{-1} is called a *nodal tachycardia* (Figure 9). Since the co-ordinated contraction of the atria and ventricles is lost (atrial kick), the preload of the ventricles are decreased by about 20%. This results in a smaller stroke volume and cardiac output. This can be appreciated if you observe the abrupt increase in the amplitude of the

pulse oximeter signal when a nodal rhythm changes to a sinus rhythm.

As is the case with a nodal bradycardia, the QRS complex, ST segment, and T waves are "normal" or may show the cause of the dysrhythmia, e.g. ischaemia. The P wave may still be present and regular, but occur inside the other parts of the ECG. It may, for example, be visible at the beginning of the QRS complex or inside the T wave. The causes and management are similar to those of a sinus tachycardia.

Figure 9 Nodal (junctional) tachycardia of about 80 min^{-1}. Note that P wave do occur but roam the ECG.

Very often, a junctional tachycardia starts out with some premature junctional beats. These foci do not depolarize the ventricles, but also the atria. Consequently, the duration between the premature beat and the next SA node-initiated beat may be slightly longer than the normal QRS-P interval (the isoelectric or diastolic time). The amount that this period is longer, is called a *compensatory period*. Although the compensatory period is not as pronounced as is the case with premature ventricular beats, they are often visible.

Table 5 Treatment of a supraventricular tachycardia with P waves

Cause	Mechanism	Treatment	Dose (about)
Intubation	Sympathetic activation	Esmolol	1 mg kg^{-1} before laryngoscopy
		Alfentanil	15 µg kg^{-1} 2 min before intubation
Hypovolaemia		Volume	5 ml kg^{-1} boluses
Vasodilatation		Phenylephrine	1 µg kg^{-1}
"Awake"		Deepen plane	Vapour, opioids
↑ PaCO$_2$ or ↓PaO$_2$		Ventilate, O$_2$	Enough
Myocardial ischaemia	Sympathetic activation	Esmolol	1 mg kg^{-1}
	Hypotension	Phenylephrine	1 µg kg^{-1}
	Low coronary flow	TNT	0.5 to 1.0 µg kg^{-1} min^{-1}
Phaeochromocytoma	Sympathetic activation	Esmolol	1 mg kg^{-1}
		MgSO$_4$	50 mg kg^{-1} then 15 mg kg^{-1} h^{-1}
Hyperthyroidism	Sympathetic activation	Propranolol	40 mg P.O or 30 µg kg^{-1} IVI
Hyperthermia	↑SA node automaticity	Treat cause	Enough
Amphetamines	Deplete NA stores	Homeostasis	Enough
Cocaine	Depletes NA stores	Homeostasis	Enough
Paroxysmal SVT	Re-entry	Adenosine	100 µg kg^{-1} to 150 µg kg^{-1}

Premature ventricular contractions (PVCs)
PVCs occur very commonly in normal hearts but are more *ominous (sudden death) in diseased hearts*, including ischaemic heart disease and hypertensive heart disease. In diseased hearts the occurrence of PVCs correlates with ventricular mass. They are caused by increased automaticity, re-entry, increased excitability, and abnormal repolarisation. The aetiology is similar to those mentioned under supraventricular tachycardias. *The PVC has the following characteristics* (Figure 10):

o They are *premature* (before one would expect the next P-QRS-T).
o They are *not preceded by a P* wave.

o They originate from a focus outside the normal conduction pathways. Therefore, the conduction of these impulses are slower, which causes the PVCs to be *much broader* and resembling a bundle branch block.
o Since they originate from an aberrant focus, the direction in which the ventricles depolarise is abnormal. Therefore, *the direction of the complex* is very often different from the normal QRS complexes.
o Since they originate from an aberrant focus, the direction in which the ventricles repolarise is also abnormal. Therefore, the *ST segment is often depressed* and the direction of the *T wave is often opposite* to that of the QRS complexes.
o Since the ventricles are still refractory by the time the next impulse from the atrium arrives, there is always *a clear compensatory pause*. There are exceptions, but by the time we have figured it out, the patient is awake and well.
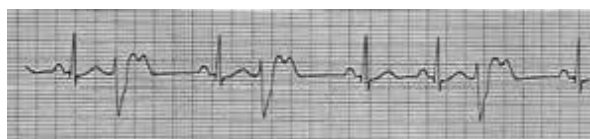
Figure 10 Ventricular premature contractions. Note the normal P wave: they occur regularly and are seen inside the abnormal T waves.

The management of PVCs are to treat the cause. Again, they should be treated when they become haemodynamically important and when they occur so often and wide-spread (originate from different foci) that the PVCs may degenerate into ventricular flutter or fibrillation. *Therefore, you must treat the PVCs per se (that means, separately from the underlying cause) in the following circumstances*:
o If they occur on the background of *heart disease*.
o If they are *multifocal* (the PVC complexes look differently), that means that multiple areas in the ventricles become pacemakers.
o If they occur on preceding T waves (*R-on-T phenomenon*). During this period, the ventricles are very vulnerable; some of the surrounding ventricle is still refractory (cannot conduct), while adjacent parts have recovered. This creates the conditions for re-entry circuits. Therefore, a R-on-T phenomenon can trigger a re-entry tachycardia, flutter or fibrillation.
o If two or more occur *in succession*.
o If > 5 per minute
o If the PVCs occur regularly, e.g. every second heart beat (1:1; pulsus bigeminus), every third heart beat (1:2; pulsus trigeminus), etc.
o And, of course, if the dysrhythmia causes a decrease in the cardiac output, which is reflected by a *decrease in blood pressure*.

Intraoperative PVCs are treated with lignocaine. The dose is about 1.5 mg kg^{-1}followed by an infusion of 2 mg kg^{-1} h^{-1}

Cardiac rhythm is monitored intraoperatively using the ECG leads that have the highest sensitivity and specificity to detect ischaemia and dysrhythmias. These are standard lead II for dysrhythmias (since II displays the P wave and inferior ischaemia the best) and precordial lead V4 or V5 (since they display lateral ischaemia the best). Use is made of the CM5, CS5, or CB5 three-lead configurations (Table 6). To display II, set the ECG on II; to display V5, put it on I.

Table 6 Intraoperative ECG monitoring

System	Red	Yellow	Black or green
CM5	Manubrium	V5 area: anterior axillary line lateral to V4 (5th intercostal space midclavicular line)	Below V5
CS5	Right subclavicular area		
CB5	Over the right scapula		

Coronary perfusion

Myocardial hypoxia (decreased perfusion and/or decreased arterial oxygen content) present with changes in stroke volume (inotropy), valve dysfunction with changes in preload, diastolic dysfunction (the ischaemic heart does not relax properly), dysrhythmias and ST segment changes, etc. This section attempts giving ***an*** (not the only) approach to the anaesthetic management of patients with myocardial ischaemia:

- Patients with myocardial ischaemia often have, and you must suspect, ischaemia or impairment of other vital organs: lungs, brain, kidneys, and gastrointestinal tract.
- No patient with symptoms of unstable myocardial ischaemia is fit for *elective* surgery.
- Patients must receive their *routine treatment*, especially β blockers and statins.
- Not all patients give/can give a history of ischaemic heart disease.
- Myocardial ischaemia is not limited to elderly patients with atherosclerosis.
- The patient with myocardial ischaemia may *present to the GP for an elective procedure*, e.g. sedation for endoscopy. However, it may also be expected from the GP in an urban emergency department or peripheral hospital to resuscitate and stabilize or anaesthetize the *emergency patient* with myocardial ischaemia before transferring a patient. The golden hour of resuscitation includes preservation of viable myocardium.
- Whether a procedure is elective or an emergency, *myocardial ischaemia should be expected from the co-morbidities*, e.g. severe hypotension of whatever cause, chest trauma (blunt or penetration), patient's history, you may be familiar with the patient's relatives, hypertension, smoking, alcoholism, DM, HIV, autoimmune disease, etc.
- The *anaesthetic management* of the patient with myocardial ischaemia for elective and emergency procedures is the same, namely *maintenance of myocardial oxygenation (oxygen delivery > oxygen consumption; Table 7).*

Table 7 Myocardial oxygen balance

Oxygen supply improved	Oxygen supply decreased	Oxygen consumption increased
Normal diastolic pressure in aortic root	$\uparrow\uparrow$ BP → $\uparrow$ wall tension → $\downarrow$ subendocardial perfusion	Systemic and pulmonary hypertension (increased afterload)
	$\downarrow\downarrow$ BP → $\downarrow$ coronary perfusion	$\uparrow$ contractility → $\uparrow$ SV → $\uparrow$ BP
	Aortic stenosis → $\downarrow$ BP	Aortic stenosis → hypertrophy
	Aortic regurgitation → $\downarrow$ BP	Aortic regurgitation → $\uparrow$ wall stress
Normal heart rate (diastolic time)	$\downarrow\downarrow$ HR → $\uparrow\uparrow$ Preload → $\uparrow$ wall tension → $\downarrow$ subendocardial perfusion	$\uparrow$ HR → $\uparrow$ CO $\uparrow$ wall tension → $\uparrow$ consumption
	$\uparrow\uparrow$ HR → $\downarrow\downarrow$ diastolic time → $\downarrow$ SV → $\downarrow$ BP → $\downarrow$ myocardial perfusion	$\uparrow$ HR → $\uparrow$ CO
$\uparrow$ Arterial O_2 content ($\uparrow$ Hb, $\uparrow$ SaO$_2$)	$\downarrow$ Arterial O_2 content ($\downarrow$ Hb, $\downarrow$ SaO$_2$, $\downarrow$ Hb-O_2 affinity)	Sympathetic stimulation, hyperthyroidism
Coronary artery patency, dilatation, low right atrial pressure (coronary sinus drains into right atrium)	Coronary artery narrowing $\uparrow\uparrow$ right atrial pressure → $\downarrow$ coronary venous drainage → $\downarrow$ coronary perfusion	

Intraoperative management of the patient with myocardial ischaemia (Table 8)

- Good *venous access* is indispensable.
- If there is time, i.e. not necessary to continue with surgery immediately, *pre-hydrate* the patient (see Chapter 18).
- It is good to have an idea of the *preoperative (premorbid) haemodynamic condition*, blood pressure, and heart rate. This allows you to calculate the allowable changes in blood pressure and heart rate. In general, you must keep the heart rate below 100 min^{-1} and the mean arterial pressure within autoregulation limits, i.e. ± 25% of the preoperative mean blood pressure.

- *While inducing the anaesthetic, you must keep an eye on the ST segments*; they must not deviate more from the baseline. Very often, one notices a shift *downwards* (subendocardial ischaemia) or *upwards* (transmural ischaemia) with decreased myocardial oxygenation (hypotension, tachycardia, very low PaO_2, and/or anaemia) or increased myocardial oxygen demand (tachycardia, increased wall stress due to increased afterload).
- *Draw up the following emergency drugs*: adrenaline, phenylephrine, glyceryl trinitrate (TNT), atropine or glycopyrrolate, and lignocaine.
- Pre-oxygenate with 80% oxygen for about 3 minutes.
- *Administer an opioid* and wait for 2 minutes. This may be morphine 150 $\mu g \ kg^{-1}$ (in the pre-hydration fluid), alfentanil 15 $\mu g \ kg^{-1}$, fentanyl 1.5 $\mu g \ kg^{-1}$, or sufentanil 0.15 $\mu g \ kg^{-1}$. All *opioids can aggravate myocardial ischaemia* since they are sympatholytic (cause vasodilatation, and therefore, hypotension). Therefore, you must be prepared to treat hypotension by administering a fluid bolus by lifting the legs, and/or intravenous fluid of about 5 ml kg^{-1} within minutes, or phenylephrine 0.5 $\mu g \ kg^{-1}$ to 1.0 $\mu g \ kg^{-1}$ or adrenaline 0.1 $\mu g \ kg^{-1}$ or ephedrine 0.1 mg kg^{-1}. The opioids decrease the dose of other induction agents, which may be omitted in very unstable patients.
- Once the haemodynamics have stabilized after the opioids, the *induction agent is administered*. The *dose of the induction agent* is determined by *pharmacological* (pre-induction opioids) and *physiological factors*, including the patient's age, haemodynamic state (hypotension, hypovolaemia) and homeostatic state (hypoxia, acidosis, anaemia, hypoproteinaemia). The pre-induction use of opioids or ketamine strengthens the effect of induction agents. (This is called *co-induction*.) Since all these physiological factors decrease the *volume of distribution* (low plasma volume) as well the *plasma protein binding*, the *free plasma concentration* increases. Therefore, dosages must be decreased.
- *With how much should the dose of the induction agent be reduced?* Most induction agents (including opioids) have a high protein binding. Therefore, it would be safe to decrease the dose *by 50% to 70%*; it is easier to give more than to resuscitate. Since ketamine has a low plasma protein binding (about 30%), and is neither cardio-depressant nor vasodilatory, it is the drug of choice in the haemodynamically unstable patient − including the patient with myocardial ischaemia. The intravenous induction dose of ketamine is 1 mg kg^{-1} to 2 mg kg^{-1}. I think *etomidate is a bad choice* since it *suppresses cortisol synthesis* for several hours − even after an induction dose.
- The patient with myocardial ischaemia deserves *tracheal intubation and mechanical ventilation* (see Chapter 13 for ventilator settings).
- *The choice of muscle relaxant depends on circumstances*. If tracheal intubation is urgent (haemodynamic instability, aspiration risk), *suxamethonium* is the drug of choice. If not, the pharmacologically purest (pharmacologically the cleanest) relaxant is cis-atracurium. If only suxamethonium and *pancuronium* are available (often the case in rural areas), intubate with suxamethonium and follow it up with small doses of pancuronium, namely 1 ED95 (i.e. about 50 $\mu g \ kg^{-1}$) every hour if necessary. But remember, if you do not have the facilities to monitor neuromuscular transmission, do not reverse pancuronium < 60 min after the last ED95. It is not wrong to use the other intermediate acting relaxants (vecuronium, atracurium).
- *Anaesthesia is maintained* with the drug that allows *haemodynamic stability*. If the patient is very unstable, resuscitation takes preference − then anaesthesia. If the patient is stable, use *a vapour such as isoflurane*. If you have halothane and enflurane only, it is not wrong to use them. Again, patients that have received and opioid or ketamine, often need *less vapour*, say about 0.5 MAC to 0.8 MAC. A ketamine infusion is also useful; the maintenance dose is 30 $\mu g \ kg^{-1} \ min^{-1}$ to 50 $\mu g \ kg^{-1} \ min^{-1}$ (2 mg $kg^{-1} \ h^{-1}$ 3 mg $kg^{-1} \ h^{-1}$). The *intermittent administration of opioids and ketamine* decrease the dose of vapours, e.g. morphine 50 $\mu g \ kg^{-1} \ h^{-1}$, fentanyl 1 $\mu g \ kg^{-1} \ h^{-1}$, sufentanil 0.1 $\mu g \ kg^{-1} \ h^{-1}$, and/or ketamine 0.1 mg $kg^{-1} \ h^{-1}$. (This is called *co-maintenance*.)
- *Intraoperative fluid therapy* depends on the volume and type of fluid lost. The endpoint should be myocardial oxygenation, i.e. an acceptable heart rate, blood pressure, and arterial blood oxygen concentration (CaO_2), i.e. an acceptable PaO_2 and haematocrit − usually > 24%. Furthermore, you should attend to the other endpoints: renal function (excretion − for what it is worth), and acceptable end-tidal CO_2 (low $PaCO_2$ − $PETCO_2$ difference, acid-base state and electrolytes (see

Chapter 20).

- Myocardial oxygen consumption must further be decreased by the prevention of hypothermia. In the trauma scenario, it is not wrong to accept mild hypothermia of about 35°C, since mild hypothermia improves neurological outcome. Regarding emergence, you will have to decide if the heart (myocardial perfusion) will cope with postoperative demands (increased oxygen consumption). It will probably be safe to awaken and extubate the patient if he/she is haemodynamically stable, will be able to sustain adequate ventilation, i.e. a P/F ratio > 300 (see Chapter 13), and has an acceptable haematocrit, and is awake, is not bleeding, and has an acceptable body temperature.
- All patients with myocardial hypoxia deserves special care in the postoperative period to ensure sustained myocardial oxygenation: on-going haemodynamic support (fluid, pharmacological), ventilator support (at least an oxygen mask), and analgesia.

Table 8 Anaesthetic plan for patients with decreased myocardial oxygenation

Phase	Activity	Agent	Dose for ideal mass	Comment
Preoperative	Evaluation	Anaesthetist	Awake	Tests, don't stop Rx, ? ACEIs
Pre-induction	Preparation	Emergency Rx	Dilutions	
	Calculate BP	Calculator	Know how	± 20% preoperative BP
	Venous access	Venous cannula	Very good	
	Pre-hydrate	Rehydration fluid	10 ml kg^{-1}	
	Resuscitate	Ringer lactate	5 ml kg^{-1} prn	As time allows
Induction	Monitor	Anaesthetist	All the time	BP, HR, ECG
	Preoxygenate	Oxygen	80% × 3 min	
	Opioid	Morphine	150 µg kg^{-1}	Co-induction. Morphine in prehydration. Wait for about 2 minutes
		Alfentanil	15 µg kg^{-1}	
		Fentanyl	1.5 µg kg^{-1}	
		Sufentanil	0.15 µg kg^{-1}	
	Rx hypotension	Volume	5 ml kg^{-1}	BP ± 20% of preoperative BP
		Phenylephrine	0.5 to 1.0 µg kg^{-1}	
		Ephedrine	0.1 mg kg^{-1}	
		Adrenaline	0.1 µg kg^{-1}	
	Hypnotic	Propofol	0.5 to 1 mg kg^{-1}	Rather to little
		Ketamine	1 to 2 mg kg^{-1}	Ketamine is the drug of choice
Intubate	Relaxant	Suxamethonium	1 mg kg^{-1}	Cricoid pressure prn
		Non-depolarizer	1 ED95	After suxamethonium
		Non-depolarizer	2 to 3 ED95	If used without SUX
	Ventilate	Ventilation	Normal PaCO$_2$, PaO$_2$	NormalPa – PETCO$_2$
Maintenance	Hypnosis	Vapour	0.7 – 1.0 MAC	Alone; depending on BP
		Ketamine	1 – 2 mg kg^{-1} h^{-1}	If used alone
		Morphine	50 µg kg^{-1} h^{-1}	*co-maintenance*
		Fentanyl	1 µg kg^{-1} h^{-1},	
		Sufentanil	0.1 µg kg^{-1} h^{-1}	
		Ketamine	0.1 mg kg^{-1} h^{-1}	
	Resuscitation	Fluid, CaO$_2$	Endpoints	Mild hypothermia?
Emergence	Extubate?	Fluid, CaO$_2$	Endpoints	High care

ACEI Angiotensin converting enzyme inhibitor

The boundaries of the heart

These structures have a profound effect on preload and afterload. Cardiac murmurs must be evaluated before elective surgery. *Pathology of the pericardium* decreases preload. These lesions include pericardial effusions, constrictive pericarditis, and traumatic pericardial tamponade. Chronic conditions allow the pericardial sack to dilate and cardiac compression occurs to a lesser extent. However, acute filling of the pericardium and constrictive lesions compress the heart. These patients are extremely sensitive for hypovolaemia.

Anaesthesia for pericardial surgery:
- *Good venous access* to allow fluid loading (preload),
- The induction agent of choice is *ketamine* since it is vasoconstrictive and positive inotropic.
- The patient is relaxed with *suxamethonium* (fast-acting, short-acting).
- *Spontaneous ventilation* is preferred to prevent increased intrathoracic pressure (decreased preload); if the patient is ventilated, small tidal volumes of about 5 ml kg^{-1} ideal mass are used.
- Pericardial surgery (constrictive of traumatic) is associated with significant *blood loss*, *cardiac perforation* with blood loss and *air embolism*, and *myocardial ischaemia* if the coronary arteries are damaged.

The particular valvular lesion will determine the haemodynamic approach to the patient. A patient with a *mitral stenosis* does better with a good preload (normovolaemia, high venous and arterial tone) and a slow heart rate (more pressure and time to fill the left ventricle through the stenotic valve). The patient may suffer circulatory collapse during hypovolaemia and a tachycardia.

With a *mitral regurgitation*, a low peripheral resistance is tolerated better. The left ventricle pumps blood back into the left atrium as well as into the aorta. A low peripheral resistance promotes forward flow into the aorta.

Mitral stenosis and regurgitation are complicated by pulmonary congestion and the development of *pulmonary hypertension*. Once pulmonary hypertension has developed, the right ventricle remodels and a *tricuspid regurgitation* is often present.

A patient with an *aortic regurgitation* prefers a low afterload (low peripheral resistance) and a higher heart rate in order to decrease the pressure and time for blood to flow back into the left ventricle. They do better with vasodilators. These patients have a very low diastolic blood pressure, which decreases coronary perfusion. Furthermore, a patient with a dilated heart is very sensitive to negative inotropes.

The patient with *aortic stenosis* is very difficult to anaesthetize. This *remodelled, ischaemic* heart is extremely dependent on coronary perfusion, and therefore an adequate diastolic blood pressure. The hypertrophic and eventually dilated heart does not tolerate a decrease in *afterload (vasodilatation) and preload (absolute or relative hypovolaemia)*. Therefore, the anaesthetic technique is based on *maintenance of preload, afterload, and inotropy, as well as a relatively low heart rate*. Vasotropic and inotropic drugs must be available to treat cardiovascular collapse, which occurs commonly in patients with severe aortic stenosis. Regional anaesthesia is not contraindicated in these patients – if you are able to prevent a decreased preload, afterload, and inotropy, and an increase in heart rate.

 Valvular lesions and mechanical valves must receive *prophylactic antibiotics*. Prosthetic heart valves often necessitate *anticoagulation*. They usually receive warfarin, the effect of which is monitored with the international normalized ratio (INR). To prevent clotting of the prosthesis the INR must be > 2. For major surgery warfarin is usually stopped and as soon the INR decreases < 2, heparin is started.

Control of the cardiovascular system
This section covers some conditions which can affect the control of the heart intraoperatively – from within the heart and from outside the heart. The autonomic nervous system modulates cardiac electrophysiology and abnormalities of autonomic function are known to increase the risk of arrhythmias. Patients may have an abnormal heart control already preoperatively as part of an **autonomic neuropathy (AN)**, which is a complication of their disease.

An AN may involve the:
- Parasympathetic or sympathetic nervous systems
- Parasympathetic and sympathetic nervous systems (pandysautonomia)
- Afferent nerves
- Efferent nerves
- Central autonomic interconnections
- Prejunctional Ca^{2+} channels, or
- Destruction of the postjunctional ACh receptors.

- Arterial baroreceptors in the aortic arch and carotid sinuses alter cardiac sympathetic and parasympathetic activity. Therefore, changes in baroreceptor activity have a large influence on the reflex control of cardiac rate and rhythm.
- An elevated sympathetic activity changes cardiac electrophysiology, which increases the risk of ventricular arrhythmias.

The presence of an AN may result in a substantial increase in mortality and morbidity. The AN may persist in a number of patients after they have recovered from the underlying disease. Patients with an AN present with a history of depression (I mention this first: I had to start somewhere, and since it may form part of several disease states), dizziness, syncope, xerophthalmia, xerostomia, palpitations, sudomotor abnormalities (anhidrosis or hyperhidrosis), impotence, bladder atony, diarrhoea, constipation, etc. A vital function that may also be affected by an AN, is control of breathing. There are many causes of autonomic neuropathy. Many of the ANs form part of rare diseases. However, to my surprise, an AN is a complication of many commonly occurring diseases (Table 9).

Table 9 Autonomic peripheral neuropathies

Metabolic and endocrine	Diabetes mellitus, primary amyloidosis, hyper- and hypothyroidism, phaeochromocytoma, acute intermittent and variegate porphyria, chronic renal failure, chronic liver disease, vitamin deficiencies
Acute and subacute	Guillain-Barré syndrome, infectious, parainfectious immune-mediated (infectious mononucleosis, coxsackie B, rubella, herpes simplex, streptococcus), malignancy, connective-tissue disorders
Immune-mediated, paraneoplastic	Malignancy, connective-tissue diseases, myasthenia gravis
Infectious	HIV, leprosy, tetanus, botulism, diphtheria, Chagas
Toxic	Alcohol, amiodarone, oncotherapeutics, organic solvents, heavy metals, marine toxins, pentamidine
Inflammatory bowel disease	Crohn's disease, ulcerative colitis
Hereditary	Real canaries. But remember to consider an AN in rare diseases.

I think that the often inexplicable intraoperative cardiac and vascular, i.e. cardiovascular instabilities (hypertension or orthostatic hypotension; tachycardia or bradycardia or several undecipherable dysrhythmias; and even sudden death) may actually be due to an undiagnosed AN. Excellent reviews have been written on it, e.g. Freeman R. Autonomic peripheral neuropathy. Lancet. 2005 Apr 2-8;365(9466):1259-1270. I will only mention physiological conditions and diseases that we see commonly and where cardiovascular instability may be expected. They present to the GP at the rural clinic and at the referral hospital operating theatre.

Age
The maturation of the ANS begins at foetal stage, both its sympathetic and parasympathetic arms, and continues after birth for a long period. An immature ANS status has been implicated in sudden infant death syndrome. Low ANS activity has been shown in premature infants both before and after their theoretical full-term age. It seems as though immaturity of the ANS is particularly important for the parasympathetic nervous system. The equalization of ANS activity (sympathetic and parasympathetic) in premature and full term infants may mask the increased sensitility to stress, more particularly in premature infants. In adults who were prematurely born, there is an earlier occurrence of cardiovascular diseases.

AN increased with increasing age. This effect of age is aggravated by obesity and the use of antihypertensive agents in the geriatric patient.

Obesity (see also Chapter 17)
In patients with an increased in body mass index, muscle and myocardial sympathetic nervous system activity is increased, while vagal tone is decreased. The arterial baroreflex function may also be affected. In obesity, the rate of noradrenaline spill over from heart and nerve firing rates is increased. The enhanced renal norepinephrine spill over may have implications for the development of hypertension.

Hyper-insulinaemia could explain the sympathetic hyperactivity. It has been shown in healthy and obese patients that acute administration of insulin activates the sympathetic nervous system and increases plasma noradrenaline levels.

It has therefore been suggested that autonomic cardiovascular control is decreased in obesity. The reduced variability of HR and BP may contribute to the increased risk of cardiovascular disease and sudden death in old obese subjects.

Diabetes (see also Chapter 17)
Diabetes mellitus is the most common cause of AN. This AN consists of axonal degeneration and segmental demyelization of sympathetic neurons that supply the splanchnic mesenteric vessels and other vascular areas, the heart, and afferent fibres from baroreceptors. Impairment of vagal control of heart rate is more common and occurs earlier than changes in the sympathetic nervous system. The cardiovascular clinical features include postural hypotension and impaired heart rate control, silent myocardial infarction and sudden death.

Malignancy and oncotherapy
Several malignancies are complicated by paraneoplastic AN. These malignancies are not rare and include lung, gastrointestinal tract, prostate, breast, bladder, kidney, pancreas, testicle, ovary, and thymus. You may have to manage patients that have received or are receiving oncotherapeutic agents. These drugs affect about all vital organs and many are neurotoxic (vincristine, cisplatin, paclitaxel).

Chronic liver disease (see also Chapter 15)
Patients with chronic liver disease (CLD) have a decreased response to vasoconstrictors. This may be due to elevated levels of vasodilators such as nitric oxide. Even mild increases in portal venous pressure can up-regulate nitric oxide synthase. In cirrhotic patients, there is an AN with a decreased baroreceptor sensitivity to hypotension. The effects of the AN is exaggerated by arterio-venous communications, altered sodium handling, as well as a cardiomyopathy. AN is implicated in the development of portal hypertension. Thiamine and pyridoxine deficiencies, increased lipid peroxidation of nerve membranes, and circulating immune complexes are implicated in the development of AN.

Chronic renal failure (see also Chapter 15)
Uraemic polyneuropathy occurs in approximately 60% of patients with chronic renal failure and can affect motor, sensory, autonomic and cranial nerves.

Porphyria (see also Chapter 11)
During an acute attack, induction of haem synthesis causes excretion of large amounts of porphyrins by the liver. These haem precursors are neurotoxic. The autonomic and peripheral nervous systems do not have a protective barrier, which makes them very vulnerable to these neurotoxins. The blood-brain barrier protects most parts of the brain from toxins, but certain areas, such as the hypothalamus and limbic system, are not protected. However, the haem precursors can cause vascular injury, which increases capillary permeability resulting in brain oedema. The peripheral nerve changes resemble a primary axonopathy. Pathological changes have been demonstrated in the vagus nerve, sympathetic nerves, brainstem, and spinal cord neurons.

Acute attacks are characterized by severe abdominal pain, autonomic instability, electrolyte disturbances (nausea, vomiting, syndrome of inappropriate secretion of ADH), and neuropsychiatric manifestations. The severity of an attack ranges from mild to fatal. Neuromuscular weakness, which may progress to quadriplegia, is the most prominent and potentially lethal neurological complication.

Sympathetic and parasympathetic cardiovascular dysfunctions occur during an acute episode. Autonomic over-activity is more prominent than autonomic failure, but often coexists. A mild parasympathetic cardiovascular dysfunction may persist between attacks and in latent acute intermittent porphyria. These patients may develop chronic hypertension.

The autonomic overactivity often presents with hypertension, tachycardia, and abdominal pain (colic). Postural hypotension occurs less commonly. Other manifestations of the AN include nausea and vomiting, severe constipation, bladder disturbances, pupillary changes, and either anhidrosis or hyperhidrosis. Cardiovascular instability with tachycardia and hyper- or hypotension occur particularly in acute intermittent porphyria.

Alcoholism
Except for impaired sweating distally, AN is uncommon in uncomplicated alcoholic peripheral neuropathy. AN with postural hypotension may occur in cases with severe Wernicke encephalopathy.

Amiodarone
A sensorimotor peripheral neuropathy occurs in about 10% of patients taking amiodarone. An AN with postural hypotension has been reported (Manolis et al., 1987).

Dysautonomia after traumatic brain injury (DTBI)
This condition occurs during the recovery phase, and may continue days to months. It is associated with an admission GCS score of 3 and a longer duration of coma and mechanical ventilation. DTBI is characterized by episodes of tachycardia, hypertension, tachypnoea, hyperthermia, increased muscle tone, and profuse sweating. It can resemble the neuroleptic malignant syndrome and serotonin syndrome.

Autonomic dysreflexia following spinal cord injury (SCI)
Autonomic dysreflexia occurs in about 85% of patients with SCI above T6. After a short-lived period of hypertension (spinal storm), hypotension occurs after SCI since tonic supraspinal excitatory drive to spinal sympathetic neurons is lost (spinal shock), which may last for weeks after injury. Thereafter, they present with increased resting heart rates and blood pressure variability, and episodes of life-threatening hypertension. Due to their sedentary lifestyle, obesity, and diabetes, cardiovascular morbidity is increased. Patients with T1 to T6 spinal cord injury have elevated sympathetic activity above the level of the lesion.

The autonomic nervous system imbalance favours sympathetic activity, resulting in tachy-arrhythmias. Arterial baroreceptors respond to an increased blood pressure by increased parasympathetic and decreased sympathetic nerves. This results in bradyarrhythmias. If not prevented or treated immediately, the hypertension may cause cerebral and subarachnoid haemorrhage, seizures, renal failure, cardiac arrhythmias, and death.

ECG changes are observed commonly in these patients, especially if body parts caudal to the spinal lesion is stimulated, e.g. tracheal suctioning, skin incision, a full ladder, bladder catheterization, labour, dural puncture, etc. These changes include axis deviation, low QRS amplitude, ventricular conduction delays, premature atrial and ventricular contractions, ST segment depression, changes in T wave amplitude, and T-wave inversion, premature atrial and ventricular contractions, profound bradycardia (especially cervical SCI), and asystole.

Parkinson's disease (PD)
In PD the main cause of dysautonomia is damage to the sympathetic postganglionic fibres causing cardiac denervation. The cardiac denervation and the resulting reduction in plasma noradrenaline levels, causes a postganglionic denervation hypersensitivity of adrenergic neurons. The denervation hypersensitivity causes a higher blood pressure to specific adrenaline doses. As for patients with diabetes, increased cardiovascular mortality has been reported in patients with different extrapyramidal disorders after myocardial infarction.

These symptoms of cardiovascular autonomic dysfunction commonly occurs in PD. Dysautonomia is part of the disease process as well as ANS adverse effects of drug treatment. The most frequent and disturbing symptom of cardiovascular autonomic dysfunction is orthostatic hypotension. Factors such as increased intrathoracic pressure, vasodilators, and hypovolaemia worsen hypotension. Supine hypertension is often associated with orthostatic hypotension. The use of dopamine receptor agonists is associated with resting hypotension and a severe decrease in orthostatic BP.

Human immunodeficiency virus (HIV)
Patients with HIV infection commonly present with symptoms of AN, including syncope, bladder and bowel dysfunction, and anhidrosis. Autonomic function is already abnormal in the early stage of the disease and occurs in up to 80% patients with AIDS. The pathogenesis of autonomic dysfunction in HIV infection is unclear. There are widespread changes in the central, peripheral, and autonomic nervous systems.

Leprosy
Leprosy is one of the most common causes of a peripheral neuropathy which may involve the ANS. The most common presentation of the AN is hyperhidrosis over the skin supplied by the affected nerves. AN also causes cardiac denervation, postural hypotension, and widespread anhidrosis.

Connective-tissue diseases
Many connective tissue (autoimmune) diseases have as part of the pathogenesis a vasculitis and neuritis, which may affect the central and peripheral nervous systems. These diseases include systemic lupus erythematosus, mixed connective-tissue disease, scleroderma, and Sjögren's syndrome.

Myasthenia gravis may cause autonomic instability.

Multiple sclerosis
It has been suggested that plaques of demyelisation may disrupt the central autonomic network. Baroreflex dysfunction is not restricted to the cardio-vagal limb of the baroreflex, but also affects the sympathetic modulation of blood vessels, causing postural intolerance and dizziness.

Fibromyalgia (FM)
Many fibromyalgia (FM) patients complain of symptoms such as palpitations and fatigue and frequently describe the inability to stand for prolonged times. One of the most frequent autonomic abnormalities in FM is a syndrome characterized by orthostatic tachycardia in the absence of orthostatic hypotension.

Cystic fibrosis (CF)
In CF there is a reduced cardiovascular sensitivity to β adrenergic stimulation. The possible mechanisms for the AN in CF are metabolic, nutritional, and immunological. CF is complicated by diabetes mellitus, chronic liver disease (67% of patients), and chronic renal failure, all of which cause an AN. Many CF patients are malnourished, as a result of an increased metabolic rate, malabsorption, and chronic illness. Malabsorption of fat may result in decreased absorption of fat-soluble vitamins, including vitamin E deficiency. In non-CF patients vitamin E deficiency contributes to the development of an AN. Administration of vitamin E may improve the AN of DM (the cardiac sympathetic to parasympathetic tone ratio). Auto-antibodies to β_2 adrenergic receptors occur in the serum of the CF patients with allergic respiratory disease.

Primary amyloidosis
AN occurs in about 20% of cases with primary amyloidosis. It accompanies or precedes the somatic neuropathy.

Intraoperative management of a patient with suspected AN
- The management depends on the particular *co-morbidities*, and treatment. You may encounter the following preoperative drugs prescribed for the AN specifically: α_1 agonist (phenylephrine), α_2 agonist (clonidine), β blockers, gabapentin (decreases the dysautonomic paroxysms in MS), the aldosterone analogue fludrocortisone (promotes sodium and water retention), and desmopressin (promotes water retention).

- *General and neuraxis anaesthesia create a state similar to an AN*: they suppresse the autonomic centres in the CNS (brain and spinal cord), affect nerve conduction, decrease the prejunctional release of neurotransmitters, and the sensitivity of postjunctional receptors.
- Since patients with an AN may have abnormal thermoregulation, *theatre temperature* must be 20°C to 22°C.
- Patients with an AN may have *decreased stomach emptying* and may regurgitate and aspirate.
- These patients may have *silent (painless) myocardial ischaemia.*
- Position the patient in a *horizontal* position.
- These patients are *extremely sensitive* to absolute (blood loss, diuresis) and relative *hypovolaemia* (vasodilatation, positioning).
- Be prepared to tilt the *theatre table* head-up or -down.
- *Volume changes* (absolute or relative) are inherent to anaesthesia and surgery. Good *venous access* is essential and w*arm intravenous fluid* must be available.
- *Ready-diluted drugs*: adrenaline, phenylephrine, ephedrine, β blockers (esmolol, propranolol, atenolol), TNT.
- These patients may react unpredictable to stimuli and drugs. Therefore, cardiac and vascular function may become very unstable intraoperatively. You must be prepared to *monitor and manage these instabilities. Invasive monitoring* is recommended; if you do not have access to invasive monitoring, you must take the blood pressure at least once per minute.
- They may be *very sensitive to anaesthetics* (induction agents, vapours, analgesics). An AN and anaesthesia depress the *control of breathing*. Assure that they are *fully awake,* that neuromuscular function has returned, and that they are breathing before you leave them.
- They deserve *high care* postoperatively.

SUMMARY

The cardiovascular system ensures perfusion of all tissues. A decrease in cardiovascular function is caused by failure of one or more of the *interdependent determinants of cardiac output*. The perioperative period is characterized by an increase in VO_2, which demands an increase in cardiac output. A decrease in cardiac output gives rise to ischaemia. Reperfusion following ischaemia is complicated by a reperfusion injury depending on the time and extent of ischaemia. Cardiovascular disease must be stratified and optimally treated before elective surgery. Treatment of cardiovascular disease must be continued during the perioperative period.

In this lecture, I often refer to *"optimisation"* of cardiovascular function. What is optimal? What is the endpoint of treatment? Probably, the return of normal function. "Return" implies regular assessment of trends. What are the trends? In this regard, you must first focus on the relative changes of the different *clinical signs* of end organ function, e.g. consciousness, wet mucous membranes, improvement of shock index, acceptable haematocrit, improvement of metabolic state (acid-base, electrolyte levels), normal respiratory rate (air hunger must disappear, haemoglobin saturation on oximeter > 90%), and increase in urine output (see Chapter 18 and 11). If a patient has reached these endpoints, he/she is out of danger and is most probably safe to transfer for further treatment. Remember, the primary physician plays an invaluable role in this regard. *Fancy monitors are not essential to start cardiovascular treatment. You must be able to identify the main problem clinically and start appropriate treatment.*

CHAPTER 13

ANAESTHETIC APPROACH TO THE RESPIRATORY SYSTEM
This Chapter must be read with Chapter 14 (Perioperative Hypoxia)

"A heavy step was heard ascending the stair, with a great wheezing and rattling as from a man who was sorely put to it for breath. Once or twice he stopped, as though the climb were too much for him, but at last he made his way to our door and entered. His appearance corresponded to the sounds which we had heard. He was an aged man, clad in seafaring garb, with an old pea-jacket buttoned up to his throat. His back was bowed, his knees were shaky, and his breathing was painfully asthmatic. As he leaned upon a thick oaken cudgel his shoulders heaved in the effort to draw the air into his lungs."

Dr Watson in *The Sign of Four*
Sherlock Holmes 1890

Key points
1. Perioperative approach to respiratory system
First principle: Functional approach
Second principle: systematic approach
Third principle: complications
Forth principle: monitoring
Fifth principle: perioperative approach
- Ventilation
- Pulmonary perfusion
- Relationship between pulmonary ventilation and perfusion
- Control of breathing

- Work of breathing
- Airway protection
2. Postoperative pulmonary complications (PPC)
- Intra-operative effects of anaesthesia and surgery
- Postoperative respiratory function
- Prevention of postoperative pulmonary complications
- The anaesthetic and surgical techniques, respiratory disease and PPC
- Postoperative management and the prevention of PPC
3. Respiratory failure

Central to the learning of anaesthesia and critical care is an appreciation of *the principles underlying uptake of O_2 from the alveoli, delivery of O_2 to body tissues, and removal of CO_2 by the lungs.* You must always have the following principles in mind when treating patients with diseases or interventions that involve ventilation.

First principle: Functional approach
The components of the respiratory system do not operate independently, but always interact; change in the one, always have an impact on the others:
- Ventilation of the alveoli
- Perfusion of the alveoli
- The relationship between alveolar ventilation and alveolar perfusion
- Diffusion of gas between the alveoli and the alveolar capillaries
- The work of breathing or ventilation
- Control of ventilation
- Airway protection

Second principle: systematic approach
Lung function (the above seven aspects) is not something that exists in isolation. It is always affected by the anatomy, physiology, and treatment of lung disease. Again, these influences do not act independently, but interact with each other:
- Anatomy of the respiratory system (patho-anatomy)
  - Upper airway: outside the wall, in the wall, in the lumen
  - Glottis
  - Lower airways
  - Alveoli
  - Blood supply
  - Lung interstitium
  - Pleurae and interpleural space
  - Thoracic wall: skeletal (anterior, posterior, lateral) and muscular (diaphragm and intercostal muscles)
  - The mediastinum: trachea and main bronchi, oesophagus, heart, great vessels, lymphatic ducts, lymph nodes, thymus

- The physiology of the respiratory system (pathophysiology)
- Therapy of respiratory and non-respiratory disease (pharmacological and non-pharmacological)

Third principle: complications
The respiratory system does not exist in isolation. It is one of the vital systems (without it, you die, finish and klaar), which is *always in two-way communication with all the other vital systems*: cardiac, vascular, renal, gastro-intestinal system (including the liver), nervous system, neuro-muscular system, musculo-skeletal system, endocrine organs, immunological, and reticulo-endothelial systems, etc. Therefore, when a patient presents with a disease involving any of these organ systems, you must look for respiratory complications.

Forth principle: monitoring
After you have evaluated the patient clinically, you must assess the grade of the respiratory system and its complications. This we call monitoring, and include *anatomical* (usually radiological), *physiological* (cardiovascular testing, lung function tests, blood gas analysis, blood biochemistry, haematological), and *pharmacological* (is therapy optimal, complications of therapy, e.g. glucocorticosteroid therapy).

Fifth principle
You must apply principle one to four *preoperatively, intraoperatively, and postoperatively*.

VENTILATION

The function of pulmonary ventilation is to supply O_2 to and to remove CO_2 from the alveoli. Oxygen and CO_2 must always be considered together. This interaction is represented in the *ideal alveolar gas equation*. The alveolar gas equation *states that the partial pressure of oxygen in the alveolar gas mixture is determined by the inspiratory PO_2, water vapour, alveolar PCO_2, and metabolism:*

$$PAO_2 = PIO_2 - (P_ACO_2/R) + K$$
$$= FiO_2(PB - PH_2O) - (P_ACO_2/R) + K$$

PAO_2 = Alveolar PO_2
PIO_2 = Inspiratory PO_2 = $(FIO_2 \times PB) - PH_2O$
$PIO_2 = FIO_2 \times (PB - PH_2O)$
FIO_2 = The fraction of O_2 in the inspiratory gas mixture. The FIO_2 of air is 0.21 or 21%
PB = Barometric pressure. In Pretoria it is 650 mm Hg (87 kPa) and at sea level, 760 mm Hg (101.3 kPa).
PH_2O = Vapour pressure of water in the lung = saturated vapour pressure = 47 mmHg
R = Respiratory coefficient = production of CO_2/consumption of O_2 = 0,8 with a mixed diet
K = a constant = about 4 mm Hg (0.13 kPa)
Breathing air *in Pretoria*, $PIO_2 = 0.21 \times (650$ mm Hg $- 47$ mm Hg) = 132.3 mm Hg.
$PACO_2$ = Alveolar PCO_2. Normally, PAO_2 is close to the arterial PCO_2 ($PaCO_2$). Since the PIO_2 at high altitude is lower, their minute ventilation is higher. Therefore, their $PaCO_2$s are lower. At sea level, the normal $PaCO_2$ is 35 mm Hg to 45 mm Hg (4.7 kPa to 6.0 kPa); in Pretoria, it is 31 mm Hg to 39 mm Hg (4.1 kPa to 5.2 kPa).

In Pretoria, PAO_2 in a young adult with a $PaCO_2$ of 35 mm Hg = 132.3 mm Hg $- (35$ mm Hg$/0.8) + 4$ mm Hg = **92.55** mm Hg. If his $PACO_2$ = 40 mm Hg, the PAO_2 is **87 mm Hg**. *At sea level* the PAO_2 in the same person ($PACO_2$ = 40 mm Hg) will be about **103 mm Hg**) Normally, the arterial partial pressure of oxygen (PaO_2) reflects PAO_2; a hypoxic gas mixture (low FiO_2) delivered to the alveoli (low PAO_2) will therefore result in a low PaO_2.

Gas movement in the respiratory system supplies fresh gas (oxygen) to and removes CO_2 from the lungs. This remark may seem trivial, but before you read further, consider (meditate) each of the

terms in the sentence, and you will soon realise how important it is.

The volume of air entering the lung during each normal breath is called the *tidal volume* (Vt). In healthy, *non-obese*, resting adults Vt ≈ 6ml kg^{-1} or about 420 ml in a 70 kg person. Vt is composed of gas ventilating the alveoli (VA), and gas not contributing to alveolar ventilation. This *wasted ventilation is called dead space* (Vd):

$$Vt = VA + Vd$$

Vd is composed of gas filling the conducting airways (anatomical dead space, Vd anat) and gas filling alveoli that do receive little blood flow (perfusion). This latter part of Vt is called the *alveolar dead space* (Vd alv).

Normally, Vd alv is the result of gravity on pulmonary blood flow; alveoli in the upper (non-dependent*) regions of the lung are better ventilated than perfused. (*"Dependent" refers to the lowest part; in the erect patient is the basal parts, i.e. next to the diaphragm dome. In the supine patient, the dependent parts are posterior, and in the prone patient are anterior.)

The sum of Vdanat and Vdalv is known as *physiological dead space* (Vdphys):
Vdphys = Vdanat + Vdalv

In the healthy awake subject the rule of "2, 4, 6" conveniently applies where
Vt = VA + Vdphys
Vt (6 ml kg^{-1}) = VA (4 ml kg^{-1}) + Vd (2 ml kg^{-1})

At a normal breathing rate (Vf) of 15 min^{-1},
minute ventilation (V min) in a 70 kg person = 420 ml × 15 min^{-1} = 6300 ml min^{-1},
while minute alveolar ventilation (VA min) = 280 ml × 15 min^{-1} = 4200ml/min.

It is important to note that the normal Vd/Vt is 1/3, or 33%. In a 70 kg person with a Vt of 420ml, 280 ml contributes to gas exchange (VA), and 140ml does not reach functional (i.e. perfused) alveoli, and do not contribute to gas exchange (Vd). Therefore, Vdphys = 140/420 = 33%.

When intubated and connected to a ventilator, the equipment (tubing, filters, connectors, compliance of the tubing, filter, etc.), further erode the Vt and is known as *apparatus dead space* (Vd app) (also see Chapter 4). Therefore, total Vd (Vdtot) is as follows:
Vdtot = Vdalv + Vdanat + Vdapp = Vdphys + Vdapp

Vdapp becomes part of the patient's respiratory system. The gas that is expired last is the alveolar gas and fills the expiratory limb of an anaesthetic circuit. If the CO_2-containing expired gas is not eliminated (washed out) from a rebreathing anaesthetic circuit, the inspiratory gas will contain CO_2. This results in an increased inspiratory PCO_2 (the capnogram baseline will be > 0 mm Hg) and the $PaCO_2$ will also increase. Remember, inspiratory gas should not contain any, or very little CO_2 – depending on the type of anaesthetic circuit, i.e. rebreathing or non-rebreathing (circle with CO_2 absorbent). In the anaesthetised, intubated and ventilated patient the Vd/Vt ratio of 0.33 increases to up to 0.5. This is mostly caused by the effect of increased intrathoracic pressure on lung perfusion; the higher intrathoracic pressure, the lower alveolar perfusion, and the higher Vd alv. In a 70 kg patient only 210 ml (50% of a Vt of 420 ml) instead of 280 ml contribute to gas exchange and the anaesthetist will have to attend to the decreased alveolar perfusion by increasing cardiac output or to limit the intrathoracic pressure.

The Vd phys can be calculated with the Bohr equation:
$$Vdphys = \frac{Vt(PACO_2 - PECO_2)}{PACO_2}$$

Or, more conveniently

$$Vdphys = \frac{Vt(PaCO_2 - PECO_2)}{PaCO_2}$$

where $PECO_2$ is the PCO_2 mixed (mean) in expired gas. If the capnogram has the normal square wave form, $PECO_2$ is about $0.5 \times PETCO_2$. *Can you see that when Vd phys increases, $PaCO_2$ increases, $PECO_2$ decreases, while the $PaCO_2 - PECO_2$ difference increases?* This is always the case with increased dead space ventilation. On the other hand, if you detect an increased $PaCO_2 - PECO_2$ difference, you must look for increased dead space ventilation, e.g. a low cardiac output. *The normal difference between $PaCO_2$ and $PETCO_2$ is about 5 mm Hg.*

Example:
$Vt = 400$ ml, $PaCO_2 = 55$ mm Hg, the capnogram has a normal form, the $PETCO_2$ is 30 mm Hg, and the $PECO_2$ is therefore 0.5×30 mm Hg $= 15$ mm Hg
Therefore,

$$Vdphys = \frac{400 \text{ ml } (55 \text{ mm Hg} - 15 \text{ mm Hg})}{55 \text{ mm Hg}}$$
$$= 400 \text{ ml}(40 \text{ mm Hg}/55 \text{ mm Hg}) = 291 \text{ ml}$$

The Vd phys/Vt ratio is 291 ml/400 ml = 0.73, which is about twice the normal ratio of about 0.3.

Vd phys increases with increasing age due to COAD-like changes in the lung. The increase in Vd phys contributes to the age-related decreased PaO_2 and increased $PaCO_2 - PETCO_2$ difference (see later). Remember, the normal difference between $PaCO_2$ and $PETCO_2$ is about 5 mm Hg.

The Vd phys in persons breathing spontaneously can be predicted from the following formula:
$$Vdphys (\%) = 33 + 0.33(age)$$

For example, the Vdphys of a 75 year old person breathing spontaneously:
$$Vdphys (\%) = 33 + 0.33(age) = 33 + 0.33(75) = 58\%$$

Remember the functions of pulmonary ventilation: oxygenation and elimination of CO_2. The lower VA min, the lower is the CO_2 excretion. *However, CO_2 is produced during aerobic metabolism.* Therefore,

$$PACO_2, \text{ and therefore } PaCO_2 \propto \text{ production of } CO_2 \text{ } (VCO_2),$$
$$\text{and } PACO_2 \text{ is } \propto 1/VA \text{ min.}$$

Therefore,
$$PACO_2 \propto VCO_2/VA \text{ min and } \mathbf{PaCO_2 \propto VCO_2/VA \text{ min}}.$$

Further, recall that

$$\mathbf{PAO_2 = PIO_2 - (P_ACO_2/R) + K}$$
$$\text{and}$$
$$\mathbf{Vd \text{ tot} = Vd \text{ alv} + Vd \text{ anat} + Vd \text{ app} = Vd \text{ phys} + Vd \text{ app}}$$

Practical implications:
- From the latter two equations it should be clear that, a *decreased VA min*, whether due to a low Vt or an increased Vd (Vd phys, Vd app) is always complicated by an *increased $PaCO_2$ and decreased PaO_2*. Likewise, an *increased VA min*, whether due to a high Vt, or high Vf is always followed by a *decreased $PaCO_2$ (hypocapnia) but a higher PAO_2 and PaO_2*.
- In the spontaneously breathing patient, VA min may increase in response to acidosis (metabolic or respiratory), hypoxia (any cause), or due to stimulation by higher brain centres (neurogenic, psychogenic).
- *Vdanat and Vdapp are constant*. Therefore, the *smaller Vt, the larger the part that Vdanat and Vdapp make out of Vt*, with a corresponding *decrease in VA*. Therefore, although a patient is ventilated with a very large V min but a high Vf (low Vt) the larger the contribution of Vdanat and

Vd app will be.

- *When VA min decreases due to an increased Vdanat,* i.e. small Vt with a normal or even high Vf, less CO_2 is eliminated from the alveoli. If VA min is normal, any factor that *increases Vdalv* (pulmonary hypoperfusion) will also decrease CO_2 elimination. Therefore, if any increase in Vd tot will hamper the elimination of CO_2 from the respiratory system, PETCO$_2$ decreases, while PACO$_2$ and PaCO$_2$ increases, with an *increased PaCO$_2$ – PETCO$_2$ difference*.

- *VA min can also decrease due a low V min (VA and Vt are acceptable).* In this case, there is a mismatch between V min and VCO$_2$. The alveoli are emptied with every expiration, but the frequency of emptying is too low. Therefore, CO_2 in the blood will accumulate. This results in an increase in both PaCO$_2$ and PACO$_2$. Since the alveolar gas reaches the upper airway, the PETCO$_2$ will be close to PACO$_2$ and PaCO$_2$. Therefore, alveolar hypoventilation that is not due to increased Vdanat or Vd app, causes hypercapnia but with a *normal PaCO$_2$ – PETCO$_2$ difference*.

- If VA min is normal (acceptable Vt, Vdphys, Vf), while *Vdapp is high* (fresh gas flow too low or exhausted CO_2 absorbent) CO_2 is rebreathed. Therefore, the PACO$_2$ and PaCO$_2$ will increase. Since alveolar emptying is normal, alveolar gas will reach the upper airway, both *PaCO$_2$ and PETCO$_2$ will be increased,* and the *PaCO$_2$ – PETCO$_2$ difference will be normal*. Since the patient breaths gas containing CO_2, the capnogram will not reach zero during inspiration. Therefore, the *capnogram baseline will be larger than zero*.

- A low PETCO$_2$ can result if VA min is relatively larger than VCO$_2$, i.e. alveolar hyperventilation. In this instance, more CO_2 is removed from the alveoli. Therefore, both the PaCO$_2$ and PETCO$_2$ will decrease, while the *PaCO$_2$ – PETCO$_2$ difference* will remain small, e.g. 28 mm Hg vs. 26 mm Hg. A low VCO$_2$ is caused by hypothermia, hypothyroidism, old age, anaesthesia per se (sleep). Remember that hyperventilation often impedes cardiac output and may therefore cause an increased *PaCO$_2$ – PETCO$_2$ difference (increased Vd phys)*.

- If the patient is *not able to increase VA min* (muscle relaxation with mechanical ventilation, inability to maintain an increased work of breathing) an increased VCO$_2$ increases *both PaCO$_2$ and PACO$_2$*. An *increased VCO$_2$* occurs during increased aerobic metabolism (stress response to surgery or trauma, hyperthyroidism, fever, malignant hyperthermia, rewarming of the hypothermic patient) or administration of CO_2 e.g. inflation of body cavities with CO_2 for laparoscopy or thoracoscopy, or as $NaHCO_3$. Remember, HCO_3^- buffers H^+ in the blood, forms H_2CO_3, which splits into CO_2 and H_2O.

- Thus, a *VA min that is low relative to VCO$_2$ and any increase in Vd tot, cause an increased PaCO$_2$*. An increased PaCO$_2$ increases the PACO$_2$ of perfused alveoli. An *increase in PACO$_2$ decreases PAO$_2$* (see alveolar gas equation). The reverse is also true. A patient with a high PaCO$_2$ may have a normal or low PETCO$_2$ and a normal (zero) or elevated inspiratory PCO$_2$ depending on the amount of Vd.

- *Hypercapnic patients present with* dyspnoea, headache, restlessness, excitement, and hallucinations. The *clinical signs include* cyanosis and hyperventilation, sympathetic nervous system stimulation (hypertension, tachycardia, and an increased myocardial irritability, sweating, and mydriasis), warm skin due to direct vasodilatation causing an elevated pulse pressure, and even myocardial depression, bradycardia, and circulatory collapse.

- *Anaesthesia causes uncoordinated respiratory muscle activity*. The diaphragm is the most important respiratory muscle, but other muscle groups, such as the intercostal muscles, co-operate to coordinate respiratory function. Anaesthesia affects the timing and distribution of neural impulses to the different respiratory muscles groups resulting in uncoordinated activity and reducing respiratory efficiency. These effects contribute to PPCs, *especially in patients with lung disease*.

PULMONARY PERFUSION

Pulmonary blood flow (Qp) equals the total cardiac output (Qt). Qt is the product of stroke volume (SV) and heart rate (HR):

$$Qt = SV \times HR$$

At rest, the SV and HR in non-obese adults, are 65 ml to 75 ml and 65 min^{-1} to 75 min^{-1}, respectively. Therefore, in a 70 kg patient, Qt = QP = 65 ml $\times$ 65 min^{-1} = **4225 ml min^{-1}.**

Under certain conditions, the whole Qt is not exposed to ventilated alveoli. This is *wasted perfusion, and is called intrapulmonary shunt* (Qs). (Remember, that wasted ventilation is called dead space, Vd.) Some alveoli, particularly in the dependent regions of the lung, are compressed and therefore not ventilated. This forms part of Qs.

$$QS/QT = (CcO_2 - CaO_2)/(CcO_2 - CmvO_2)$$

QS/QT = shunt fraction or ratio
Qs = alveolar shunt
Qt = cardiac output
CcO_2 = O_2 concentration in alveolar capillary blood
CaO_2 = O_2 concentration in lung capillary blood
$CmvO_2$ = O_2 concentration in mixed venous blood (blood in the pulmonary artery)

CcO_2 represents the oxygen concentration in capillaries perfusing *ventilated alveoli*. It is calculated using the alveolar gas equation. *Mixed venous blood* represents blood returning to the heart following delivery of O_2 and uptake of CO_2 from tissue cells. Since the O_2 and CO_2 content of venous blood in the SVC (representing the upper body) and IVC (representing the lower body) differ significantly, proper mixing must first be allowed before a representative mixed venous specimen may be obtained. In practise, this sample must be taken beyond at least one valve (i.e. from the right ventricle) or preferably beyond two valves (i.e. from the pulmonary artery). The normal $PmvO_2 \approx 40mmHg$ ($SmvO_2 \approx 70\%$) and represents the O_2 content in blood arriving at the alveoli-capillary interface.

A low $PmvO_2$ is caused by a high extraction of O_2 from the arterial blood or low contact time between the mixed venous (mv) blood and the alveolus. The *high extraction* may be due to a low oxygen flux (see Chapter 14) an *increased O_2 consumption* (VO_2). A limited amount of O_2 can be added. The lower the $PmvO_2$, the lower PaO_2 will be. A very low $PmvO_2$ will also decrease Qp (HPV), which contributes to a low PaO_2. If the shunt fraction (Qs/Qt) is large, more mixed venous blood will reach the left heart without being oxygenated. This is called *venous admixture*. A low $CmvO_2$ can also increase the shunt fraction. Can you see why?

The *oxygenation of mixed venous blood is limited by the time that a red blood cell spends in contact with the respiratory membrane* (alveoli/capillary interface). Normally, this is about 0.75 s for an individual RBC. However, the $PmvO_2$ reaches P_AO_2 values after only about 0.25 s. If the $PmvO_2$ is substantially lower than 40 mmHg, 0.75 s is too short for O_2 to diffuse across the alveolo-capillary membrane. Therefore, PaO_2 will be lower. *A high Qt will shorten the contact time* in the alveolar capillaries, which may aggravate venous admixture.

The Qs/Qt is calculated from the oxygen concentration in ideal (ventilated) alveolar capillaries, arterial blood, and mixed venous blood. The normal Qs/Qt ratio is about 2%. A high Qs/Qt ratio means that a high fraction of the cardiac output (Qt) perfuses alveoli that are not ventilated. Therefore, blood in the alveolar capillaries is not oxygenated, resulting in a low CaO_2. The higher the shunt ratio, the less is the effect of an increased FIO_2.

There is also an entity called an *intracardiac shunt, which also causes venous admixture*. This happens when the blood from the right side of the heart is shunted away from the lungs directly to the left side of the heart via an intracardiac connection. The most common cause is Tetralogy of Fallot. This congenital heart lesion consists of two primary defects and two secondary defects, namely right ventricular outflow obstruction resulting in right ventricular hypertrophy, and an *overriding aorta* over a *ventricular septal defect*. Deoxygenated blood is therefore shunted from the right ventricle to the left ventricle, which pumps the blood to the systemic circulation. *These children are therefore cyanotic*. Now, you will understand that a *right-to-left intracardiac shunt decreases Qp and causes dead space ventilation*.

Lung volume and Qp have an influence on pulmonary vascular resistance. At *low lung* volumes, extra-alveolar capillaries are compressed, while at large lung volumes, alveolar capillaries are stretched. Both conditions will increase pulmonary vascular resistance, and therefore decrease Qp. Pulmonary vascular resistance is the least at functional residual capacity, i.e. lung volume at the end of normal expiration.

An increased Qp recruits alveolar capillaries (more capillaries open). The higher Qp, the lower the pulmonary vascular resistance is (larger capillaries), while a low Qp results in a higher pulmonary vascular resistance. These are *mechanical effects*. However, *long-standing high Qp*, e.g. in patients with large left-to-right lesions (e.g. a ventricular septal defect, atrial septal defect, and patent ductus arteriosus) will give rise to hypertrophy of the media of the pulmonary arteries. In these

patients (mostly babies and small children), the left-to-right shunt can be very large. With these lesions, more blood is shunted to the lungs (Qp), while less blood reaches the systemic circulation (Qsys).

Normally, the ratio of Qp/Qsys = 1. *With left-to-right congenital heart disease*, the Qp/Qsys increases, e.g. to > 3 with a large VSD. The lungs are overflowed with blood and the alveoli are often wet (oedema). Therefore, left-to-right lesions cause an *intrapulmonary shunt*. *With cyanotic heart lesions*, the Qp/Qsys is always < 1. These lungs are under-perfused (oligaemic) with blood with wet alveoli. Therefore, right-to-left lesions cause an *extrapulmonary shunt*, i.e. increased pulmonary dead space. The chronic hypoxaemia in patients with right-to-left cardiac lesions stimulates erythropoiesis, which results in polycythaemia and increased blood viscosity. Therefore, both patients with left-to-right and those with right-to-left lesions may develop an increased pulmonary vascular resistance (PVR) and eventually pulmonary hypertension.

Pulmonary vascular resistance is influenced by the tone *in the pulmonary arteriolar walls*. Any condition that decreases the PO_2 in the pulmonary arterial blood, called mixed venous blood (see Chapter 14), increases PVR. Therefore, all patients with a low PAO_2 (the most important mechanism), low PaO_2, or low Qt will have some degree of increased PVR, i.e. pulmonary hypertension. This phenomenon is called *hypoxic pulmonary vasoconstriction (HPV)*. The function of HPV is to direct blood away from under-ventilated (Low PAO_2) lung zones. *PVR is also increased by an acidosis* (decreased pH) – metabolic (decreased HCO_3^-) or respiratory (increased PCO_2).

Any factor that prevents alveolar capillary perfusion will increase alveolar dead space (Vd alv). Some of these frequently occur during anaesthesia, i.e. hypotension, low cardiac output, high inspiratory pressures, pulmonary emboli, and incomplete emptying of alveoli (COAD or inappropriate levels of PEEP). *Dead space ventilation* is always characterized by decreased gas exchange and consequently *decreased excretion of CO_2*. This is reflected by a low $PETCO_2$ (seen on the capnogram) but an increased $PaCO_2$ (*increased $PaCO_2$ – $PETCO_2$ difference*), e.g. 45 mm Hg vs. 26 mm Hg.

Practical implication:
- During systemic hypotension, pulmonary hypotension co-exists: *A low Qt is always accompanied by a decrease in Qp and an increase in pulmonary vascular resistance.* Since pulmonary blood pressure – unlike systemic blood pressure – is not routinely measured during anaesthesia, we tend to ignore it.
- An early sign of *pulmonary hypotension* (low Qp) may be an acute mild to moderate decrease in the $PETCO_2$ (seen on the capnogram) resulting from increased Vd ventilation. (This of course if no changes having been made to the ventilator settings.)
- Remember, all patients with left *cardiac failure*, whatever the cause, will eventually develop *congestion of the lungs* (pulmonary venous blood pushing back to the alveoli) and increased pulmonary arteriolar tone. *Therefore, all patients with respiratory failure or cardiac failure have varying degrees of pulmonary hypertension.*
- *Positive pressure ventilation and PEEP* increases intrathoracic pressure and the difference between intra- and extra-cardiac pressures. These factors *decrease venous return and consequently preload*. In hypovolaemic patients, this decreases cardiac output, which results in the neuroendocrine response to positive pressure ventilation, namely fluid retention (increased aldosterone and vasopressin). In hypervolaemic patients, e.g. in inotropic cardiac failure, the decreased preload may benefit the overloaded heart and improve cardiac output. During positive pressure ventilation, the difference between the intra- and extravascular pressures of the pulmonary artery and of the aorta decreases, resulting in *decreased afterload*. This improves cardiac output. These phenomena illustrate the very important principle of **heart lung interaction**.[17][18]

RELATIONSHIP BETWEEN PULMONARY VENTILATION AND PERFUSION

From the discussion above, it should be clear that pulmonary ventilation and perfusion must always be considered together. In healthy persons, volumes of gas (ventilation) and blood (perfusion) are perfectly matched (VA min ≈ 4200 ml min^{-1} and Qt ≈ 4225 ml min^{-1}). The ratio between VA min and Qt is called *the V/Q ratio*. Ideally, the V/Q ratio = 1. This is true in *some* regions of the lung. The normal *physiological shunt* (2% of the cardiac output) is responsible for the normal 2 mm Hg difference between the PAO_2 and PaO_2.

The physiological shunt is caused mainly by the bronchial circulation: the bronchi receive their blood supply not from the pulmonary arterial system (deoxygenated blood), but from the bronchial arteries from the aorta. This blood perfuses the conductive airways in the thorax, is deoxygenated, and drains into the pulmonary veins. Therefore, the bronchial blood flow (2% of Qt) comes from the left heart (oxygenated) and returns to the left heart (deoxygenated).

The V/Q ratio is a very important concept. The ratio may be very large (V > Q); when Q = 0, V/Q = infinity, and is called *pure dead space ventilation*, e.g. during a cardiac arrest (Qt = 0). V may be very small (V < Q); when V = 0, V/Q = 0, and is called *pure shunt*, e.g. total cessation of ventilation from any cause. A V/Q ratio smaller than infinity but larger than 0, is called a *V/Q mismatch or V/Q disturbance*. When the main cause of inadequate blood oxygenation is purely due to a decreased Qt (and thus Qp), the V/Q is larger than 1; when the main cause of inadequate blood oxygenation is purely due to a decreased VA min, the V/Q is smaller than 1. Diseases that affect the *lung parenchyma* (alveoli, blood vessels, interstitium, lymphatic vessels) usually cause a *mix of regional V/Q disturbances*; in some places large, in some places small. *The main disturbance* can usually be predicted from *the pathology*. Whatever the pathology, a *V/Q mismatch causes decreased oxygenation (decreased PaO_2)* and hypercapnia, whereof the degree is determined by the size of the mismatch.

If a patient is breathing spontaneously, a low PaO_2 may initially stimulate breathing (causing hypocapnia) but hypercapnia ensues once the patient cannot sustain the hyperventilation. The mechanisms of hypoxic (ventilatory problems) and stagnation hypoxia (perfusion problems) are always V/Q mismatches. *Therefore, if a patient is hypoxic, you must always exclude a V/Q mismatch* (See Chapter 14).

V/Q mismatch is worse in *neonates and the elderly*. The normal *PaO_2 in a neonate* at sea level is about 85 mm Hg. The PaO_2 in persons breathing air can be predicted using the following formulae:
At sea level the predicted PaO_2 = 104 – 0.24(age) mm Hg
In Pretoria, the predicted PaO_2 = 88 – 0.24(age) mm Hg.

For example, in Pretoria the predicted PaO_2 in a 75-year-old person breathing air is
88 – 0.24(75) = 70 mm Hg.

Practical implications of V/Q mismatch:
- When the V/Q ratio is about 1, $PAO_2 \approx PaO_2$ and $PACO_2 \approx PaCO_2$. The further the V/Q ratio departs from 1 (in either direction), the larger the differences. Can you work out how these entities will change with changes in the V/Q ratio changing from zero (pure shunt) to infinity (pure dead space)?
- V/Q mismatch always occurs upon *induction of anaesthesia*:
  - *Loss of muscle* tone causes upward shift of the diaphragm and medial shift of the thoracic cage. This causes atelectasis of especially the *dependent lung regions* and is called *micro-atelectasis (or compression atelectasis)*, which is a major cause of *low V/Q ratios* intraoperatively. This often *necessitates an increased FiO_2* to maintain an acceptable SaO_2, i.e. > 90%.
  - Decreased Qt is caused by *vasodilatation and myocardial suppression*. This leads to an *increase in the V/Q ratio*.
  - These anaesthesia-induced V/Q mismatches are *aggravated by lung and heart disease*.
  - The *nearer* the surgery is *to the diaphragm*, the greater the disturbance.
  - V/Q mismatches are worse with *open abdominal and thoracic procedures* than with video-

assisted minimally invasive procedures (laparoscopic, thoracoscopic).

- o Atelectasis is worsened by the administration of *high concentrations of oxygen* (high FiO_2) since the oxygen is absorbed by the capillaries. This decreases the alveolar volume and is called *absorption atelectasis*. Therefore, you should always try to administer oxygen only sufficient to maintain an SaO_2 of higher than about 94%. Higher concentrations are unnecessary and detrimental (atelectasis, O_2 free radical injury).
- o The procedure- and anaesthesia-induced atelectasis *often persists for days into the postoperative period* and contributes to *postoperative lung complications* (hypoxia, pneumonia).
- o Aggravating conditions are often the cause of postponement or referral of procedures; postponed to *optimalize lung function* (infection, bronchospasm, cardiac failure) or referral to a centre that have facilities for *postoperative ventilatory support*.
- o *Management of V/Q mismatch* include ventilatory support (improved VA min) and/or circulatory support (Qt).

- • *Ventilatory support* (**"V"** in V/Q) (see also Chapter 4)
  - o *Counteract microatelectasis* by the application of
    1. positive end-expiratory pressure *(PEEP)* of about 5 cm H_2O in adults,
    2. **limitation of the FiO_2** (prevents absorption atelectasis) – preferably to < 80%, and
    3. regular (every 40 minutes) **recruitment** of atelectatic lung regions by the application of sustained (8 seconds) of pressure (40 cm H_2O) in the lungs.

    When you keep the lung open in this way (*open lung strategy*), you prevent the repeated collapsing and reopening of alveoli (*atelectrauma*)
  - o Give a Vt of 6 ml kg^{-1} to 8 ml kg^{-1}*ideal body mass.* High Vts over-stretch the alveoli (*volutrauma)*, while high inspiratory pressures can rupture alveoli or bullae (*barotrauma)*. Therefore, the Vt should be as low as possible, while the peak inspiratory pressures should be < 35 cm H_2O.
  - o High intrathoracic pressures (large Vt or high PEEP) may increase the oxygenation of blood at alveoli (decreased shunt and improved PaO_2), but may decrease systemic oxygenation since the high pressures decrease venous return to the heart and increase PVR (increased Vd).
  - o *Adjusting the Vf* to maintain "*eucapnia (normal $PaCO_2$)*", which usually is 12 min^{-1} to 15 min^{-1}.
  - o The endpoints of ventilatory support are "normoxia and normocapnia"
  - o What is "*eucapnia (normal $PaCO_2$)*"? If a patient has a $PaCO_2$ that is within the normal range for altitude (in Pretoria, 31 mm Hg to 39 mm Hg) the endpoint of ventilatory support is also within the normal range. If patients were hyperventilating before ventilatory support (e.g. early ARDS), they are usually hypocapnic, and the endpoint is a $PaCO_2$ in the normal range. If the patient has a disease that makes him chronically hypercapnic (e.g. COAD), you must keep the $PaCO_2$ eucapnic for that patient, e.g. 50 mm Hg. If you would normalize this chronic $PaCO_2$, compensated by a metabolic alkalosis with normal pH of the cerebrospinal fluid (CSF), the patient will develop a severe metabolic alkalosis, with a further increase in CSF pH.
  - o What is "*normoxia, i.e. a normal PaO_2 and arterial haemoglobin saturation (SaO2)*"? Patients with chronic hypercapnia depend on their hypoxic drive for ventilation (since the CSF pH has normalized). It is not wrong to normalize their PaO_2s and oxygen saturations intraoperatively, but you must return the PaO_2s and saturations to low levels. Otherwise, they will not breathe. Moreover, remember that the anaesthetic vapours and benzodiazepines suppress the hypoxic drive of ventilation. Sedation with benzodiazepines and anaesthetic vapour as low as 0.2 MAC, can abolish the hypoxic drive and render these patients apnoeic.
- • *Circulatory support (**"Q"** in V/Q)*
  - o Most anaesthetic agents (except ketamine) are vasodilators and therefore cause relative hypovolaemia. Most anaesthetic agents are negative inotropic (except opioids and perhaps ketamine) and chronotropic (except ketamine). These effects may decrease Qt and thereby increase Vd.
  - o *Hypovolaemic* patients, patients with *cardiac disease*, and patients receiving *cardiovascular drugs* are more susceptible to these side effects.

o The *cardiovascular effects* of anaesthetics (effect on Qt) are treated by volume loading (e.g. Ringer lactate), vasoconstrictors (e.g. phenylephrine), inotropic support (e.g. adrenaline), or positive chronotropic agents (e.g. atropine)

CONTROL OF BREATHING

Breathing is controlled by central and peripheral mechanisms:

Central

- Spontaneous breathing results from rhythmic neural activity in respiratory centres in the brainstem. The basic rhythm originates in the *medulla oblongata* (dorsal inspiratory and ventral expiratory neurons).
- Respiratory rate and rhythm is fine-tuned by two *pontine areas* influencing the dorsal (inspiratory) medullary centre, namely a lower pontine (apneustic) excitatory and an upper pontine (pneumotaxic) centre.
- H^+-*sensitive chemoreceptors* in the medullary centre are stimulated by a low *pH in the cerebrospinal fluid* (CSF). The CSF pH decreases with an increase in CSF PCO_2. Any pathology that *decreases CSF pH* stimulates these receptors. These include any cause of cerebral hypoxia (increases local lactate and local PCO_2) (See Chapter 14 for causes of hypoxia).
- The medullary centre is stimulated by $PaCO_2$s of more than about 50 mm Hg.
- *In neonates*, this centre is *suppressed* by a low PaO_2 and increased $PaCO_2$.

Peripheral

- *Chemoreceptors sensitive to PaO_2* in the carotid body and the aortic arch bodies react to PaO_2. In humans, the *increase of ventilation in response* to a low PaO_2 is mediated entirely by the peripheral chemoreceptors. Stimulation starts at a PaO_2 of less than about 100 mm Hg. The carotid bodies contain inhibitory dopaminergic interneurons, which inhibit the impulses from the carotid bodies via the sinus nerve (carotid sinus branch of n glossopharyngeus).
- *Chemoreceptors sensitive to a decrease in pH* occur in the carotid bodies. These receptors are *stimulated by a low pH* – whether it is caused by a metabolic (low HCO_3^-) or respiratory acidosis (high $PaCO_2$).
- *Juxta-capillary receptors* occur in the lung interstitium between the capillary and alveolar walls. They are *stimulated by lung congestion* and results in rapid shallow breathing. They play a role in *dyspnoea* in patients with heart failure and interstitial lung disease.
- *Irritation receptors* between the epithelial cells of the trachea and bronchi are stimulated by noxious and cold gasses. Afferent and efferent impulses are conducted by the vagal nerve. The responses include *bronchoconstriction and tachypnoea.*
- *In infants*, large tidal volumes stimulate *stretch receptors* in airway smooth muscle. Stimulation of these receptors results in a *decreased ventilatory rate* (Hering-Breuer reflex). In adults this response is observed only at high tidal volumes (> 1000 ml).
- *Practical implications*
- The medullary respiratory centres are very sensitive to the suppressant effect of opioids. Opioids cause a decrease in minute volume – mostly by a decrease in tidal volume (hypopnoea), while ventilatory rate is often unaffected. High doses cause apnoea. An immediate and dose-dependent reduction in ventilation is seen following an intravenous dose of morphine. This may be of little consequence in the healthy patient, but may have grave consequences in patients with limited ventilatory reserve, e.g. the elderly.
- Stimulation of dopaminergic receptors in the carotid body inhibits the hypoxic and acidotic drive of ventilation. Therefore, antidopaminergic drugs such as the phenothiazines and droperidol can stimulate ventilation. The *analeptic drug doxapram*, sensitises the peripheral chemoreceptors.
- The sensitivity of the carotid bodies is decreased by *benzodiazepines*, e.g. midazolam.
- The *anaesthetic vapours* completely suppress the sensitivity of the peripheral chemoreceptors at concentrations of as low as 0.2 MAC. Remember, anaesthesia often includes several suppressants of ventilation, including a benzodiazepine, an opioid, and a volatile agent. The patient may be awake and breathing is stimulated by suctioning of the throat, extubation, transport to the recovery

area, and pain. However, the patient may stop breathing once left unstimulated.

- *Chronic hypercapnia*, as seen in some patients with chronic obstructive airways disease (COAD), causes a chronic increase in $PaCO_2$, and consequently an increase in CSF PCO_2. The high CSF $[H^+]$ is buffered by HCO_3^-, which *normalizes the CSF pH*. Chronic hypercapnia will therefore render the central respiratory centre *insensitive to CO_2*. If these patients' $PaCO_2$s are normalized intraoperatively, the CSF $[H^+]$ decreases (alkalosis). That may also happen when normal patients are hyperventilated intraoperatively. These patients hypoventilate and may develop apnoea postoperatively. This is a cause of postoperative hypoxia, and is called *post-hyperventilation hypoxia*.
- Since the central centres of c*hronically hypercapnic patients* are insensitive to CO_2, they *rely on a low PaO_2 to stimulate ventilation* (*hypoxic drive*). They might therefore develop apnoea when they receive a high FiO_2 or benzodiazepines.

WORK OF BREATHING

Work is done to bring about gas movement in the airways and volume change of the lung. This is called the work of breathing (WOB). This work moves the lungs and the thoracic wall. In the spontaneously breathing person, the respiratory muscles use energy; in the patient that cannot breath, a ventilator does this work. Resistance must be overcome to inflate the lungs. ***Any factor that decreases the ability to maintain the work of breathing causes hypoventilation, hypercapnia, and hypoxia.*** Two types of structures exert the resistance: elastic structures and non-elastic structures.

Pressure (Pe) is necessary to overcome *elastic resistance (Re)* exerted by the elastic tissue in the lungs and thoracic wall. Elasticity gives structures the ability to resume their resting length (size) and form after they have been stretched. *Non-elastic resistance* is caused by tissue molecules that move over each other when the structure is stretched (*viscous resistance*) and friction caused by *gas flow (Faw)* in the airways, i.e. airflow resistance. Normally, Faw is responsible for about 80% and viscous resistance for about 20% of non-elastic resistance. *Pressure (Pne)* is needed to overcome *total non-elastic resistance(Rne)*:

$$Rne = \frac{Pressure\ to\ overcome\ Rne}{Airway\ flow} = \frac{Pne\ (cm\ H_2O)}{Faw\ (L\ s^{-1})}$$

In elastic tissue, there is a linear relationship between the force that stretches the organ and the change in length. This relationship is called compliance (C). Lung compliance (CL) means the change in volume (tidal volume, Vt) for the change in pressure (Pe) (Figure 1):

$$CL = 0.5 \times \Delta V/\Delta P = 0.5 \times Vt/Pe$$

The lung has its own compliance (CL) and the chest wall has its own compliance (Ccw). The relationship between total compliance (Ct), CL, and Ccw is: $1/Ct = 1/CL + 1/Ccw$

The lungs do however not behave completely as a spring (completely elastic). Therefore, CL is not completely dependent on elastin tissue. A thin fluid layer lining the alveoli causes deviation from complete elasticity. The surface tension (non-elastic) of the fluid lining counteracts increase in lung volume. *The Type II pneumocytes* in the alveolar walls secrete a surface tension reducing substance (surfactant). Surfactant consists mainly of the phospholipid dipalmitoyl phosphatidyl choline. *Surfactant decreases surface tension and improves CL.*

Before air (or any gas) can be inspired, the elastic (Re) and non-elastic resistance (Rne) must be overcome. The pressure necessary to overcome Re is Pe and to overcome Rne is Pne. The total pressure is the transpulmonary pressure (PTP):
PTP = Pe + Pne
But Rne = Pne/Faw, which means that Pne = Rne × Faw,
and Ct = Vt/Pe, which means that Pe = Vt/Ct (remember, Ct consists of two components, Ccw and CL)
Therefore,

$$\textbf{PTP} = \textbf{0.5} \times \textbf{Vt/Ct} + (\textbf{Rne} \times \textbf{Faw}).$$

Diseases that *decrease compliance are called restrictive diseases*, while diseases that mainly *increase airflow resistance are called obstructive diseases*. *Obstructive diseases* cause increased airflow and *turbulence*. The turbulence is clinically detectable by stridor with obstruction in the larger airways and a wheeze with small airway obstruction. The obstruction may affect different phases of breathing:
- *Mainly inspiratory* flow caused by extrathoracic obstruction, e.g. foreign body or tumour
- *Mainly expiratory* flow caused by intrathoracic lesion. Since the thoracic volume decreases during expiration, airway diameter decreases, which aggravates the obstruction, e.g. intrabronchial lesions, asthma, COAD (bronchoconstriction plus airway collapse)
- *During both in- and expiration*, e.g. a fixed obstruction of the trachea, e.g. foreign body, mediastinal mass compressing

the trachea.

In Figure 1, the WOB of inspiration during normal breathing is the sum of the elastic WOB (triangle ABC; remember, the area of the triangle is $0.5 \times AB \times BC$) and of non-elastic (airway resistance + tissue resistance) WOB (area ADBA). Normal expiration is a passive process (does not need muscle activity) and uses the potential energy gained and stored by the elastic tissue. The non-elastic (airway resistance + tissue resistance) part of WOB during expiration (ABEA) is supplied by the elastic recoil supplied by the elastic tissue. The difference between the areas ABC and ABEA is lost as heat. This diagram is called a *compliance curve* and is often available on the spirometry function of anaesthetic and intensive care monitors. *Please ask the anaesthetist to demonstrate this to you.*

Practical implications of Figures 1and 2
- Figure 1 demonstrates that if the compliance of the lung is higher, the slope of line AB is steeper, but when it is lower (restrictive), the slope is flatter.
- If airway narrowing increases inspiratory WOB, the area of ADBO increases and the total WOB increases.
- If airway narrowing hampers expiration, the passive recoil of the lungs may be deficient to overcome airway resistance to the extent that expiration becomes active. In that case, the curve BEA will extend to the left of AC. Then, the area of ABEA > ABC.
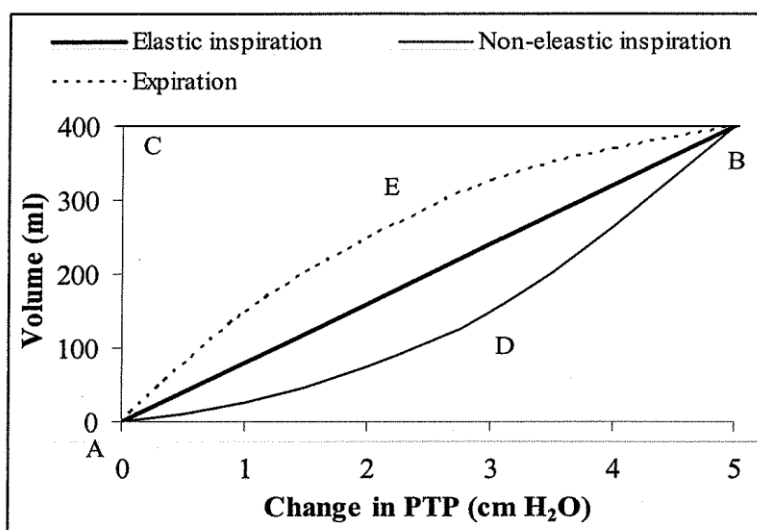
Figure 1 The work of breathing in the awake spontaneously breathing patient.
- Figure 2 demonstrates that the *mechanical characteristics of the lung during anaesthesia* (during spontaneous *and mechanical ventilation*) are that of *restriction and obstruction. Restriction* is caused by *micro-atelectasis*, while *airway narrowing* causes obstruction. The basis of airway narrowing is the *decrease in thoracic volume*.
- Therefore, the slope of the compliance curve is much flatter, while both in- and expiratory non-elastic WOB is increased. This is demonstrated in Figure 2 where the slope of AB is flatter (400 ml/20 cm H_2O instead of 400 ml/5 cm H_2O) and the areas of ADBA and ABEA are much larger.
- Therefore, hypoventilation during spontaneous breathing in anaesthetized patients is very common – especially in patients with an increased WOB preoperatively.
- *The obstructive component makes PETCO$_2$ as an indicator of adequate ventilation unreliable* since airway collapse occurs before expiration is completed. Therefore, PETCO$_2$ does not reflect PACO$_2$ and PaCO$_2$ may be much higher than PETCO$_2$.
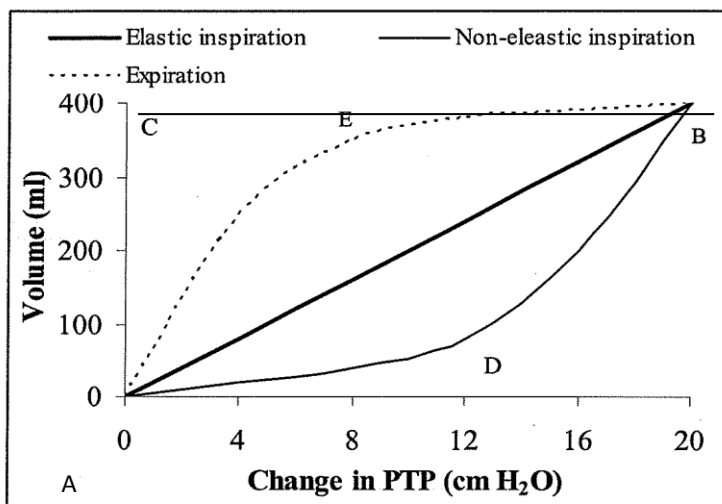
Figure 2 Work of breathing and respiratory rate in the anaesthetized patient (note that the scale of the x-axis differs from Figure 1)

The student must appreciate the therapeutic implications of the WOB:

- *A low compliance and a low tidal volume will increase the inspiratory elastic WOB (Pe = Vt/Ct).* In order to decrease the WOB, these patients with a *low Ct will have a low Vt*, and consequently a high respiratory rate; shallow fast breathing as seen in dyspnoea. This is the normal mechanical characteristic of the lungs of infants. This may be caused by any factor that decreases elasticity of tissue – from the skin to the alveolus, e.g. burns, scleroderma, abnormal thoracic skeleton (rib fractures, kyphoscoliosis), pleural fibrosis, interstitial fibrosis, interstitial oedema, alveolar oedema, alveolar exudates, etc.

- *An increase in non-elastic resistance increases the inspiratory non-elastic WOB (Pne = Rne × Faw)*. Rne consists of airflow resistance and non-elastic tissue resistance. If Rne increases, airflow (Faw) must decrease to limit non-elastic WOB. Therefore, patients with airway narrowing will have a decrease Faw. Since Faw is lower, more time is necessary to draw a tidal volume. Therefore, the patient will have a *low respiratory rate and a large tidal volume*. This abnormality is observed in patients with airway obstruction from any cause from the upper airway (e.g. tumour, infection such as Ludwig angina, foreign body, retropharyngeal haematoma, laryngospasm, etc.) to the bronchi (foreign body, tumour).

- *Patients with increased airway resistance during expiration* (asthma, COAD), will have a decreased Faw during *expiration*. Therefore, they have a prolonged expiration.

- *Non-elastic tissue resistance is increased by any increase in non-elastic tissue* from the skin to the alveolus, including bandages, fat, and larger pleural effusions.

- *At rest, the respiratory muscles use about 3% of the total oxygen supplied to the body*. During normal exercise, the WOB increases, while the respiratory muscles still receive about 3% of the oxygen – but the total oxygen delivery may have increased as much as 25-fold. Since any pathology that increase the WOB will also increase the oxygen consumption, an increase in oxygen delivery to the muscles is required. *If the cardio-respiratory system cannot increase the oxygen to sustain the WOB, the patient becomes exhausted, followed by respiratory failure.*

- That explains why *all patients with respiratory failure* (caused by any factor from the brain, neuromuscular junction, muscle, lung, or airways) or *cardiac failure* require *respiratory support* (from bronchodilatation, supplemental oxygen, to intubation and ventilation); these patients *cannot sustain the increased WOB* or supply the respiratory muscles with oxygen to do deliver the *normal WOB*.

- *The clinical distinction between changes in elastic and non-elastic resistance is not always clear*. Very often, diseases cause changes in both, i.e. an increase in Rne and a decrease in Ct. *Diseases that cause an increase in the WOB often cause hypoxia and hypercapnia* stimulate ventilation. The cause of the increased WOB is therefore not always apparent from the breathing pattern. *When exhaustion ensues*, all patients will eventually hypoventilate, become hypoxic, hypercapnic, and

will eventually become unconscious.

- Airway devices (endotracheal tube, laryngeal mask, etc.) influence non-elastic resistance (Rne).
- *Several surgical factors influence the WOB, which necessitate intubation and ventilation intraoperatively.* These include, position (Trendelenburg, prone), inflation of the abdominal cavity (laparoscopy), abdominal distension (ascites, tumours, obstruction, obesity).
- *Any anaesthetic factor that prevents the ability to sustain WOB* necessitates ventilatory support. These include any suppression from the cerebral cortex to the neuromuscular junction.
- *The non-elastic resistance to breathing (Rne), and therefore the non-elastic WOB is increased by anaesthesia-related decrease in airway diameter:*
  o *loss of muscle tone* of the upper airway,
  o *decrease in thoracic volume decrease intrathoracic airway diameter,*
  o anaesthetic drugs, e.g. atracurium and morphine, may release histamine and other *inflammatory mediators* resulting in bronchoconstriction with decreased diameter of the airways.
- All the anaesthetic vapours and ketamine are potent bronchodilators and relieve bronchospasm.
- Approach to intraoperative bronchospasm:
  o Make the correct diagnosis. Exclude other causes of increased inspiratory pressures, e.g. obstruction in the endotracheal tube, secretions, kinking of the tube or anaesthetic circuit, and a pneumothorax.
  o Bronchospasm (spasm of bronchial muscle) is characterized by increased peak inspiratory pressures, relatively normal plateau inspiratory pressures, delayed expiration. (You must distinguish between broncho- and laryngospasm; see Chapter 3)
  o Delayed expiration causes auto-PEEP. That means that inspiration begins before expiration of gas has been completed. That increases inspiratory pressure further and may cause a pneumothorax.
  o Delayed expiration decreases the rate at which CO_2 from the alveoli reaches the capnograph. Therefore, the ascending limb of the capnogram is flatter, the plateau is not horizontal but slanting upwards, and the end-expiratory CO_2 is lower, since the alveolar gas does not reach the upper airway. Consequently, the $PaCO_2$ rises, which causes the $PaCO_2 - PETCO_2$ to increase.
  o The treatment of intraoperative bronchospasm:
    1. Remove the stimulus, e.g. irritation of the airway (carinal stimulation by the ET tube).
    2. The management of intraoperative bronchospasm does not differ from that used in the emergency department, namely of a β_2 agonist such as salbutamol inhalation or intravenous salbutamol and glucocorticosteroids. Some anaesthetic agents have bronchodiltory properties and are used as adjuvants in the treatment of bronchospasm. These include the anaesthetic vapours, ketamine (the anticholinergic antisialogogue bronchodilator glycopyrrolate about 10 μg kg^{-1} followed by ketamine 1 mg kg^{-1}).
- **The type of abnormal WOB often determines ventilator** settings, namely Vt, Vf, inspiratory pressure, flow, the **inspiratory:inspiratory ratio, PEEP (increases CL), FiO$_2$, etc. (Table 1; see also Chapter 4)**
  o *With obstructive pulmonary disease* (COPD, bronchospasm) the *main problem is expiration and hyperinflation with a large functional residual capacity (FRC)*. With COPD hyperinflation is aggravated by the closing of small airways before expiration has been completed (they have a high lung volume left at the end of expiration, i.e. they have a *high closing volume*. Therefore, patients with obstructive lung mechanics require a *long expiratory time*, i.e. an *I:E ratio* of say 1:3 or even 1:4. Another way to increase the expiratory time is to increase the whole respiratory cycle by *decreasing the respiratory rate*, which necessitates an *increased Vt* (nearer to 8 ml kg^{-1}). In order to keep the airways open during expiration to decrease the closing volume, a *small amount of PEEP* may be helpful, say $\leq$ 5 cm H_2O. Since these patients may have lung bullae, which are very susceptible to barotrauma, peak inspiratory pressures should be limited to < 30 cm H_2O. It may therefore be better to *use pressure controlled (PCV) ventilation*. When using PCV, *spirometry* is used to measure the size of the Vt obtained, and pressure can be adjusted accordingly.
  o *With restrictive pulmonary disease* (obesity, abdominal distension, lung fibrosis, pulmonary oedema, ARDS) the *main problem is inspiration and atelectasis with low lung volumes (low*

FRC). Although restrictive diseases may affect small airways, closing volumes are usually not elevated. Therefore, patients with restrictive lung mechanics require a *long inspiratory time*, i.e. an *I:E ratio of say 1:2 or even 1:1* or 1.5:1 (inverse ratio ventilation). Since lung compliance is so low, Ppeak is high. To decrease Ppeak, *Vt must be decrease (≤ 6 ml kg^{-1})*, and consequently, the *respiratory rate increased*. In order to keep the alveoli open during the whole ventilatory cycle, higher *PEEP* levels are often used (≥ 5 cm H$_2$O). Since high pressures may aggravate alveolar trauma, Ppeak should be limited to < 35 cm H$_2$O. As is the case with obstructive lung mechanics, it may better to *PCV ventilation*.

AIRWAY PROTECTION (See also Chapter 3)

Respiratory function is dependent on an open uncontaminated airway:
- Anaesthetic gases and the presence of an endotracheal tube *suppress mucociliary activity*. It results in delayed clearance of pathogens and retention of secretions.
- *Activity of respiratory inflammatory cells is impaired*, especially during prolonged surgery and anaesthesia. This results in an increased susceptibility to postoperative infections
- Depressed consciousness leads to loss of protective airway reflexes, including the cough and swallow reflexes. Loss of these reflexes may lead to loss of airway tone, aspiration of foreign material, and airway obstruction. These reflexes are dependent on sensation of the upper and lower airways, an afferent nerve, a centre in the central nervous system, an efferent pathway, and an effector. Anaesthetic drugs can depress the protective reflexes at each of the components of the reflex path:
  - *Decreased sensation* of the upper and lower airways is caused by the application of *topical anaesthetic to the mucosae* or *upper airway* nerve blocks.
  - Topical anaesthesia of the upper airway causes loss of proprioception. Proprioception contributes to airway patency (the airway "feels" if it is open or not). Loss of sensation of the upper airway takes away the ability to swallow, may lead to airway obstruction and soiling of the lungs.
  - *Suppression of the central nervous system* (all sedative anaesthetics) depresses the reflexes and predisposes to loss of airway muscle tone and sensation.
  - *Any suppression of efferent nerve function* (e.g. an upper airway block) or neuromuscular transmission suppresses the motor function of the upper airway, and may lead to airway obstruction and contamination.
  - *Increased sensitivity of the airway reflexes* may increase airway reactivity. This causes coughing, gagging, laryngospasm (see Chapter 3), increased airway secretions, vomiting, and bronchospasm. This happens at light planes of anaesthesia when the reflexes are disinhibited. Therefore, do not stimulate an airway (laryngoscopy, intubate, extubate, insert upper airway devices) unless the patient is deeply anaesthetized and relaxed or wait until he is fully awake.

Table 1 Ventilator settings and mechanical lung characteristics (general guide lines for adults)

Lung type	MV	Vt	RR	PEEP	I:E	Ppeak	Pplat	FiO$_2$	Endpoint SaO$_2$[c]	Endpoint PaCO$_2$[d]
Normal	70 - 100	6 - 8	12	5	1:2	< 30	< 25	Enough	92 - 98	31 - 39
Obstructive[a]	70 - 100	8	8 - 12	≤ 5	1:3	< 30	< 25	Enough	> 88 - 90	≥ 39
Restrictive[b]	70 - 100	6	12 - 16	≥ 5	1:2 - 1:1	< 35	< 30	Enough	> 88 - 90	≥ 39

MV, minute volume (ml kg^{-1} lean body mass); Vt, tidal volume (ml kg^{-1} ideal body mass); RR respiratory rate; PEEP, positive end-expiratory pressure (cm H$_2$O), I:E, inspiratory:expiratory ratio; Ppeak, peak inspiratory pressure (cm H$_2$O); Pplat, plateau inspiratory pressure (cm H$_2$O).
a E.g. COPD, bronchospasm b E.g. ARDS, lung fibrosis, morbid obesity
c Arterial Hb saturation: the higher the hct, the lower the acceptable SaO$_2$, e.g. severe COPD → ↓ PaO$_2$ → ↑↑ Hct; the lower the hct, the poorer a low SaO$_2$ is tolerated. High PaO$_2$ in chronic hypercapnia can cause apnoea since chronic hypercapnia blunts the central (CO$_2$ → ↓pH in CSF); these patients are dependent on a low PaO$_2$ to stimulate the peripheral (carotid and aortic arch) chemoreceptors.
d Arterial PCO$_2$ in Pretoria; at sea level, 35 mm Hg to 45 mm Hg. Chronic hypercapnia associated with obstructive lung mechanics should not be normalized, since you will cause a severe alkalosis. In restrictive pathology, the principle of *permissive hypercapnia* applies to *avoid ventilator-associated lung injury*, i.e. *barotrauma* (too high pressures), *volutrauma* (too high tidal volumes), *atelectrauma* (repeated collapse of alveoli; prevented with PEEP), and *biotrauma* (mechanical lung injury due to baro-, volu, and atelectrauma cause an inflammatory reaction in the lung, which aggravates lung dysfunction)

POSTOPERATIVE PULMONARY COMPLICATIONS (PPC)

Patients with *respiratory disease are at increased risk* for postoperative pulmonary complications (PPCs) such as atelectasis and pneumonia. PPCs are caused by a variety of *intra-operative and post-operative factors. These factors cause abnormal ventilation, lung perfusion, V/Q mismatch, control of ventilation, and work of breathing. These effects contribute to PPC, especially in patients with respiratory disease (from the mouth to the thoracic wall).*

Intra-operative effects of anaesthesia and surgery
- *Uncoordinated respiratory muscle activity.*
- *Increased airway resistance.*
- *Suppression of normal mucociliary activity.*
- *Impairment of activity of respiratory inflammatory cells.*

Postoperative respiratory function
Postoperative atelectasis occurs commonly, especially in the elderly, obesity, patients with lung disease, and procedures close to the diaphragm (thoracotomy, upper abdomen). There is an increased respiratory rate, smaller tidal volume, a decreased functional residual capacity (FRC), and a decreased vital capacity (VC) (see Appendix). These factors contribute to an increased WOB and V/Q matching, which result in postoperative hypoxemia. Three postoperative phenomena contribute to these changes:

- *Disruption of respiratory muscles by surgery*. During the initial stages of healing following laparotomy, abdominal muscles do not function normally.
- *Pain.* To minimize postoperative pain, patients may voluntarily limit the use of respiratory muscles (shallow breathing). Suppression of ventilation by opioids aggravate hypoventilation.
- *Inhibitory reflexes*. Cholecystectomy activates vagal afferents producing reflex inhibition of diaphragm activity.

Prevention of postoperative pulmonary complications
*Pre-operative optimisation, rescheduling if necessary and possible, and assessment of the **benefit-risk ratio**.*

- *Assess the general physical status* and treat reversible abnormality, e.g. malnutrition (including obesity) and anaemia.
- Previously, patients, especially children, with an *upper airway infection* were postponed for about two weeks. Currently, there is no agreement regarding cancellation of patients with an upper airway infection. The airways of patients with upper airway infections are very sensitive, and elective procedures must preferably be postponed. This applies especially to:
  o Small children: their airways are still very small and a little inflammation causes a relatively large increase in resistance. Children contract upper airway infections regularly.
  o Patients with a history of hyperactive airways (asthma)
  o If the patient coughs, which points to irritated airways
  o Systemic signs of infection: fever, leukocytosis, and an increased C-reactive protein.
- *Treat reversible lung pathology.* These include secretions, infection, and bronchospasm. *Asthmatics* must preferably undergo lung function tests to determine the reversibility of bronchospasm. If treatment is not optimal, elective procedures must be postponed. Treatment must continue up to surgery and be continued into the postoperative period.
- Patients with *pneumonia* must be postponed until the pneumonia has been resolved.
- Patients with *lung tuberculosis* must not be infective anymore. The effects of the anti-tuberculosis treatment and chronic illness, including HIV, must be taken into account. Patients are infective until at least 2 months of treatment is completed.
- Large *pneumothoraxes and pleural effusions* must preferably be drained before induction of anaesthesia or as soon as possible after induction of anaesthesia.
- *Ventilated patients from the intensive care unit* (ICU) must be stable enough to transport to the operating theatre. The intraoperative ventilator settings must be as close as possible to those in the ICU.
- *Cessation of smoking* as long as is possible before surgery. Smoking has the following effects:
  o Nicotine is an adrenergic agonist, which increases blood pressure, increases myocardial O_2 demand, and reduces *coronary blood flow*.
  o CO (carbon monoxide) in cigarette smoke, apart from its negative inotropic effect, combines avidly with haemoglobin to form *HbCO (carboxyhaemoglobin)*, which cannot carry O_2. This effect is reduced 12 hours to 24 hours after abstinence; after 12 hours P50 of haemoglobin increases from 23 mm Hg to 26 mm Hg, and the [HbCO] decreases from 7% to 1%.
  o Cigarette smoke reduces ciliary and immunological function in the lung that takes up to 2 months to recover.
- *Sedative premedication should be avoided* in patients with lung disease, since all sedatives may cause hypoventilation.
- The anaesthetist and surgeon must decide preoperatively if the patient will survive routine *postoperative care*, or whether specialized care will be required. That is often a reason for postponement of surgery in patients with impaired lung function.
- *In this regard it is comforting to keep in mind that, as with other mortals, surgeons are not quite beyond the restraints of everyday didactic laws. They also, in order to arrive, firstly need to learn **how** to operate, then, **when** to operate, and eventually, **when not** to operate – and the years given to man is only seventy!*

Anaesthetic and surgical techniques, respiratory disease, and PPC
- *Avoid endotracheal intubation* when feasible. Consider the use of one of a variety of available *supra-glottic airway devices* (SGDs), e.g. a laryngeal mask airway (LMA). This may help prevent bronchospasm *specifically in patients with reactive airways*. In this population the following also aids in preventing bronchospasm:
  o Propofol is the **induction agents of choice**. However, airway reactivity cannot be prevented even by propofol should airway (e.g. laryngoscopy) or other (e.g. placement of urinary catheter or skin incision) stimulation occur prior to a *sufficient depth of anaesthesia*. If a patient *with*

active bronchospasm needs anaesthesia, ketamine is useful as induction agent, but does not suppress airway reflexes to the extent that allows insertion of a SGA.

- o Volatile agents are the **maintenance anaesthetics of choice** (as opposed to TIVA) because of their excellent bronchodilating properties. In this regard, Halothane and Sevoflurane are the most appropriate choices. Desflurane must be avoided because of its irritant properties.
- *Regional techniques*. Plexus blocks, peripheral blocks, and local infiltration of local anaesthetics should be used if possible.
- *Laparoscopic surgery* reduces the duration of surgery and the degree of surgical trauma. Laparoscopic techniques are preferable but may not completely eliminate PPCs.
- *Continued contraction of the diaphragm by avoiding* neuromuscular *blocking agents* and by maintaining *spontaneous breathing*. This will require, in all but the briefest of cases, some form of ventilatory support. If administration of a muscle relaxant is mandatory, be vigilant in avoiding postoperative muscle weakness.

Continued contraction of the diaphragm and other respiratory muscles reduces V/Q mismatching resulting in improved uptake of O_2 and removal of CO_2. Options include SIMV (Synchronised Intermittent Mandatory Ventilation) and PSV (Pressure Support Ventilation). During PSV the spontaneously breathing patient initiates an inspiratory effort and the inspiratory volume is augmented or increased by positive pressure support from the ventilator.

- Consider *recruitment manoeuvres* (lung expansion followed by PEEP) to decrease atelectasis.
- *Avoidance of high FiO$_2$s* reduces *absorption atelectasis*.
- *Avoid high pressure or large tidal volume ventilation*, which may cause lung injury. Do not insist on hypo- or normocapnia at the expense of high ventilatory pressures. Modest and controlled increases in $PaCO_2$ are probably not harmful.
- *Adequate hydration* allows mobilization of airway secretions.
- *Physiotherapy*

Postoperative management and the prevention of PPC

- *Muscle strength*. Maintain tracheal intubation until *full reversal* of neuromuscular drugs is achieved. If available, neuromuscular monitoring should be used.
- *Analgesia* is paramount, especially after major chest or abdominal surgery. Use multimodal therapy to maximise analgesia, including NSAIDs, regional analgesia, dexmedetomidine, etc. *Avoid opioids* that may depress ventilation.
- *Early mobilization and physiotherapy* promotes the clearance of secretion, decreases atelectasis, and may decrease the incidence of pulmonary embolism.

RESPIRATORY FAILURE

As the two primary functions of the lungs are oxygenation of blood, and removing CO_2 from blood, respiratory failure can therefore be divided into two types: *hypoxaemic (Type I) and hypercapnic failure (Type II)*. *Type I* respiratory failure is present when the PaO_2 is < 60mmHg *when the patient is breathing room air*. Type II respiratory failure) is present when the $PaCO_2$ is > 50mmHg *when breathing room air* (Table 1).

Table 1 Respiratory failure

	Type I Respiratory Failure	**Type II Respiratory Failure****
PaO_2	< 60 mmHg	< 60 mmHg
$PaCO_2$	Normal or low	> 50 mmHg
Mechanism	Failure of gas exchange across alveolar membrane to capillaries	Reduction in VA due to a decrease in Vt or Vf
Examples	• Chest infection • Asthma • Pulmonary oedema • Pulmonary embolus	• Acute exacerbation of COPD • Non-respiratory: Opioids, head injury

** A subgroup of these patients may be sensitive to high concentrations of O_2. Normally respiratory drive is controlled by chemoreceptors that detect rising $PaCO_2$ and stimulate breathing. It is thought that some patients with chronically high $PaCO_2$ lose this drive to breathe, and rely instead on hypoxia, which under normal physiological conditions plays only minor role. Consequently, high concentrations of supplemental O_2 may cause apnoea – although there is a body of opinion that does not believe this hypothesis.

Appendix

Lung volumes and capacities

Lung volumes are single volumes, while capacities are made up of more than lung volume. The normal values (ml kg^{-1}) are given in brackets (men/women). These values are influence by age, race, body habitus, fitness, etc. You may remember the normal values for tidal volume, functional residual capacity, and vital capacity.

Inspiratory reserve volume (47/25)	Inspiratory capacity (54/32)	Vital capacity (**68/42**)	Total lung capacity (85/58)
Tidal volume (**7/7**)			
Expiratory reserve volume (14/10)	Functional residual capacity (**31/26**)		
Residual volume (17/16)			

CHAPTER 14

PERIOPERATIVE HYPOXIA
(You must know Chapters 4, 12, 13, 18, and 20 to appreciate this chapter)

Key points
- Hypoxia kills
- Definitions of hypoxia, hypoxaemia, oxygen flux
- Types of hypoxia: Stagnation, anaemic, hypoxic, toxic
- Factors contributing to perioperative hypoxia
- The causes of hypoxia and their pathophysiology
- The alveolar gas equation
- The role of alveolar ventilation (V_A) and PCO_2
- Causes of a low perioperative V_A

- Causes of increased perioperative production of CO_2 (VCO_2)
- The ventilation-perfusion ratio (V_A/Q_T)
- Prevention and treatment of hypoxia
- Monitoring of oxygenation
- Remember the brain is more sensitive to hypoxia than the heart. By the time you see a bradycardia from hypoxia the brain will be severely affected.
- At this altitude (Pretoria), one is slightly hypoxic compared to sea level.

Patients work hard during and after surgery; they need substrate (oxygen, nutrients) to repair injured tissue. Where does the *extra substrate* come from? It is supplied from the *patient's reserves*, i.e. *nutritional state* from where nutrients can be mobilized, and by the *cardio-vascular-respiratory reserves*, which increase the *oxygen supply* during the period of tissue injury and repair. This response to injury forms part of the *stress response* (see Chapter 17).

If the patient is unable to supply substrate during the stress response and tissue repair, a state of *homeostatic failure* with *multiorgan failure* ensues. Therefore, patients who are unable to supply substrate to survive the stress response and to repair injured tissue will need *perioperative (pre-, intra, and postoperative) homeostatic support to survive*. This *homeostatic support includes* preoperative optimization, intraoperative support, and additional postoperative physiological care. *Without this reserve and support, the morbidity and mortality is high.*

How much reserve does the patient need? Nutritional reserve is usually detectable from the routine full blood count and blood biochemistry (albumin, other markers of nutritional state). Regarding the cardio-respiratory reserve before surgery, we look at the patient's premorbid (before the operation or trauma) ability to increase the oxygen consumption (VO_2) and, of course, oxygen supply.

The VO_2 in an adult is about 3.5 ml kg^{-1} min^{-1} or 10(body mass)$^{0.75}$for all sizes of patients. This 3.5 ml kg^{-1} min^{-1} is called one metabolic unit (MET). One MET is the VO_2 during rest; just sitting or lying down *doing nothing*. In order to survive major surgery, a *patient must be able to maintain a VO_2 of about 5 ml kg^{-1} min^{-1} postoperatively; that is about 1.5 METs. You must understand this concept very well since it affects outcome.*

How does one know that the patient will be able to maintain about 5 ml kg^{-1} min^{-1} postoperatively? The patient must achieve at least *4 METs preoperatively. How much is 4 METs?* It includes light garden work, housework, e.g. sweeping the floor, raking leaves together, mowing the lawn, etc.

Why 4 METs preoperatively? If a person exercises continuously for 24 hours, starting at a his /her maximal VO_2 ability, this performance will decrease to about 45% of the baseline VO_2 after 24 hours. If this maximum performance is 4 METs, *45% of 4 METs will be left, which is about 1.5 METs*. If a patient is maximally treated and still not capable to achieve 4 METs preoperatively, he/she will not have the metabolic reserve to sustain homeostasis postoperatively and the chances for a poor outcome increases. Therefore, measures must be taken to decrease oxygen demands and increase oxygen supply postoperatively, e.g. postoperative artificial ventilation to decrease the work of breathing, improve cardiac output, etc.

Hypoxia is a deficiency of oxygen at tissue level.

Hypoxaemia is low concentration of oxygen in arterial blood (CaO_2). The normal CaO_2 is about 210 ml L^{-1}.

The CaO_2 is the sum of the O_2 bound to haemoglobin and dissolved in the plasma. When haemoglobin is fully (100% or 1.0) saturated with oxygen (SaO_2), temperature is normal, and the acid-base state is normal, it carries 1.39 ml of O_2 (oxygen binding capacity). The amount of oxygen dissolved in plasma (PaO_2) depends on the partial pressure of oxygen and temperature (see Chapter 20). At normal body temperature, plasma carries 0.031 ml of O_2 per mm Hg per litre of blood (solubility coefficient). Therefore,

$$CaO_2 = ([Hb]\ g\ L^{-1} \times 1.39\ ml\ g^{-1} \times SaO_2) + (0.031\ ml\ L^{-1}\ mm\ Hg^{-1} \times PaO_2\ mm\ Hg).$$

Example:

What is the CaO_2 in a patient with a haemoglobin concentration of 10 g% and a PaO_2 of 45 mm Hg?

Remember: 10 g% = 10 g dL^{-1} = 10 g per 100 ml = 100 g L^{-1}.

The SaO_2 in a patient with a PaO_2 of 45 mm Hg is about 70% or 0.7 (It is not necessary to know what the SO_2s are at different PO_2s; you get that from the blood gas analysis.)

$CaO_2 = ([Hb]\ g\ L^{-1} \times 1.39\ ml\ g^{-1} \times SaO_2) + (0.031\ ml\ L^{-1}\ mm\ Hg^{-1} \times PaO_2\ mm\ Hg).$
$\quad = 100\ g\ L^{-1} \times 1.39\ ml\ g^{-1} \times 0.7 + 0.031\ ml\ L^{-1}\ mm\ Hg^{-1} \times 45mm\ Hg$
$\quad = 139\ ml\ L^{-1} \times 0.7 + 1.395\ ml\ L^{-1} = 97.3 + 1.395\ ml\ L^{-1} = 98.695\ \ ml\ L^{-1} \approx 99\ ml\ L^{-1}.$

The amount of oxygen transported by the blood to the tissue per minute is the **oxygen flux** (DO_2). This is the $CaO_2 \times$ the volume of blood (L min^{-1}) leaving the left ventricle per minute, i.e. the cardiac output (Qt). Therefore,

$$DO_2 = Qt\ L\ min^{-1} \times CaO_2\ ml\ L^{-1}$$
$$= Qt\ ml\ L^{-1} \times ([Hb]\ g\ L^{-1} \times 1.39\ ml\ g^{-1} \times SaO_2 + 0.031\ ml\ L^{-1}\ mm\ Hg^{-1} \times PaO_2\ mm\ Hg$$

This is called the *oxygen flux formula*

Example:

What is the DO_2 of the patient in the previous example if he has a cardiac output of 4 L min^{-1}?

$DO_2 = Qt\ L\ min^{-1} \times CaO_2\ ml\ L^{-1} = 4\ L\ min^{-1} \times 98.7\ ml\ L^{-1} = 394.8 \approx$ **395 ml min^{-1}**

Is this normal? In adults, the normal DO_2 is about 1000 ml min^{-1} or about 15 ml kg^{-1} min^{-1}.

Exercise: Calculate the DO_2 in a patient with a Hb of 15 g%, a PO_2 of 100 mm Hg (SaO_2 of 99%) and a cardiac output of 5 L min^{-1}.

The DO_2 depends on body size. Therefore, DO_2 is often expressed as an index, namely the DO_2 index. Instead of using cardiac output, we use cardiac index (CI= Qt/(body surface area in m)^2

The normal DO_2 index is about 600 ml min^{-1} m^{-2}.

Example: What is the DO_2 index in the patient in the previous example? He has a body mass of 60 kg, 1.6 m tall and has a body surface area of about 1.63 m^2.

DO_2 index = 395 ml min^{-1}/1.63 m^2 = 242.3 ml min^{-1} $m^{-2} \approx$ 242 ml min^{-1} m^{-2}

The above patient visits you in your GP practice.

He tells you that he gets tired when he puts on his clothes in the morning. He visited the cardiologist last week; the cardiac sonar report gives a cardiac output of 4 L min^{-1}.

Is he fit for his cholecystectomy next week?

Is this DO_2 enough if this patient has to undergo major surgery? No. Why not?

Answer: Preoperatively, he needs at least 4 METs:

4×3.5 ml kg^{-1} $min^{-1} = 4 \times 3.5$ ml kg^{-1} $min^{-1} \times 60$ kg = 840 ml^{-1} min^{-1}

At rest (1 MET) he needs 3.5 ml kg^{-1} $min^{-1} \times 60$ kg = 210 ml min^{-1}. **His DO_2 reserve is only 395 ml min^{-1} – 210 ml min^{-1} = 185 ml min^{-1}**

Can you see why he gets dyspnoeic when he gets dressed? He is not going to survive the operation.

What are you going to do?
You must increase his DO_2 first.
How?
You must increase these components of the DO_2 to increase his DO_2 reserve to
$$840 \text{ ml}^{-1} \text{ min}^{-1} – 210 \text{ ml min}^{-1} = 630 \text{ ml min}^{-1}.$$
How?
He must stop smoking, you must treat his COPD with physiotherapy and bronchodilators (increase PaO_2 and SaO_2).
You must treat his peptic ulcer and reflux and improve his diet (increase [Hb]).
You must treat his hypertension and cardiac failure (improve Qt).

What were the results of your interventions?
You see him two months later. What is his condition?
He can mow the lawn with ease now.
His Hb is 13g% and his saturation on your pulse oximeter is 95%.
Is he fit for surgery now? Let us calculate it:
His exercise tolerance is much better. Let us say that his Qt has improved to 5 L min^{-1}.
A patient with a PaO_2 of > 60 mm Hg has a saturation of > 90%. Let us say his PaO_2 is 70 mm Hg. Therefore, his DO_2 at rest is as follows:
$DO_2 = Qt \text{ ml L}^{-1} \times ([Hb] \text{ g L}^{-1} \times 1.39 \text{ ml g}^{-1} \times SaO_2 + 0.031 \text{ ml L}^{-1} \text{ mm Hg}^{-1} \times PaO_2 \text{ mm Hg})$
$\quad = 5 \text{ ml L}^{-1} \times (130 \text{ g L}^{-1} \times 1.39 \text{ ml g}^{-1} \times 0.95 + 0.031 \text{ ml L}^{-1} \text{ mm Hg}^{-1} \times 70 \text{ mm Hg})$
$\quad = \textbf{869 ml min}^{\textbf{-1}}$
The DO_2 reserve is 869 ml min^{-1} – 210 ml min^{-1} = 659 ml min^{-1}, which is > 630 ml min^{-1}.

Will he survive surgery now? Yes – *if he does not bleed a lot and if his respiratory and cardiac function does not deteriorate postoperatively*. If you do not optimise his cardio-respiratory and oxygen carrying capacity, he will from hypoxia postoperatively.

This example demonstrates the basic task of a doctor: to maintain DO_2. There is no systemic disease in the book that does not eventually affect one or more components of the DO_2. Tell me if you find one!

A condition that decreases any of the factors in the oxygen flux formula gives rise to hypoxia:
A decrease in Qt causes *stagnation* (ischaemic) hypoxia
A decrease in Hb causes *anaemic* hypoxia
A decrease in SaO_2 or PaO_2 causes *hypoxic* hypoxia
A decrease in oxygen binding capacity or an inability to consume oxygen causes *toxic hypoxia,* e.g. CO and cyanide poisoning.

All these types of hypoxia can occur pre-, intra- and postoperatively. Although not all causes of hypoxia can be eliminated preoperatively, the condition of the patient must be *optimized as far as practically possible before elective surgery*. In the case of *life-saving emergency procedures*, strategy must be in place to treat the patient appropriately. All patients that are hypoxic preoperatively, run the risk to become more hypoxic intra- and postoperatively, resulting in an increase in morbidity and mortality.

The following factors contribute to peri-operative hypoxia:
- Duration and type of surgery ⎫ Affects VO_2
- General anaesthesia
- Smoking
- The extremes of age (prematurity, the elderly) ⎫ Affects DO_2
- ASA status (All diseases with systemic complications) ⎭

CAUSES OF PERIOPERATIVE HYPOXIA (TABLE 1)

Hypoxic hypoxia (hypoxaemia)
Hypoxic hypoxia causes hypoxaemia, i.e. a low PaO_2 and SaO_2. The factors affecting oxygenation of blood are ventilation (Vm), perfusion (Qt), diffusion, control of ventilation, and the V/Q ratio (see Chapter 13). Abnormalities in any one of these cause a decrease in PaO_2 and SaO_2. Hypoxic hypoxia exists if the PaO_2 is < 60 mm Hg (< 8 kPa) and SaO_2 is < 90%. Remember the following equations (see Chapter 13):

The alveolar gas equation:
$$PAO_2 = PIO_2 - (PACO_2/R) + 4$$

PAO_2 = Alveolar PO_2
PIO_2 = Inspiratory PO_2 = (FIO$_2$ x PB) – PH$_2$O
FIO_2 = Inspiratory O_2-fraction =   0.21 for air
PB = Barometric pressure = approximately 650mmHg (87 kPa) in Pretoria
PH$_2$O = Saturated vapour pressure of water = 47 mmHg
P_ACO_2 = Alveolar PCO_2
R = Respiratory coefficient = approximately 0.8 when on mixed diet (carbohydrates, proteins, fat)

The alveolar CO$_2$ equation:
$$PACO_2 = KVCO_2/VA$$

$PACO_2$ = Alveolar PCO_2
K = constant
VCO_2 = CO_2 production
VA = alveolar ventilation

The dead space equations:
$$Vdtot = Vdalv + Vdanat + Vdapp = Vdphys + Vdapp$$
$$Vd\ phys/Vt = (PACO_2 - PECO_2)/PACO_2$$

Vdtot = total dead space
Vdalv = alveolar dead space
Vdanat = anatomical dead space
Vdapp = apparatus dead space
Vdphys = physiological dead space
Vt = tidal volume
$PECO_2$ = Mean expiratory PCO_2

The alveolar shunt equation:
$$Q_S/Q_T = (C_CO_2 - C_aO_2)/(C_CO_2 - CmvO_2)$$

Qs = alveolar shunt
Qt = cardiac output
CcO_2 = O_2 concentration in lung capillary blood
CaO_2 = O_2 concentration in arterial blood
$CmvO_2$ = O_2 concentration in mixed venous blood, i.e. blood drawn from the right ventricle or, preferably, the pulmonary artery (see Chapter 13)

Oxygen consumption
$$VO_2 = Q_T(CaO_2 - CmvO_2)$$

A very useful formula results from the combination of the alveolar shunt and VO$_2$ equations
$$CaO_2 = CcO_2 - (Q_T/VO_2)[(Q_S/Q_T)/(1- Q_S/Q_T)]$$

The causes of hypoxaemia can be deduced from the above equations:

- $\downarrow FIO_2$: Hypoxic gas mixtures, diffusion hypoxia caused by Nitrous oxide ($\uparrow PAN_2O$)
Decreased inspired O_2 tension
Causes include breathing circuit disconnections, faulty gas pipes, using anaesthetic machines without a hypoxic guard (see Chapter 4).
- *Low PB*: High altitude.
  $\downarrow$ PB $\rightarrow\downarrow$ FIO$_2\rightarrow\downarrow$ PIO$_2\rightarrow\downarrow$ PAO$_2\rightarrow\downarrow$ PaO$_2$ and SaO$_2$
- *Hypoventilation*
  $\downarrow$ VA $\rightarrow\uparrow$ PACO$_2\rightarrow\downarrow$ PAO$_2\rightarrow\downarrow$PaO$_2$ and SaO$_2$
  During general anaesthesia many patients hypoventilate. This causes an increased PaCO$_2$ and decreased PaO$_2$. The management consists of adjustment of ventilation (increased Vm, decreased Vd) and/or increase of the FiO$_2$. VA decreases pre-, intra, and postoperatively:
  o *Preoperatively*: Pathology of the central nervous system, suppression of ventilation, neuropathy, myopathy, or lung disease.
  o *Intraoperatively*: Preoperative conditions, central (opioids) and peripheral (benzodiazepines, anaesthetic vapours) suppression of ventilation in the spontaneously breathing patient, high spinal block, N. phrenicus block (high spinal block, brachial or cervical plexus block), pneumothorax, splinting of the diaphragm, microatelectasis of the lungs, wrong ventilator settings, uncoupling of ventilator, and saturated soda lime.

- o *Postoperatively (see also Chapter 30)*:Preoperative conditions,central (opioids, post-hyperventilation hypoxia) and peripheral (even 0.2 MAC inhalant, benzodiazepines) suppression of ventilation, residual curarezation, airway obstruction, decreased functional residual capacity (after thoracic and upper abdominal surgery), and postoperative sleep apnoea.
- *Increased VCO_2*

  $\uparrow VCO_2 \rightarrow \uparrow PaCO_2 \rightarrow \uparrow PAO_2 \rightarrow \downarrow PaO_2$ and SaO_2

  CO_2 production may increase pre-, intra, and postoperatively:
  - o *Preoperative*: Sepsis, hyperthyroidism.
  - o *Intraoperative*: Hyperthyroidism, sepsis, malignant hyperthermia, intravenous CO_2 (as bicarbonate and citrate and CO_2 in bank blood), defective apparatus (CO_2 in fresh gas).
  - o *Postoperative*: Stress response to surgery, hypothermia (increased VO_2 due to shivering and non-shivering thermogenesis).
- *Diffusion abnormality*
- *Dead space ventilation*

  $\uparrow Vdphys$ or $\downarrow Vt \rightarrow \uparrow PACO_2 + \downarrow PECO_2 \rightarrow \uparrow PACO_2 \rightarrow \downarrow PAO_2 \rightarrow \downarrow PaO_2$ and SaO_2

  The main causes of dead space ventilation are a low cardiac output, high alveolar pressures (decreases alveolar perfusion) and low tidal volumes (relative increased anatomical dead space)
- *Ventilation-perfusion (V/Q) mismatching: The (VA/Qt) ratio*

  The total pulmonary perfusion (Qt) must be functional, i.e. it must perfuse ventilated alveoli, and *vice versa*. V/Q mismatching is always complicated by a decreased PaO_2. Management consists of improvement of perfusion (Qt) to alveoli (decreased Vdalv), and improved VA (decreased shunt). Often, both these aspects should be addressed, i.e. improved cardiac output and improved ventilation, respectively.
- *Low mixed venous O_2 concentration ($CmvO_2$)*

  A low $CmvO_2$ is caused by a high extraction of O_2 from the arterial blood or low contact time between the mixed venous blood and the alveolus (very high Qt). The high extraction may be due to a low DO_2, or an increased VO_2. A limited amount of O_2 can be added. The lower the $CmvO_2$,the lower CaO_2 will be. A very low $CmvO_2$ contributes to hypoxic pulmonary vasoconstriction, which will decrease pulmonary blood flow and consequently increase the V/Q ratio and lower PaO_2. If the shunt fraction is higher, more mixed venous blood will reach the left heart without being oxygenated. This is called *venous admixture*.

Table 1 Differentiation of the 8 causes of hypoxaemia

Mechanism	Effect on $PaCO_2$	A-a O_2 difference	Response to 100% O_2
$\downarrow FiO_2$	$\downarrow$* or $\leftrightarrow$	$\leftrightarrow$	$\uparrow$
$\downarrow VA$	$\uparrow$	$\leftrightarrow$	$\uparrow$
$\uparrow VCO_2$	$\uparrow$	$\leftrightarrow$	$\uparrow$
$\downarrow$ Diffusion	$\downarrow$* or $\leftrightarrow$	$\uparrow$	$\uparrow$
$\uparrow Vdphys$	$\uparrow$	$\leftrightarrow$	$\uparrow$
$\uparrow Qs/Qt$	$\downarrow$* or $\leftrightarrow$	$\uparrow$	No if Qs high
V/Q mismatch	$\downarrow$* or $\leftrightarrow$	$\uparrow$	No if $\downarrow\downarrow$ or $\uparrow\uparrow$
Low $PmvO_2$	$\downarrow$* or $\leftrightarrow$	$\uparrow$	$\uparrow$

* if the patient hyperventilates

Stagnation hypoxia (see Chapter 12)
In stagnation hypoxia, *blood flow* to the periphery and the lungs is decreased. Stagnation hypoxia is caused by any decrease in *cardiac output* (Qt). A decrease in Qt *decreases DO_2*. This results in a higher extraction of oxygen from arterial blood resulting in a *low $SmvO_2$*. Stagnation hypoxia does also cause increased *dead space ventilation*, with an increased in the V/Q ratio, resulting in hypoxaemia. Stagnation hypoxia from cardiac origin (*cardiac failure*) can also cause pulmonary oedema. Pulmonary oedema causes decreased VA with an increase in the *shunt fraction*, which also causes hypoxaemia. The pulmonary oedema increases the work of breathing, causing hypoventilation and, therefore hypoxaemia.

Stagnation hypoxia is not only caused by the *cardiac component* of Qt, but also the *intravascular volume*. Therefore, all *hypovolaemic* patients have stagnation hypoxia.

Anaemic hypoxia
If you have a normal heart, intravascular volume, and ventilation, but the blood cannot carry oxygen, DO_2 decreases. Therefore, the heart and ventilation must work harder to maintain DO_2. Therefore, patients with a low Qt (cardiovascular pathology) or SaO_2 and PaO_2 (ventilation pathology) or low haemoglobin binding capacity (severe acidosis, CO toxicity) do not tolerate a low haemoglobin concentration. (CO toxicity causes a functional anaemia – there is haemoglobin, but it cannot bind oxygen.)

Chronic hypoxaemic patients, e.g. patient with COPD, stimulate haemopoiesis and become polycythaemic. Due to the high [Hb], they have a low SaO_2 and PaO_2, but a normal CaO_2 and maintain DO_2. Therefore, patients with ventilatory failure do not tolerate anaemia.

An important aspect of [Hb] is myocardial oxygenation. If there is isolated stagnation hypoxia in the heart, i.e. myocardial ischaemia, the myocardium becomes more dependent on CaO_2. Therefore, patients with ischaemic heart disease do not tolerate hypoxaemia or anaemia.

Since patients with cardiovascular or ventilatory impairment do not tolerate anaemia well, the blood transfusion trigger may be higher than in those patients with a normal cardiovascular and ventilatory function (see Chapter 18).

Toxic hypoxia
You may find a patient with no primary cardiac, ventilatory, or haemoglobin abnormality, but he is hypoxic. This is due to factors that:
- impairs the ability of *haemoglobin to bind oxygen*, e.g. carbon monoxide poisoning and methaemoglobinaemia (Fe^{3+} instead of Fe^{2+}),
- *release oxygen*, e.g. methaemoglobinaemia due to oxidizing substances in patients with deficient reductases, such as glucose-6-phosphate dehydrogenase deficiency, or
- inhibits the *inability of cells to consume oxygen*, e.g. *mitochondrial failure*, (high levels of nitric oxide (NO) in septic shock, cyanide toxicity, and antiretroviral drugs) or if arterial blood bypasses capillaries due to the opening of *arteriolo-venular shunts* in septic shock. During septic shock, the enzyme that produces NO (inducible nitric oxide synthase, iNOS) is induced and NO production increases. NO is responsible for both inhibition of oxidative phosphorylation and opening of *arteriolo-venular shunts.*

In CO toxicity CaO_2 is very low, since the haemoglobin binding capacity is $<< 1.39$ ml g^{-1}. In methaemoglobinaemia, the binding capacity is not only decreased, the oxygen that binds, is not released (the dissociation curve is shifted to the left).

TREATMENT OF PERIOPERATIVE HYPOXIA

Prevention
- *Preoperative* optimization: anatomical e.g. drainage of pleural effusion; physiological and pharmacological by treating the components of DO_2 (physiotherapy to get rid of secretions, bronchodilators, antibiotics, treat hypertension, cardiac failure, myocardial ischaemia,, anaemia, etc, etc, etc.)
- *Postponement* of elective surgery to *prevent aspiration pneumonia* by *postponing* elective surgery. If you cannot attain optimal levels of the DO_2 components, the patient will probably have low preoperative METs and therefore will need *supplemental postoperative care*. You must postpone surgery if this option is not available.

Treatment of the cause

- *Increase CaO_2* by the administration of *oxygen* (increase $FIO_2 \rightarrow \uparrow PaO_2$ and SaO_2, decrease $PaCO_2$ by improving VA, decreasing Vdphys (increase Qt and Vt), and/or blood transfusion.
- *Improve VA* by removing suppressants of ventilation, reverse neuromuscular blockade, re-expansion of atelectatic lung (intubate, ventilate, PEEP, drain pleural effusions, etc.), decrease the work of breathing (treat bronchospasm, pulmonary oedema, increased intra-abdominal pressure, etc.), and adjust the ventilator.
- *Regarding the work of breathing* (see Chapter 13): Any factor that causes hypoxia stimulates ventilation, which increases the work of breathing. That is why you would, e.g. have to intubate a patient with normal lungs but with severe cardiac failure. Remember, the diaphragm is perfused by blood from the heart! Lung and extrapulmonary lesion that increase the work of breathing will eventually cause ventilatory failure. A high work of breathing does not only decrease VA, but also increases VO_2. Therefore, these patients are also very sensitive to a decreased Qt and anaemia.
- *Lower Vd* by improving Qt (transfuse, treat cardiac failure, decrease intrathoracic pressure).
- Improve *haemoglobin binding* capacity – to bind and to release enough oxygen (treat toxicity).
- *Improve VO_2* by treating septic shock and cyanide toxicity.
- *If VO_2 is very high*, e.g. hyperthermia, hyperthyroidism, you can improve the DO_2 relative to VO_2 by treating the cause of the high VO_2.

MONITORING OF OXYGENATION

- **Qt (also see Chapter 18):** blood pressure, pulse, preload (central venous pressure, pulmonary artery wedge pressure, pulse pressure variation), urinary output, blood gas analysis (acid-base status), $SmvO_2$ or $CmvO_2$ (a low $SmvO_2$ or $CmvO_2$ with adequate CaO_2 and normal VO_2 means a low Qt) and direct measurement of Qt using the pulmonary artery catheter.
- **Haemoglobin concentration.** Direct measurement, haematocrit
- **SaO_2 (also see Chapter 20):** Pulse oximetry (SpO_2), arterial blood gas analysis
- **PaO_2 (also see Chapter 20):** Arterial blood gas analysis

In patients with CO toxicity (blood appears red) and methaemoglobinaemia (blood is bluish) SaO_2 and SpO_2 are low, but PaO_2 is normal or high.

- **FIO_2 (also see Chapters 4 and 20):** Anaesthetic gas analysis
- **$PACO_2$ (also see Chapter 20):** The capnograph measures end-tidal PCO_2 ($PETCO_2$). In the absence of large VA/Qt disturbances, there is only a small difference between $PACO_2$ and $PETCO_2$ (during anaesthesia $PETCO_2$ is about 5 mmHg lower than $PaCO_2$). Big differences indicate significant VA/Qt disturbances (high). You can also get a rough idea of mix expiratory PCO_2 to calculate Vdphys ($PECO_2 \approx 0.5\ PETCO_2$)
- **$PaCO_2$** Arterial blood gas analysis
- **Mixed venous blood gas analysis (also see Chapters 18 and 20):** The value of mixed venous blood gas analysis is often underestimated. It gives valuable information regarding the oxygen balance, i.e. the oxygen flux versus the consumption. A low venous saturation ($SmvO_2$) ($< 60\%$), indicates a low CaO_2 (low Hb and/or SaO_2) and/or low Qt. As resuscitation progresses, $SmvO_2$ and $PETCO_2$ increase and the lactic acidosis disappears (base deficit decreases). If a pulmonary artery catheter is not available, *central venous (right atrial) blood is also useful*; central venous blood (CVP) is interpreted in the same way as mixed venous blood.

$CmvO_2$ and CaO_2 are also used to calculate oxygen consumption and extraction ratio (see Chapter 18). If you know how much oxygen is extracted from a particular volume of arterial blood ($CaO_2 - CmvO_2$), and you know how much blood has perfused the body, i.e. Qt, you can calculate the consumption:

$$VO_2 = Qt(CaO_2 - CmvO_2)$$

The normal CaO_2 is about 210 ml L^{-1} and the normal resting $CmvO_2$ about 135 ml L^{-1}. Therefore the VO_2 with a Qt of about 5 L min^{-1}, is

5 L min^{-1}(210 ml L^{-1} – 135 ml L^{-1}) = 380 ml min^{-1}.

The oxygen extraction ratio (OER) = $CaO_2 - CmvO_2/CaO_2$

    = (210 –135)/210

    = 0.36 or 36% (normal 0.22 to 0.30)

($CaO_2 - CmvO_2/CaO_2$ can be replace by $SaO_2 - SmvO_2/SaO_2$)

But in this patient,
DO_2 is 5 L min^{-1} × 210 ml L^{-1} = 1050 L min^{-1}.
There is a large reserve (about 3 × VO_2).

If DO_2 would decrease, while VO_2 remains unchanged, VO_2 will be unaffected until this reserve has been exhausted. That means that up to that point *VO_2 is DO_2 independent*. If DO_2 decreases below VO_2, VO_2 will also decrease and is said to be *DO_2 dependent*. This point of DO_2 is the critical DO_2 or DO_2crit. If DO_2 decreases below DO_2crit, anaerobic metabolism ensues, lactate production increases and the patient develops a metabolic acidosis. At DO_2crit, the OER is > 0.5. Therefore, you can identify DO_2crit by using only SaO_2 (or even SpO_2) and a central venous gas analysis ($ScvpO_2$). $SmvO_2$ is about 0.8 × $ScvpO_2$.
Example:
SpO_2 is 99%, $ScvpO_2$ is 45%. What is the OER? ~~Is~~
OER = (99% - 45%)/99% = 0.55 or 55%.
Is DO_2> VO_2? Probably not.
Why does a OER > 0.5 indicate DO_2crit?
In healthy adults, DO_2crit is about 7 ml kg^{-1} min^{-1}, while the VO_2 is about 3.5 ml kg^{-1} min^{-1}.
Therefore the critical OER is (7 ml kg^{-1} min^{-1}– 3.5 ml kg^{-1} min^{-1})/7 ml kg^{-1} min^{-1} = 0.5.

A *$SmvO_2$ and $ScvpO_2$* may not only decrease in the critically ill patient, but may also *increase and even look like arterial blood*. This happens when VO_2 decreases, e.g. septic shock and cyanide toxicity.

By using the parameters mentioned above, all the other indicators of tissue oxygenation can be calculated and applied.

SUMMARY

In this chapter, a summary was given about factors that affect oxygen supply and oxygen demand. These include cardiovascular, ventilatory, and metabolic components. You must be able to monitor tissue oxygenation and identify hypoxia, its causes, and mechanisms. Thereafter, you must be able to treat the cause appropriately.

CHAPTER 15

CARDIOPULMONARY RESUSCITATION

Key points

- Failure to recognize signs of sudden cardiac arrest (SCA) or signs of impending cardiac arrest will lead to delayed intervention.
- CPR must me initiated without delay, irrespective of the level of skill of the care giver.
- The 2010 CPR guidelines emphasize the importance of chest compressions, which have now become the first step in the CPR sequence (CAB in place of ABC).
- Although ventilation may be an important step in some cases of arrest (e.g. primary asphyxia), excessive and inappropriate ventilation is

- detrimental.
- Rapid defibrillation is an essential life saving for specific peri-arrest rhythms.
- Always consider reversible causes of cardiac arrest (the Hs and Ts).
- Ideally, especially during in-hospital cardiac arrest, skilled providers should work as a team.
- Resuscitation and CPR during the perioperative period in unique and therefore should be tailored individually to each specific clinical scenario.
- A detailed knowledge of the most up to date resuscitation algorithms is essential.

CPR is a *set of coordinated actions* to improve survival following cardiac arrest. Regardless of the scenario (patient, aetiology of arrest, place of arrest, or level of care), the fundamental principles of any resuscitative effort are the links of the *chain of survival.* If these are applied effectively, survival can approach 50%. Unfortunately, figures vary greatly (5% and50%).

The heterogeneity surrounding sudden cardiac arrest (SCA) implies that no single approach to CPR is possible or practical. Yet, all resuscitation efforts must be based on the *chain of survival*.

Principles of resuscitation

- *Chain of survival*
  - *Immediate recognition* of arrest and appropriate activation of support systems
  - *CPR* without delay
  - Appropriate *electrical therapy* i.e. defibrillation
  - *Advanced care* as soon as possible
  - *Care after* cardiac arrest improves outcome.
- *Initial steps include*
  - Optimisation of *cardio-pulmonary function* and re-establishment of organ perfusion.
  - Consultation with expert opinion.
  - Transport to an appropriate level of care i.e. intensive care unit.
  - Search and management of causes and precipitants to prevent recurrent arrest.
- *Subsequently*
  - Consider therapeutic *hypothermia*.
  - Identify and treat a*cute coronary syndromes* (ACS).
  - Institute lung protective *ventilation*.
  - Be objective about *prognosis and termination* of resuscitation efforts.

Defining cardiac arrest

Recognition of SCA is not always easy, especially for inexperienced health care providers. The 2010 CPR guidelines is base the recognition of SCA on *assessing unresponsiveness and absence of normal breathing*. Note the latter phrasing: *"Absence of normal breathing" implies gasping breaths or no breathing*.

Perioperative Cardiac Arrest

SCA can often be avoided by applying basic medical knowledge, especially *basic cardiopulmonary physiology*.

In the *perioperative period*, circumstances under which SCA can deteriorate to pulseless cardiac arrest *differ totally* from other scenarios of SCA. During the perioperative period, patients present

with a *variety of pathologies*, which make each resuscitation unique. SCA can often be avoided by applying basic medical knowledge, especially *basic cardiopulmonary physiology*.

Cardiac arrest attributable to anaesthesia falls into one of *two categories*: medication-related and airway-, or ventilation-related. Most cases of anaesthesia-related cardiac arrests are associated with the intraoperative use of *neuromuscular blocking* agents, occur at *emergence*, or in the *recovery room*.

Hypovolaemia is a very common contributor to perioperative SCA. Unlike other SCA scenarios, the most common dysrhythmias encountered are *bradydysrhythmias and asystole*. Fortunately, the outcomes are less dismal during the perioperative period, since a *direct cause* can usually be identified and corrected.

Perioperative *physiological monitoring* gives us a unique advantage in identifying cardiac arrest and allows intervention before SCA occurs. Therefore perioperative (from induction of anaesthesia to discharge from anaesthesia personnel care), cardiac arrests are usually *witnessed* events, which originate from various aetiologies, but are *usually identifiable*. Since all anaesthesia-attributable cardiac arrests are related to airway management and medication administration, these aspects are important in prevention of SCA.

SCA in children do not occur commonly, the aetiology is diverse, and frequently preventable. VF is also uncommon in children (5-15%). As with adults, rapid defibrillation markedly improves survival.

Characteristics of perioperative SCA
- *The environments* in which SCA can deteriorate to pulseless cardiac arrest *differ.*
- Perioperative *physiological monitoring* gives us a unique advantage in identifying cardiac arrest and allows intervention before SCA occurs. Therefore perioperative (from induction of anaesthesia to discharge from anaesthesia personnel care), cardiac arrests are usually *witnessed* events, which originate from various aetiologies, but are *usually identifiable*.
- Patients present with a *variety of pathologies*, which makes each resuscitation unique.
- *Cardiac arrest attributable to anaesthesia* falls into one of *two categories*: medication-related and airway-, or ventilation-related. Most cases of anaesthesia-related cardiac arrests are associated with the intraoperative use of *neuromuscular blocking* agents, occur at *emergence*, or in the *recovery room.*
- *Hypovolaemia* is a very common contributor to perioperative SCA. Unlike other SCA scenarios, the most common dysrhythmias encountered are *bradydysrhythmias and asystole*. Outcomes are better after since a *direct cause* can usually be identified and corrected.
- Prevention of SCA is easier since all anaesthesia-attributable cardiac arrests are related to airway management and medication administration.

Perioperative SCA is associated with:
- Emergency surgery
- After hours
- Haemorrhage
- Protracted intraoperative hypotension
- ASA Score
- End-organ failure
- Diabetes mellitus
- A primary ECG rhythm
- High risk surgery
- Duration of surgery

Adult basic life support (BLS)
Basic life support skills lay the foundation of CPR and an important part in determining return of spontaneous circulation (ROSC) and ultimately survival. There is *no substitute for well-preformed BLS*. There is a distinction between BLS for the layperson and the health care provider (Figure 1, Table 1).

Simplified Adult BLS
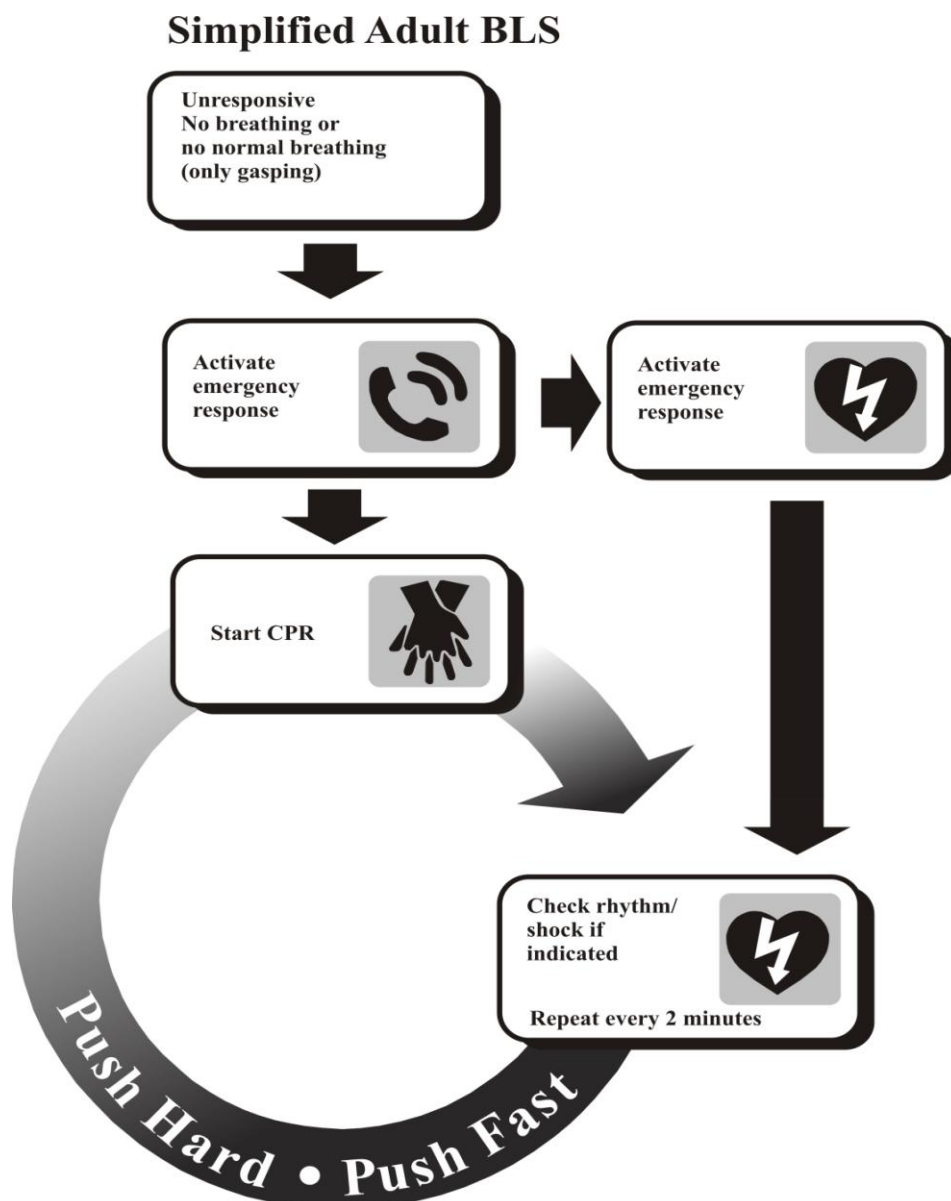
Figure 1 BLS for the layperson

- *Recognition of arrest and early defibrillation*
  The first step in any resuscitation scenario is the timeous recognize cardiac arrest and to activate an emergency response system. For *out-of-hospital arrest*, this ensuring *safety of the scene* and having the emergency *services notified*. During an *in-hospital* or perioperative arrest this implies getting support from staff or activating a resuscitation team.

Diagnosis of cardiac arrest
- *Unresponsive* patient with no, or lack of normal *breathing*. During SCA, occasional gasps may be incorrectly interpreted as breathing efforts. These guidelines are *not applicable in ventilated patients during general anaesthesia.*
- *Pupils* dilate within a minute after SCA. Various drugs used in anaesthesia may make this sign unreliable.
- *Central cyanosis*
- *No bleeding* from surgical wounds
- Profound *hypotension*
- Sudden decrease in *end tidal CO_2* (PETCO$_2$)
- *ECG* signs, e.g. VF

- CPR should also be immediately commenced in situations where cardiac output has critically decreased, e.g. profound hypotension and low $PETCO_2$, i.e. < 20 mm Hg.

Table 1 Recommendations for CPR healthcare providers

Component	Adults	Children	Infants
Recognition	**UNRESPONSIVE**		
	No breathing, not breathing normally (e.g. gasping)	No breathing or only gasping	
	No pulse palpated within 10 s (HCP only)		
CPR sequence	CAB	CAB	CAB
	CIRCULATION		
Compression rate	At least 100 min^{-1}		
Compression depth	At least 5 cm	At least 1/3 AP depth; ± 5 cm	At least 1/3 AP depth; ± 4 cm
Chest wall recoil	Allow complete recoil between compression		
	HCPs rotate compressors every 2 minutes		
Compression interruptions	Minimize interruptions in chest compressions Attempt to limit interruptions to < 10 s		
	AIRWAY		
Airway	Head tilt-chin lit (HCP suspected trauma: jaw thrust)		
	BREATHING		
Compression: ventilation ratio (until advanced away placed)	30:2 (1 or 2 rescuers)	Single rescuer 30:2 2 rescuers 15:2	Single rescuer 30:2 2 rescuers 15:2
Ventilations: When rescuer untrained or trained and not proficient	Compressions only		
Ventilations with advanced airway (HCP)	1 breath every 6 – 8 s (8 –10 breaths min^{-1}) Asynchronous with chest compressions About 1 per breath Visible chest rise		
Defibrillation	Attach and use AED as soon as available. Minimize interruptions in chest compression before and after shock, resume CPR beginning with compressions immediately after each shock.		

CAB **C**ompression-**A**irway-**B**reathing; HCP health care professionals; AED automated electrical defibrillator

The 2010 guidelines have *de-emphasised the checking for breathing and pulse*; it is difficult and wastes time. If a pulse check is performed by a health care professional (HCP), is should take < 10 s. There is also no evidence that suggests that checking for breathing, coughing or movement is superior when checking for adequate circulation.

A defibrillator is life saving and must be immediate availability in any health care environment, especially in theatre. Therefore, a thorough *knowledge of their operation* is important. Defibrillators must be *maintained and tested* regularly. Delays in defibrillation occur in about 15% of perioperative cardiac arrests and are associated with higher mortality. Apart from the increase in peripheral and lung perfusion (observed as an increase in end-tidal CO_2) defibrillation with resumption of perfusion immediately improves coronary perfusion.

Chest compressions
The patient should be placed on a *firm surface*, in a supine position. Backboards are useful, but should not delay CPR and care must be taken to not displace lines/tubes. Compressions are done over the *lower part of the s*ternum to a depth of *5 cm*. A compression rate of at least *100/min* is ideal. Fatigue can cause inadequate compressions. Therefore, switch chest compressors approximately every two minutes. This should be done during an intervention (e.g. defibrillator application) and the changeover should be limited to less than 5 seconds.

During *sternal compression*, the *heart is compressed* between the sternum and the spine, resulting in the ejection of blood into the systemic circulation. The *increase in intrathoracic pressure forces blood out of the thorax*.

During CPR, cardiac output is at most 30% of normal. *Most of the blood flow* is directed towards supra-diaphragmatic organs of which the *heart and brain* are the most important. *Vasopressors* do improve the flow to these vital organs, but may reduce perfusion of other organs. Measures of adequate CPR:

- A *$PETCO_2$*> 20 mm Hg. A sustained $ETCO_2$< 10 mm Hg points to poor outcome.
- A sustained diastolic pressure of at least 40 mm Hg
- Coronary perfusion pressure of 20 mm Hg

Why compressions take preference over ventilation

- Lungs usually contain enough oxygen to prevent serious hypoxia. The FRC contains approximately 480 ml when breathing air.
- Chest compression results in ventilation.
- Neurons are more resistant to hypoxia that ischaemia.
- It is usually easier to commence compressions. Hence the emphasis in the current guidelines on "Hand-only-CPR".
- Compressions may cause spontaneous defibrillation, if initiated before the myocardium becomes hypoxic.

Compression:ventilation ratio

Currently a ratio of *30 compressions:2 ventilations* is recommended. Once an advanced airway is in place there is no need to synchronize these.

Airway management and ventilation

The *CAB CPR sequence* has been replaced the ABC sequence. This reflects growing evidence of the *importance of chest compressions*. Therefore, airway interventions must not delay chest compressions. As soon as an *advanced airway device* is in place, compression-ventilation *synchronization is unnecessary*. With any of these devices in place, compression must be done at a rate of at least 100 min^{-1}, without interruptions. One breath every seven seconds is adequate.

The simple *head tilt-chin lift manoeuvre* improves ventilation is most patients. This should only be done in patients with no evidence of *head and neck trauma*. In such cases, a *jaw thrust* without head extension is recommended

The *primary goal* of assisted ventilation during CPR is *oxygenation – not CO_2 elimination*. All rescue breaths must achieve a tidal volume sufficient to *visibly raise the chest*. If mechanical ventilations is used, care should still be taken NOT to over-inflate the lungs by applying the principles of *lung protective ventilation*, i.e. using a tidal volume of 6 ml kg^{-1} to 7 ml kg^{-1} (see Chapters 4 and 13). *Excessive ventilation* increases intrathoracic pressure, which *decreases venous return and* an already low *cardiac output*.

Ventilation with airway devices (Table 1)

All anaesthetists must master the skill of *bag-mask ventilation*. Its use is not recommended during lone rescuer CPR but ideally requires two operators.

Ventilation bags with a capacity 1 L or 2 L is usually used. Compression of one or two thirds provides an adequate tidal volume, i.e. a visible chest rise. Each breath is administered over one second and time for complete expiration is necessary.

Endotracheal intubation is not part of the resuscitation guidelines, but may be performed if it does not delay the CPR cycle. *Supraglottic airway devices, e.g. the laryngeal mask airway* or *Combitube,*

are easier to place and do not necessarily require the same level of skill as does endotracheal intubation.

Table 1 Ventilation with airway devices

Bag-mask device	Masks
Non-jam inlet valve	Made from transparent material
Pressure relief valve with bypass	Create a tight seal
Reservoir (high concentration of oxygen)	Fit over mouth and nose
Non-rebreathing outlet valve	Oxygen inlet for insufflation
Standard 15 mm/22 mm fittings	15 mm/22 mm connectors
Adult, paediatric and neonatal sizes	One adult and several paediatric sizes

The routine use of *cricoid pressure* during placement of airway devices or ventilation is no longer recommended in the latest 2010 guidelines. The *adverse effects of cricoid pressure* include:
- Interference with placement of airway devices
- Distortion of the line of vision (see Chapter 3)
- Stimulates a swallow reflex and lower the tone of the oesophageal sphincter
- May complicate intubation
- Rupture of the oesophagus if the patient would vomit
- Pressure on other structures e.g. the carotid artery
- It is contraindicated in neck trauma. Therefore, *bimanual cricoid pressure* must be done.

Electrical Therapy

A delay of CPR or defibrillation reduces survival from SCA. *Immediate CPR prolongs VF*, delays the onset of asystole, and extends the windows for successful defibrillation. Mortality increases by 10% every minute that passes. There is insufficient evidence to either support or refute the application of CPR before defibrillation. However, in monitored patients, as is the case during the perioperative period, the *time from VF to defibrillation should be under 3 minutes*. However, a period of immediate *CPR before defibrillation* may be beneficial *after prolonged collapse*.

Ventricular fibrillation (VF) is the most common initial dysrhythmia in out-of-hospital cardiac arrest. Early defibrillation is important since:
- The majority of SCA victims have VF.
- Early defibrillation is the only treatment for VF.
- Delayed defibrillation reduces survival. VF is also uncommon in children (5-15%). As in adults, rapid defibrillation markedly improves survival.
- VF is followed by asystole, which as dismal outcome.

Defibrillation shocks are characterized by:
- The amount of *energy* applied e.g. 200 J
- The discharge *waveform*, i.e. monophasic or biphasic

Defibrillation waveforms are generated by the discharge of energy stored in a capacitor through a patient.

Waveforms describe energy (J) or current (Amp) delivered over a particular time. Remember, although we choose an energy setting in Joule, it is *actually the resulting current (Ampere) that defibrillates or cardioverts the myocardium*. Using an energy level of 360J, *monophasic defibrillators* evokes a *positive wave only* and can deliver more than 60 amps. However, *high-energy defibrillation causes substantial post-shock myocardial injury. High peak currents result in myocardial dysfunction.* Therefore, increased levels of myocardial enzymes do not necessarily myocardial infarction after defibrillation.

With *biphasic* truncated exponential (BTE) defibrillators, the energy delivery occurs in two phases at *lower peak currents* (Figure 2). The *first phase* is a positive deflection and represents current flow

from the sternal to the apical paddles. The *second phase is negative* and depicts a current in the opposite direction. The *advantages of BTE defibrillators* are that they are smaller, have longer battery lives, compensates for differences in patient impedance (resistance between the paddles), match the performance of monophasic defibrillators, but at *lower energy levels*.
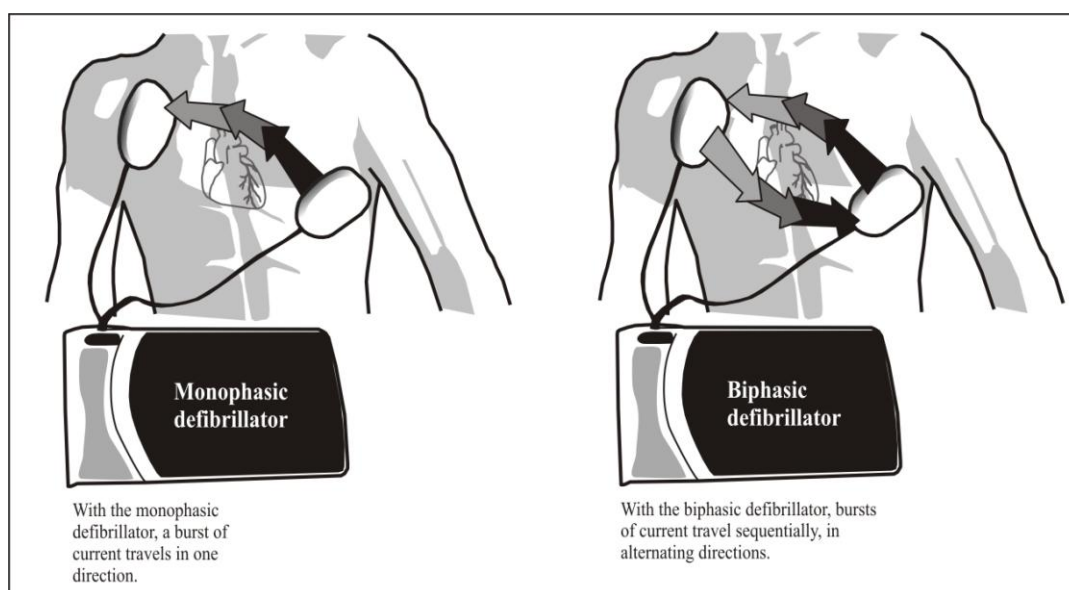
Figure 2 Monophasic and biphasic defibrillation

Modern defibrillators deliver a *current-based shock*. There is evidence that current-based defibrillation (Amp)is superior to energy based defibrillation (J). The *indications and recommended energy levels* for electrical therapy are summarized in Tables 2 and 3.

Table 2 Indications and recommended energy levels for electrical therapy

Dysrhythmia	Electrical therapy
Ventricular fibrillation (VF)	Defibrillate with 150J BP, or 360 J MP
Pulseless ventricular tachycardia (VT)	Defibrillate with 150J BP, or 360 J MP
Monomorphic VT *with pulse*	Cardioversion with 100 J†
Unstable regular and narrow QRS complex tachycardia	Cardioversion with 50 J†
Unstable irregular and narrow QRS complex tachycardia, e.g. atrial fibrillation	Cardioversion with 100 J†
Paediatric**	2 J kg^{-1} to 4 J kg^{-1}, maximum 10 J kg^{-1}

*Unstable refers to a poor or deteriorating haemodynamics, e.g. hypotension, syncope, loss of consciousness, chest pain, etc

**The actual upper safe limit for defibrillation in children is not known, and doses as high as 10Jkg^{-1} have been used;

† When using biphasic devices, consult the manufacturer for recommendation. Usually, initial biphasic doses of 100 J to 120 J are used, and increased as needed.

MP monophasic; BP biphasic.

*Automated External Defibrillators (AED)*are recommended for use by *lay rescuers*. These are aimed at minimizing the delay in "Time to first shock". AEDs are use voice and visual prompts to guide safe defibrillation and can *markedly improve CPR success – even in in-hospital SCA*.

The *steps for automated external defibrillation* are as follows:

- *Activate:* Power on the AED. This activates the voice prompts for guidance in all subsequent steps. Some devices may power up automatically when the lid of the case is opened.
- *Attach:* Choose the correct *adhesive pads* and place these on the patient's bare chest. Use a paediatric pads/system for patients less than 8 years of age, if available.
- *Analyse:* Some devices will automatically analyse the rhythm while other may require you do push a button. Always remain clear of the patient during analysis.

- *Administer:* The AED will advise whether or not a shock is required. Clear the patient: "I'm clear, you are clear, all clear, oxygen clear!" Only then press the shock button.
- The use of AED is recommended in children aged between 1 and 8 years (with a paediatric dose attenuator system). Manual defibrillation is recommended for infants (<1 year).

Use of defibrillation paddles and self-adhesive pads
- Any of four *positions* may be used:
  o Antero-lateral (the default position, Figure 4)
  o Antero-posterior: the apex paddle is positioned between the left scapula and the spine.
  o Anterior-left/right infrascapular: The infraclavicular (sternal) paddle is positioned below the right or left scapula, while the apical paddle is still at the apex.
- The recommend sizes for paddles / self-adhesive pads are sizes 8 to 12. *Smaller sizes* can lead to *myocardial necrosis*.
- To reduce transthoracic impedance, *defibrillation paste/gel* must be used, when using handheld paddles. The use of water based lubricants (KY) or saline is NOT recommended.
- There have been reports of *fires ignited by sparks from incorrectly used defibrillators*, especially in the presence of *oxygen-enriched air*. Therefore, oxygen tubing must be removed from the patient during defibrillation ("I'm clear, you're clear, all clear, *oxygen clear*!").
- The use of *self-adhesive pads and good chest wall contact* can minimize sparks ignition during defibrillation. *Gel pads are preferable* to electrode pastes and gels, because pastes and gels may spread between the paddles, creating the potential for a spark.

Cardioversion (electrical and pharmacological) for tachycardia in adults (Figure 3)
Electro-cardioversion, is when a *shock is delivered on the R wave* of a QRS complex to convert an abnormal rhythm back to sinus rhythm. This synchronization avoids shock delivery during the relative refractory period of the cardiac cycle (on the T wave), when a shock could produce VF. This is also the reason why the *precordial thump is no longer recommended* (Commotio Cordis).

The steps of synchronized cardioversion is as follows:
- Sedate the patient if necessary. If the patient is unstable, proceed immediately with cardioversion.
- Turn on the defibrillator and attach the monitor leads. Ensure that the rhythm is adequately displayed.
- Position the pads or paddles.
- Have an assistant to engage the SYNC function (synchronized). The assistant must *activate the SYNC MODE after delivery of each synchronized shock*. Most defibrillators default back to the unsynchronized mode after delivery of a synchronized shock. An unsynchronized shock will produce VF.
- Look for marks on the QRS complexes. If may be necessary to enlarge the complexes (adjust the gain).
- Select the appropriate starting energy level (increase as needed). *When using biphasic devices one should consult the manufacturer for specific recommendation. Initial biphasic doses of 100 J to 120 J are usually used, and escalated as needed:*
  o Atrial fibrillation: 100 J
  o VT (with Pulse): 100 J
  o SVT and atrial flutter: 50J
  o *As a rule of thumb*, when the rhythm is regular, cardioversion can be started with 100 J, while 200 J is used for an irregular rhythm.
- Clear the patient: "I'm clear, you're clear, all clear, oxygen clear!"
- Charge the defibrillator.
- Deliver the shock by holding down the discharge buttons on the manual pads or by pressing the button on the defibrillator.
- Check the monitor. If the tachycardia persists, increase the energy level and shock again after the *SYNC FUNCTION* has been activated.

```
┌─────────────────────────────────────────────┐
│   Assess appropriateness for clinical condition  │
│  Heart rate typically ≥ 150 min if tachyarrhythmia │
└─────────────────────────────────────────────┘
                    ↓
┌─────────────────────────────────────────────┐
│      Identify and treat underlying cause        │
└─────────────────────────────────────────────┘
                    ↓
```

Persistent tachyarrhythmia causing		Synchronized cardioversion
• Hypotension? • Acute altered mental state? • Ischaemic chest discomfort? • Acute heart failure?	Yes →	• Consider sedation • If narrow-complex, consider adenosine

↓ No

Wide QRS? ≥ 0.12 s	Yes →	• IV access and 12-lead ECG if available • Consider adenosine only if regular and monomorphic • Consider antiarrhythmic infusion • Consider expert consultation

↓ No

• IV access and 12-lead ECG if available
• Vagal manoeuvres
• Adenosine (if regular)
• Â-blocker or Ca-channel blocker
• Consider expert consultation

Doses and details

Synchronised cardioversion
• Initial recommended doses:
• Narrow regular: 50 J to 100 J
• Narrow irregular: 120 J to 200 J biphasic or 200 J monophasic
• Wide regular: 100 J
• Wide irregular: defibrillation dose (NOT synchronised)

Adenosine IV dose:
First dose: 6 mg rapid IV push, flush with saline
Second dose: 12 mg if required

Antiarrhythmic infusions for stable wide-QRS-complex tachycardia

Procainamide IV dose:
20 mg min^{-1} to 50 mg min^{-1} until arrhythmia suppressed, hypotension ensues, QRS duration increases > 50%, or maximum dose 17 mg kg^{-1} given.
Maintain infusion: 1 mg min^{-1} to 4 mg min^{-1}
Avoid if prolonged QT or CHF

Amiodarone IV dose
First dose: 150 mg over 10 min
Repeat as needed if ventricular tachycardia recurs.
Follow by maintenance infusion of 1 mg min^{-1} for first 6 h

Sotalol IV dose
100 mg (15 mg kg^{-1}) over 5 min.
Avoid if prolonged QT

Figure 3 Cardioversion (electrical and pharmacological) for tachycardia in adults

Electrical (pacing) and pharmacological management of bradycardia in adults (Figure 4)
This is the treatment of choice when a patient has a *symptomatic bradycardia* with signs of poor perfusion. Many manufacturers of *defibrillators now include pacing mode* in manual devices. Practitioners must be familiar with the indications, techniques, and hazards of TCP.

The indications for TCP are as follows:
• Haemodynamically unstable bradycardia

- In the setting of acute coronary syndrome (ACS):
  - o Symptomatic sinus bradycardia
  - o Mobitz type II second-degree AV block
  - o Third-degree AV block
  - o New or alternating bundle branch block or bifascicular block
- Bradycardia with symptomatic ventricular escape
- Overdrive pacing of refractory tachycardias

Precautions when using TCP:
- *Contraindicated* in hypothermia and asystole
- Sedation and analgesia may be indicated.
- The carotid pulse is unreliable to confirm mechanical capture.

Steps of TCP
- Place pacing *electrodes* according to package instructions.
- Switch to *pacing mode.*
- Set demand *rate to 60 min^{-1}*. External pacemakers have either fixed rates (asynchronous pacing) or demand rates.
- Increase the *current output* stepwise and set it at 2 mA above the dose at which consistent capture is observed.
- *Confirm mechanical capture* by detecting a reliable peripheral pulse or by pulse oximetry
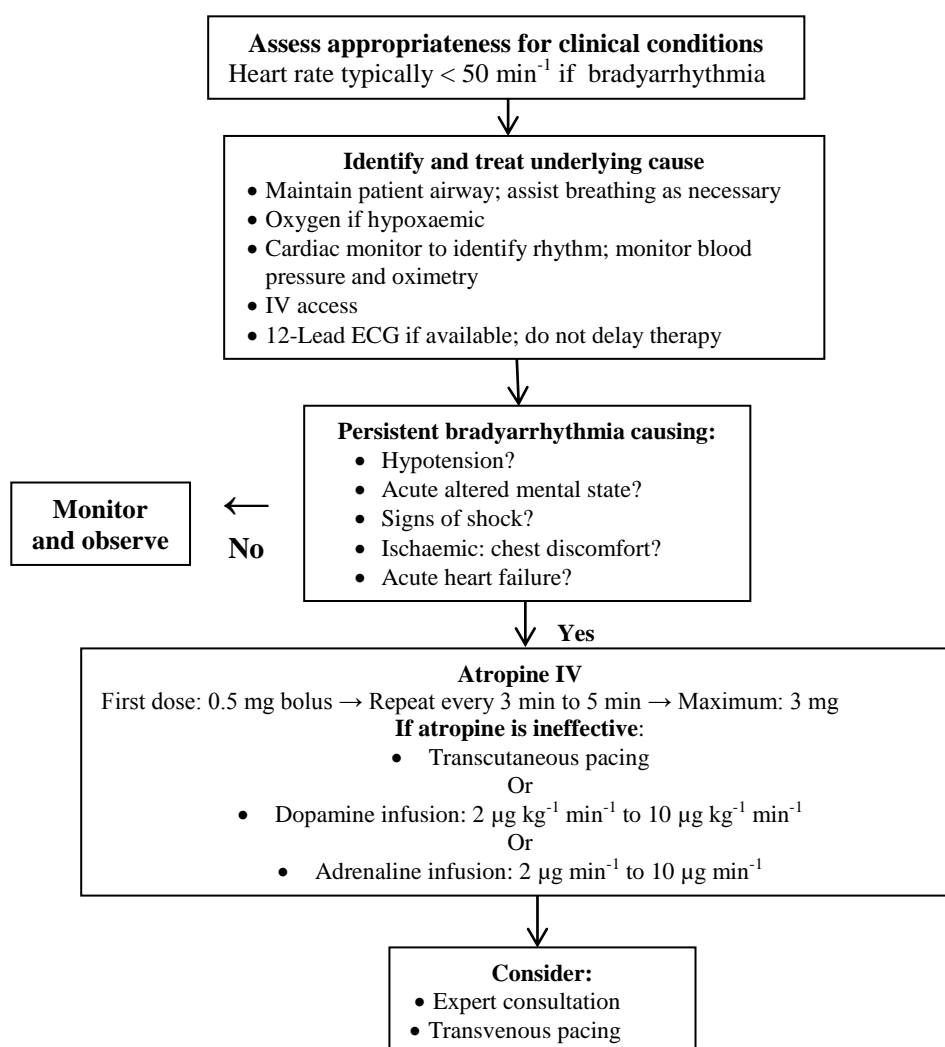
Figure 4 Electrical and pharmacological management of bradycardia with pulse in adults

Perioperative cardiac arrest: Anaesthesiology perspective
Cardiac arrest during anaesthesia is a *rare event*, but is *distinct from SCA in other settings*. It is *usually witnessed* and often anticipated. The *respons*e to an arrest is also prompt and focused. *Outcome* is fortunately markedly better, which can be attributed to detailed *knowledge* about the patient as well as resources available in the theatre environment.

Common Perioperative causes of cardiac arrest
- *Attributable directly to anaesthesia*
  - *Intravenous or inhalant overdose*
  - High neuraxial block
  - Drug administration errors
  - Pharmacogenetic disease e.g. malignant hyperthermia
- Respiratory
  - *Hypoxemia*
  - Auto PEEP
  - Bronchospasm.
  - Tension pneumothorax
- *Cardiovascular*
  - *Hypovolaemia*
  - Reflexes, e.g. vasovagal reflex, oculo-cardiac, traction of intestines, dilatation of orifices
  - Tension pneumothorax
  - Anaphylaxis, transfusion reaction (see Chapter 12)
  - Electrolyte imbalance (particularly potassium)
  - Severe pulmonary hypertension
  - Increased intra-abdominal pressure
  - Pacemaker failure
  - Prolonged QT syndrome
  - Acute coronary syndrome (ACS)
  - Pulmonary embolism
  - Gas embolism
  - Electroconvulsive therapy
- *Cardio-pulmonary interaction*

Cardio-pulmonary interaction must be kept in mind as a cause of cardiac arrest. Ventilatory support should aim to ensure adequate oxygenation and practitioners must adhere to the principles of lung protective ventilation (Chapter 4); the *smallest tidal volumes and lowest rates* must be used. *Overzealous ventilation* is a frequently overlooked contributing factor to perioperative circulatory compromise. This can exacerbate the haemodynamic compromise. This is particularly true for patients suffering from *obstructive lung disease*. In these patients, the wrong ventilatory mode can prevent adequate expiration (*auto-PEEP*). Auto-PEEP increases *intrathoracic pressure*, which prevents cardiac filling. The elimination of auto-PEEP leads to rapid improvement, and should be among the first considerations in patients with an unstable circulation. The cardio-pulmonary interaction also *explains cardiac arrest caused by a tension pneumothorax.*

Pre-arrest (pre-emptive) management of cardiac arrest (rescue)
SCA in the perioperative period *typically occurs as a consequence* of a *progression of either hypoxemia or a circulatory process. Failure to recognize such a progression, or to pre-empt an arrest ("rescue") is an all too common "cause" of perioperative cardiac arrest. Therefore, a*naesthetists must have a clear *understanding* of how to *identify* a crisis and must *act promptly and appropriately.* Hypoxia and its causes are discussed in Chapter 14.

Management of intraoperative cardiac arrest (Figure 5):
- Inform the surgeon. If possible, all surgery should be stopped.
- Place the theatre table in Trendelenburg position.

- Stop all anaesthetic drugs.
- Ventilate with 100% oxygen.
- Initiate BLS/ACLS resuscitation.
- Seek reversible causes of cardiac arrest.

Escalating care

When increasing care is becomes necessary to maintain cardio-respiratory function, one should give serious consideration to escalating the level of monitoring simultaneously. Time-consuming insertion of arterial and central venous catheters will assist in monitoring the unstable patient and guide treatment. ***However, the placement of these monitors should NOT take precedence over supportive measures***.

Care after cardiac arrest (Figure 6)

A new addition to the 2010 AHA Guidelines is an algorithm that focuses on continued stepwise care after return of spontaneous circulation (ROSC). The goal is improvement of patient survival and quality of life. The major contributors to early mortality (usually within the first 24hours) are cardiovascular instability and brain injury.

In the general adult population, the most common cause of cardiac arrest is cardiovascular disease and myocardial ischaemia. These conditions per se contribute to mortality, even after ROSC. Therefore, it is importance to *exclude and promptly treat acute coronary syndromes*.

The only intervention that have been demonstrated to improve neurological outcome is therapeutic hypothermia (32°C to 34°C), and this must be considered in all patient unable to follow verbal commands following ROSC (Figure 7).

The main components of care after ROSC are:
- *Escalation of monitoring and care*, i.e. invasive monitoring and intensive care admission
- Targeted temperature management, namely therapeutic hypothermia (32°C to 34°C)and management of pyrexia
- Goal-directed organ specific evaluation and support, e.g. cardiovascular, pulmonary, and renal support in the critical care setting.
- Goal directed application of *cardiovascular drugs*: mean arterial pressure of 65mmHg and a central venous oxygen saturation of at least 70%
- Targeted *medical management* e.g. glucose control
- *Seizure* control
- *Prognostication* by means of expert neurological assessment and imaging, e.g. brain SPECT

Organ preservation for donation and transplant

Shout for help/activate emergency response

Start CPR
- Give oxygen
- Attach monitor/defibrillator

Return of spontaneous circulation

Check rhythm **If VT/VF Shock**

2 minutes

Continuous CPR

Continuous CPR

Drug therapy
IV/IO access
Adrenaline every 3 min to 5 min
Amiodarone for refractory VT/VF

Consider advanced airway
Quantitative waveform capnography

Treat reversible causes

Monitor CPR quality

Post-cardiac arrest care

- **CPR quality**
- Push hard (5 cm) and fast (> 100 min^{-1}) and allow complete chest recoil.
- Minimize interruptions in compressions.
- Avoid excessive ventilation.
- Rotate compressor every 2 minutes
- If no advanced airway, 30:2 compression-ventilation ratio.
- Quantitative waveform capnography: If $PECO_2 < 10$ mm Hg, attempt to improve CPR quality.
- Intra-arterial pressure: If relaxation phase (diastolic) pressure < 20 mm Hg, attempt to improve CPR quality.

Return of spontaneous circulation
- Pulse and blood pressure
- Abrupt increase in $PETCO_2$ (typically ≥ 40 mm Hg)
- Spontaneous arterial pressure waves with intra-arterial monitoring

Shock energy
- **Biphasic:** manufacturer recommendation (120 J to 200 J); if unknown, use maximum available. Second and subsequent doses should be equivalent, and higher doses may be considered.
- **Monophasic:** 360 J

Drug therapy
- Adrenaline IV/IO dose: 1 mg every 3 min to 5 min
- Vasopressin IV/IO dose: 40 U can replace first or second dose of adrenaline
- Amiodarone IV/IO dose: First dose: 300 mg bolus. Second dose: 150 mg

Advanced airway
- Supraglottic advanced airway or ET intubation
- Waveform capnography to confirm and monitor ET tube placement
- 8 to 10 breaths per minute with continuous chest compressions

Reversible causes
- Hypovolaemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo/hyperkalaemia
- Hypothermia
- Tension pneumothorax
- Tamponade (cardiac)
- Toxins
- Thrombosis (pulmonary)
- Thrombosis (coronary)

Figure 5 Management of intraoperative cardiac arrest in adults (New Circular ACLS algorithm)

```
┌─────────────────────────────────────────┐
│      Return of spontaneous circulation    │
└─────────────────────────────────────────┘
                    │
                    ▼
┌─────────────────────────────────────────────────────┐
│         Optimise ventilation and oxygenation          │
│  • Maintain oxygen saturation ≥ 94%                   │
│  • Consider advanced airway and waveform capnography  │
│  • Do not hyperventilate                              │
└─────────────────────────────────────────────────────┘
                    │
                    ▼
┌─────────────────────────────────────────┐
│    Treat hypotension (SBP < 90 mm Hg)     │
│  • IV/IO bolus                            │
│  • Vasopressor infusion                   │
│  • Consider treatable causes              │
│  • 12-lead ECG                            │
└─────────────────────────────────────────┘
                    │
                    ▼
```

Consider induced hypothermia ◄── No ── **Follow commands?**

Coronary reperfusion ◄── Yes ── **STEMI** Or High suspicion of **AMI** ── No ──► **Advanced critical care**

Doses/Details

Ventilation/Oxygenation
Avoid excessive ventilation
Start at 10 to 12 breaths per minute and titrate to target $PETCO_2$ of 35 mm Hg to 40 mm Hg
When feasible, titrate FiO_2 to minimum necessary to achieve $SpO_2 \geq 94\%$

IV Bolus
1 to 2 L Ringer lactate.
If inducing hyperthermia, may use 4°C fluid.

Adrenaline IV infusion
0.1 $\mu g\ kg^{-1}\ min^{-1}$ to 0.5 $\mu g\ kg^{-1}\ min^{-1}$ (in 70 kg adult: 7 $\mu g\ min^{-1}$ to 35 $\mu g\ min^{-1}$)

Dopamine IV infusion
5 $\mu g\ kg^{-1}\ min^{-1}$ to 10 $\mu g\ kg^{-1}\ min^{-1}$

Noradrenaline IV infusion
0.1 $\mu g\ kg^{-1}\ min^{-1}$ to 0.5 $\mu g\ kg^{-1}\ min^{-1}$ (in 70 kg adult: 7 $\mu g\ min^{-1}$ to 35 $\mu g\ min^{-1}$)

Reversible causes

- Hypovolaemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypo/hyperkalaemia
- Hypothermia
- Tension pneumothorax
- Tamponade (cardiac)
- Toxins
- Thrombosis (pulmonary)
- Thrombosis (coronary)

Figure 6 Care after cardiac arrest

```
┌─────────────────────────────────────────────┐
│ Post-cardiac arrest coma patient admitted to │
│ ICU                                          │
│ Cisatracurium bolus of 0.1 mg kg⁻1 followed  │
│ by infusion 0.1 mg kg⁻1 h⁻1                  │
└─────────────────────────────────────────────┘
```

Post-cardiac arrest coma patient admitted to ICU Cisatracurium bolus of 0.1 mg kg^{-1} followed by infusion 0.1 mg kg^{-1} h^{-1}

Apply BIS sensor

Aberrant EEG waves or disproportionately high SR percentage for the BIS

BIS < 40

BIS 40 to 60

BIS > 60 with SR

Start remifentanil 6 µg kg^{-1} h^{-1}

Start remifentanil 6 µg kg^{-1} h^{-1} and lowest dose of propofol to maintain values in this range

Request urgent EEG. If electrical seizures or status epilepticus, start specific treatment

After 12 h to 24 h of treatment, discontinue hypothermia and allow a slow controlled rewarming. At 36ºC, stop cisatracurium. When TOF > 0.9, stop propofol. Start to decrease remifentanil slowly to permit neurological evaluation.

Figure 7 Therapeutic hypothermia after cardiac arrest

Bibliography and suggested reading

1. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science. Circulation. 2010 Nov; 122(18): S639.
2. Braz LG, Modolo MS, Do-Nascimento P, et al. Perioperative Cardiac Arrest: a study of 53718anesthetics over 9 years from a Brazilian teaching Hospital. BJA. 2006 March 24; 96(5): 569-57.
3. Mhyre JM, Ramachandran SK, Kheterethal S, et al. Delayed time to Defibrillation after intraoperative and periprocedural cardiac arrest. Anesthesiology 2010 October; 113(4): 782-93.
4. Sprung J, Flick RP, Gleich SJ, Weinganen TN. Perioperative Cardiac Arrests. Signa Vitae 2008; 3(2): 8-12.
5. Odendaal CL. Cardiopulmonary-cerebral resuscitation. S Afr J AnaesthAnalg 2010; 16(2); 45-60.
6. McGlinch BP, White RD. Cardiopulmonary Resuscitation: Basic and Advanced Life Support. In: RD Miller et al, editors. Miller's Anesthesia. 7th Edition.
7. Respiratory Physiology and Anesthesia. In: GE Morgan et al. Clinical Anesthesiology. 4th Edition.
8. Chamorro C et al. Therapeutic Hypothermia after Cardiac arrest: A systematic review. AnesthAnalg 2010; 110: 1328-35.
9. Michard F. Changes in Arterial Pressure during Mechanical Ventilation. Anesthesiology 2005; 103: 419-28.

CHAPTER 16

ANAESTHESIA, THE KIDNEY, AND THE LIVER

Key points
Anaesthesia and the kidney
- Physiology of urine production
- Pathogenesis of acute perioperative renal failure
- Preoperative approach to the patient at risk to develop kidney injury
- Factors aggravating renal dysfunction
- Effects of anaesthesia and surgery on renal function
- Choice of anaesthetic technique and intraoperative considerations
- Perioperative monitoring of renal function
- Approach to intraoperative oliguria

Anaesthesia and liver disease
- **Functions of the liver**
- Splanchnic and liver blood flow, regulation of liver perfusion
- The liver and intermediary metabolism

- Coagulation
- Haem and bilirubin metabolism
- Erythropoiesis
- Endocrine function
- Immune and inflammatory responses
- Pharmacokinetics: Xenobiotic clearance (See you pharmacology lectures)
- Multisystem complications of liver disease
- Assessment of Liver Dysfunction
- Intraoperative management of patients with liver failure
- Postoperative management of the patient with liver failure
- Post-operative jaundice

In this chapter, the interactions between anaesthesia, surgery, kidney disease, and liver disease are discussed. As is the case with other organ systems, the student must always keep in mind the anatomy, physiology, pharmacology, and monitoring of these systems. Further, if you detect an abnormality in one organ system, it will usually have multiorgan effects. The kidneys and liver play a pivotal role in body function and dysfunction contributes significantly to perioperative morbidity and mortality.

ANAESTHESIA AND RENAL DISEASE[19]

Perioperative acute renal failure (ARF) is a significant complication associated with anaesthesia and surgery. Perioperative ARF accounts for more than half of all patients requiring acute haemodialysis. The mortality rate for perioperative ARF remains high, ranges from 20% to 80%, depending on comorbidities (other diseases), e.g. ischaemic heart disease, hypertension, diabetes mellitus, etc.). Although perioperative ARF can result from multiple causes, *over 90% of cases are associated with relative hypovolaemia and renal ischaemia.*

The *meaning of relative hypovolaemia* is a low cardiac output due to a large vascular capacity or space (vasodilatation, vasoplegia) and/or the correct or excessive volume but inability to pump it to where it is needed (*cardiac failure*) and/or insufficient vascular conduits (*peripheral vascular disease*). In *relative hypovolaemia*, the patient has a normal or large volume (*absolute hypervolaemia*) but the *volume is maldistributed or afunctional.* For the current discussion, the term *vasodilatation* refers to *pharmacological* (exogenous) vasodilatation, as well as *pathological vasodilatation* due to processes such as anaphylaxis (see Chapter 12) and septic shock (endogenous).

Oliguria may be the *first intraoperative clinical sign of renal hypoperfusion.* Although oliguria is a *normal protective response* to conserve sodium and water in acute hypovolaemia, there is a *narrow window of about 30 minutes to 60 minutes* between the onset of protective oliguria and the *start of ischemic acute tubular necrosis* (ATN). The progression to ATN is even *shorter in pre-existing renal impairment*, and exposure to toxins (e.g. radiocontrast, myoglobinuria, and haemoglobinuria), or sepsis. Therefore, patients who are at risk to develop ATN must be identified preoperatively in order to prevent further deterioration.

(*For a comprehensive list of prerenal, renal, and postrenal causes of acute renal failure, revise your internal medicine notes. All these causes are encountered in the perioperative setting. In this lecture, the scenarios or factors, which the anaesthetist must contend with very often, are highlighted.*)

Physiology of urine production
Renal perfusion and glomerular filtration
The *normal basal renal blood flow (RBF)* is 300 ml 100 g^{-1} min^{-1} to 500 ml 100 g^{-1} min^{-1} (1000 ml min^{-1} to 1250 ml min^{-1}), which is more than in most other organs (the brain receives about 50 ml 100 g^{-1} min^{-1} and the heart 70 ml 100 g^{-1} min^{-1}). Therefore, the *oxygen supply to the kidneys greatly exceeds their consumption*. (This explains why oxygen saturation in the inferior vena cava blood is higher than in the superior vena cava.) All blood passes though glomeruli. About 10% of RBF is filtered, resulting in an *average* glomerular filtration rate (GFR) of approximately 125 ml min^{-1}; this figure reflects mainly the perfusion of the cortical glomeruli since the inner medulla and papilla receive only about 10% of the RBF.

The cortex contains most of the glomeruli, and receives more than 90% of the RBF. This ensures glomerular filtration and reabsorption of solute. Blood flow to the medulla (vasa recta from the juxta medullary nephrons) is lower (5% to 10%) to preserve the osmotic gradient necessary to concentrate urine. The *medullary thick ascending limbs* of the loops of Henle (MTAL) are metabolically very active (reabsorption and secretion). The PO$_2$ in the cortex is about 55 mm Hg and 10 mm Hg in the medulla. In the cortex, the oxygen extraction ratio (oxygen consumption/delivery) is 0.2, but 0.8 in the medulla. Therefore, the MTALs of the loop are exceptionally sensitive to hypoxic injury.

The heterogeneity of intrarenal perfusion and metabolic rate (cortex vs. medulla) contributes to the pathophysiology of ischemic ARF. The balance between cortical and medullary perfusion is maintained by intrarenal vasoconstrictors (angiotensin, vasopressin, noradrenaline (NA), PGF$_2$, thromboxane A$_2$) and vasodilators (NO, PGE$_1$, PGE$_2$, dopamine, adenosine). An imbalance between the vasoconstrictors and -dilators impairs the already precarious medullary blood flow. In the outer medulla, where the metabolically active MTALs are, hypoxia causes tubular and endothelial oedema and adherence of neutrophils. This causes congestion, which aggravates ischaemia.

With decreased RBF (ischaemia), a series of systemic and renal compensatory responses preserve GFR. When RBF decreases to < 50% for at least 40 to 60 minutes, the GFR decreases relatively more than RBF; GFR decreases to < 5% of normal at a RBF of 25% to 50% of normal. Once tubular pathology has occurred, GFR remains low.

Autoregulation of renal blood flow
RBF is, as is the case in other vital organs, such as the brain and heart, influenced by *autoregulation*. That means that at mean arterial pressures of between 80 mm Hg and 180 mm Hg RBF is maintained at about 300 ml 100 g^{-1} min^{-1} and GFR at about 50 ml min^{-1}. The opposite occurs with hypotension. If the blood pressure decreases, activation of several vasoconstrictors and salt- and water-conserving mechanisms are activated. In *hypertensive patients*, the autoregulatory plateau in vital organs shifts to the right (see Chapter 12).

Renal autoregulation is governed by three mechanisms, namely the tone in the afferent arterioles, tone in the efferent arterioles, and hormonal and neural (sympathetic) responses:

* *Afferent arteriolar dilation* increases the proportion of cardiac output that perfuses the kidney. The afferent arterioles react to reductions in blood pressure by vasodilatation. This property represents a relaxation response or *myogenic reflex*.
* The kidney also possesses a *tubuloglomerular feedback* system (TGF):
  ↑ blood pressure → ↑ GFR → ↑ *delivery of NaCl to the macula densa* cells of the thick ascending loop in the juxta-glomerular apparatus → *vasoconstriction of the afferent* arteriole → ↓ RBF → ↓ GFR. However, a *decreased NaCl delivery to the macula densa* in the cortical portion of the thick ascending loop of Henle results in *relaxation of the afferent* arteriole, which improves the GFR. TGF is disturbed in insulin-dependent diabetics and in patients receiving ACEIs.
* The macula densa *also responds to a reduced NaCl delivery by stimulating renin secreting renin* from the granular cells of the juxta-glomerular apparatus response. This is followed by the formation of angiotensin II (AII), which increases afferent efferent arteriolar resistance.[xvi] Therefore, if *NaCl delivery* to the juxta-glomerular apparatus *decreases afferent and efferent arteriolar resistance increases*. An increase in afferent and efferent arteriole resistance decreases glomerular plasma flow *but GFR is preserved*. The high renal vascular resistance contributes to the maintenance of systemic blood pressure without compromising filtration. At low concentrations, NA constricts efferent arterioles (sympathetic NS).
* *Hormonal and neural responses* improve renal perfusion pressure by increasing intravascular volume, indirectly increasing cardiac output.

Remember, urine *production is not dependent on autoregulation,* since a urinary flow is linked to the hydrostatic pressure in the peritubular capillaries; the higher the pressure, the less the reabsorption of water and the higher the urine flow, and vice versa. Therefore, oliguria responds to an increase in blood pressure. *This is called pressure diuresis*.

Autoregulation is disrupted by angiotensin converting enzyme inhibitors (ACEIs), cyclooxygenase inhibitors, anaesthetic agents, sepsis, acute renal failure (ARF), and cardiopulmonary bypass. *The common factor* in all these insults is *a decrease in perfusion* during *hypotension*. Renal perfusion is restored in all these conditions if blood pressure is restored – even if

---

[xvi] Please note: AII constricts both afferent and efferent arterioles – not the efferent arteriole only, as has been thought previously.

vasoconstrictors are used to increase blood pressure. Remember, all organs that have lost blood flow autoregulation, *become strictly dependent on blood pressure* to maintain organ perfusion (brain, heart, liver, kidney, etc.). *Therefore, the notion that flow is more important than blood pressure is misleading, since flow is determined by pressure and resistance (the two components of autoregulation).*

An increase in cardiac output increases renal blood flow (RBF) – *if the blood pressure is lower than the autoregulatory limits in the renal artery.* This means that an *increased cardiac output accompanied by hypotension, e.g. septic shock, is accompanied by a decreased RBF, decreased GFR, and oliguria.*

Formation of urine and clearance
Clearance of waste products by the kidneys is determined by their delivery to the kidneys (*renal blood flow*) and the ability of the kidneys to remove them from the blood (*glomerular filtration*). *The formation of urine* depends on RBF (cardiac output, autoregulation, intrarenal cortico-medullary distribution), glomerular filtration rate (GFR), tubular function (reabsorption and secretion), and *urine effluent*. All these functions are influenced by the autonomic nervous system, as well as endocrine, paracrine and autocrine substances. Obstruction in flow of urine from the kidney to the bladder increases tubular pressure and pressure in the Bowman capsule, which decreases GFR.

GFR depends on the hydrostatic pressure in the glomerular capillaries (Pgc), the pressure in the capsule of Bowman (Pcb), and the oncotic pressure in the plasma (Ppo). These factors represent the Starling forces that determine the hydrostatic forces across the glomerular-capsule membrane: $GFR = Kf \times (Pgp - Pcb - Ppo)$
Kf is the glomerular filtration coefficient. It is an indication of the integrity of the glomerular basement membrane, namely permeability and surface area. An increase in cardiac output increases renal blood flow (RBF) and Pgp.

Theoretically, the effects of varying concentrations of plasma proteins (Ppo) may influence GFR and urine production. Therefore, a low Ppo will cause an increased GFR and vice versa. However, an increase in plasma protein (albumin) maintains intravascular blood volume and consequently, cardiac output. Therefore, the volume effect of an increased Ppo offsets its antidiuretic effect. Obstruction distal to the kidney increases intratubular pressure and pressure in the Bowman capsule, which decreases glomerular filtration.

In an adult, the glomeruli filter about 180 L day^{-1} of which about 99% is reabsorbed and 1% (1 L to 2 L) is excreted as urine. A minimum daily urine volume (solvent) of 400 ml to 500 ml is required to clear nitrogenous waste products (solute). The *counter current multiplier system* in the loop of Henle plays a critical role in the conservation of water and sodium and thereby concentrating the tubular fluid and urine and is dependent on the effect of vasopressin on the distal convoluted tubules and collecting ducts. The *counter current diffusion* system is dependent on blood flow in the long medullary vasa recta (and therefore on RBF and autoregulation) and is responsible for the movement of solute (mainly urea) out of the interstitium into the descending vasa recta and water from the descending vasa recta into the interstitium. Water reabsorbed from the descending loop of Henley and collecting ducts is mopped up by the ascending vasa recta.

The *major hormonal factors determining conservation of filtered salt and water* are aldosterone, antidiuretic hormone, atrial natriuretic peptide, and prostaglandins. A *low* concentration of sodium in the thick ascending tubule *stimulates* its *macula densa* cells (chemoreceptors), which stimulates the *granular cells* of the afferent arterioles to secrete *renin*. Renin catalyses the formation of *angiotensin I* from angiotensinogen (from the liver). *AII* is split from angiotensin I by *angiotensin-converting enzyme* (ACE) in the lungs.

AII causes vasoconstriction of both the afferent and efferent arterioles, resulting in a decrease in renal perfusion and GFR. Angiotensin II also stimulates the production of *aldosterone by the adrenal cortex. Aldosterone* stimulates reabsorption of sodium, which is follow by chloride and water in the distal tubule and collecting ducts. Remember that angiotensin II does not only affect renal function, but has wide-spread effects (heart, brain, autonomic nervous system, etc. It is also responsible for endothelial senescence via its stimulation of oxygen free radical production.

Vasopressin increases blood volume, deceases plasma osmolality, decreases urine production, and increases urine osmolality (See also Chapter 17).

Vasopressin (antidiuretic hormone) is released from the posterior hypophysis in response to increased blood osmolality (hypothalamic *osmoreceptors*), hypovolaemia and hypotension (*volume and baroreceptors* in the atria, aorta arch, and carotid sinuses), hypercapnia, and stress (it is a *stress hormone*). The plasma osmolality threshold for the secretion of vasopressin is about 280 mOsm kg^{-1}. It works mainly on the *collecting ducts* (V_2 receptors) where it increases *reabsorption of water*. It also enhances the reabsorption of NaCl from the thick ascending loop of Henle. This contributes to the maintenance of a hypertonic medulla and movement of water out of the collecting ducts (*counter current multiplier*).

Atrial natriuretic peptide (ANP) causes systemic vasodilatation and promotes renal excretion of sodium and water by increasing glomerular filtration. ANP maintains urine production in patients with cardiac failure (hypervolaemia). *ANP can be regarded as the endogenous ACEI.* This explains the decreased urine production when intracardiac pressure decreases, e.g. after cardiac valve replacements.

Natriuretic peptide is secreted by the cardiac atria (Type A), brain (Type B), and endothelium of large blood vessels (Type C) in response to increased intracardiac and vascular volume. *Natriuretic peptide has the following effects:*

- It *decreases systemic blood pressure* by *relaxing vascular smooth muscle* (antagonizes endothelin), *reducing sympathetic stimulation* (competitive antagonist of NA, non-competitive antagonist of angiotensin II), and *decreasing renin secretion*, and by inhibiting the release of *aldosterone* from the adrenal cortex.
- *ANP (and the synthetic anaritide)* improves GFR by dilating afferent while constricting efferent arterioles.
- It blocks *tubular reabsorption of sodium and chloride*.
- It inhibits *redistribution of renal medullary blood flow.*
- ANP *inhibits vasopressin* secretion, its effect on V2 receptors in the collecting ducts.
- ANP *inhibits the reabsorption of NaCl* from the medullary collecting ducts (*anti-aldosterone effect*).

The kidneys produce *prostaglandins*. They are autocrine substances, produced in small amounts, and have local short-lived effects. *They are renal protective mainly by vasodilatation* of the juxta medullary arteries and maintenance of the inner cortical blood flow. Prostaglandins are synthesized from tissue phospholipid (Figure 1). The production of vasodilatory prostaglandins PGD_2, PGE_2, and PCI_2 is stimulated by an adequate oxygen supply, while the production of the vasoconstrictive prostaglandins is enhanced by a lack of oxygen. During haemodynamic instability and *adrenergic stimulation, PGE_2 decreases the vasoconstrictive effect of AII on the afferent arterioles and maintains RBF*. Inhibition of prostaglandin production during normal hydration, perfusion, and sodium balance does not affect renal function. However, *during vasoconstriction* (hypovolaemia, hypotension) renal prostaglandins are essential for preserving adequate renal perfusion. Since nonsteroidal anti-inflammatory drugs (*NSAIDs*) inhibit cyclooxygenase activity, and thereby make the *afferent arteriole* susceptible to the systemic vasoconstrictive effect of AII and catecholamines, *they impair kidney perfusion during hypoxia* (hypoperfusion, hypoxaemia, and anaemia).

Dopamine contributes to blood pressure control through its vasodilatory and natriuretic effects. However, *evidence is lacking* that *diuretic doses* of dopamine (and the synthetic D_1 agonists) improves outcome of oliguria. *Inotropic and vasoconstrictive doses* of dopamine increase cardiac output, blood pressure, and RBF. These can promote urine production.

Dopamine binds to D_1 and D_2 receptors. D_1 receptors occur in the splanchnic and renal vessels, but also in proximal tubule and MTAL and are stimulated by dopamine and synthetic agonists, dopexamine and fenoldopam. Stimulation of D_1 receptors causes renal vasodilatation (increased RBF and GFR). D_1 receptor stimulation inhibits the Na^+-H^+ antiporter in the proximal tubule Na^+-K^+ ATPase and in the MTAL. It decreases the sodium-retaining effect of NA and A II. D_2 *receptors* occur presynaptically in postganglionic sympathetic nerves where their stimulation inhibits releases of NA. This causes vasodilatation and explains the hypotensive effect of dopamine at low doses (1 μg kg^{-1} min^{-1} to 3 μg kg^{-1} min^{-1}). D_2 stimulation enhances D_1 effects.
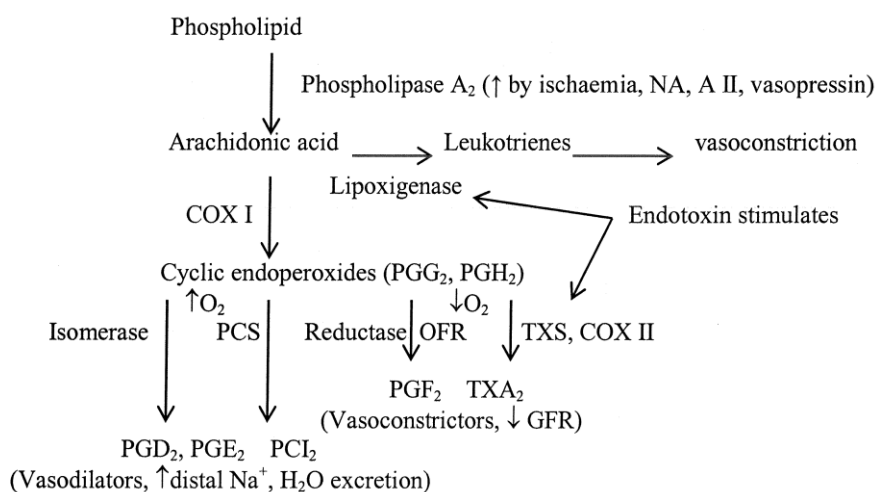
Figure 1 Renal prostaglandin (PG) synthesis. The vasodilatory PGs are formed in the presence of adequate perfusion and O_2, oppose the effect of AII, NA and vasopressin, and protect the kidneys from ischaemia. The vasoconstrictor PGs are formed during hypoxia and ischaemia. COX I Cyclooxygenase I, PCS Prostacyclin synthetase; OFR Oxygen free radicals, oxidative stress; COX cyclooxygenase; TXS thromboxane synthetase; PCI_2 Prostacyclin; TXA_2 Thromboxane A_2.

Pathogenesis of acute perioperative renal failure

Acute intraoperative oliguria or anuria is usually caused by renal ischaemia (*prerenal oliguria*). Other intraoperative causes are pathology distal to the renal pelvis; including trauma and catheter obstruction (always exclude this cause). The causes of acute perioperative renal failure are summarized in Table 1.

Table 1 Aetiology of acute perioperative renal failure

Cause	Aetiology	Examples
Prerenal (ischaemia)	↓ Preload	• Absolute hypovolaemia: Haemorrhage • Dehydration: gastrointestinal, skin (scalded skin syndrome, burns), kidney (diuretics, glucosuria, ethanol), exposure of organ cavities (thorax, abdomen). • Redistribution (trauma, sepsis, burns), • Relative hypovolaemia: Vasodilatation (sepsis, cirrhosis, anaphylaxis), vasodilators (glyceryl trinitrate, anaesthetic drugs) • Decreased venous return: Positive pressure ventilation, pulmonary embolus, atrial fibrillation, cardiac tamponade, tension pneumothorax
	↓ Cardiac pump	Myocardial ischemia, dilated cardiomyopathy, dysrhythmia, valvular abnormality, negative inotrope (β blocker, calcium channel blocker, **anaesthetic drugs**)
	↓ Renal BP despite normal preload and heart function	Acute renal arterial obstruction (thrombosis, embolus, dissecting aortic aneurysm, and cross-clamping of the aorta).
	↓ Renal autoregulation	• Vasodilator prostaglandins (NSAIDs) • Afferent and efferent balance (ACEIs) • DA_2 receptors (metoclopramide administration). • Mean BP < 80 mm Hg
Intrinsic	Acute tubular necrosis	Prolonged prerenal events Nephrotoxins: days after aminoglycosides, hours after radiocontrast, pigment (myoglobinuria, haemoglobinuria)
	Vasculitis or acute glomerulonephritis	• Underlying disease process: SLE, scleroderma, post-streptococcal • Malignant hypertension • Preeclampsia
	Interstitial nephritis	• Allergic: methicillin, NSAIDs, captopril • Infection: bacterial acute pyelonephritis, viral (CMV), fungal Candida) • Cancer: lymphoma, leukaemia
Postrenal	Obstruction	Stones, ureters, catheter are the least common, but easiest to treat.

Acute prerenal renal failure progresses to *acute tubular necrosis* (vasomotor nephropathy, or ischemic tubular injury). Ischaemic kidneys are more vulnerable in the presence of pre-existing disease (diabetes mellitus, autoimmune disease), nephrotoxic agents (altered intrarenal blood distribution and autoregulation), and certain procedures (cardiovascular, liver, kidney, intravascular radiocontrast).

Tubular injury is the most common cause of perioperative acute renal failure and is often initiated by renal ischaemia (*prerenal uraemia*). Brief (*hours to days,* depending on premorbid function) renal ischaemia usually cause *reversible renal failure (oliguria)* but prolonged severe ischaemia causes widespread necrosis with *irreversible failure (ATN with often abrupt anuria)*. This leads to *retention of water and nitrogenous end products, as well as disruption of electrolyte and acid-base balance*. This occurs at a *GFR < 15 ml min^{-1}* and renal replacement therapy (dialysis) is the only therapeutic option.

It is important to *distinguish between acute and chronic renal failure*. Most patients with *acute renal failure* presenting for surgery are critically ill. Acute renal failure can be *pre-renal* (dehydration, decreased perfusion), *renal* (intrinsic renal disease, drugs, etc.), or *postrenal* (obstruction of both ureters, bladder outlet). However, whether the cause of renal failure is prerenal or post renal, they eventually lead to intrinsic renal pathology, while intrinsic renal failure has prerenal complications (cardiac failure, hypertension, uraemic pericarditis, hypervolaemia, pulmonary oedema, biochemical disturbances, anaemia, thrombocytopathy, and neuropathy). If left untreated, acute renal failure is fatal if patients do not receive renal replacement therapy (dialysis).

Early ischaemic changes (***within about 30 minutes of renal ischaemia***) are reversible. Within an hour

of ischaemia, the proximal tubular brush border starts to slough, and cell membrane bullae obstruct the proximal tubules. After hours of ischaemia, tubular pressure rises and passive retrograde flow starts. After a day, casts obstruct the distal tubules.

Renal ischaemia (read, hypotension) must not be tolerated since GFR does not improve immediately if RBF is not restored within one to two hours. This vulnerable period is shorter in cells with a high oxygen demand, but with an already perilous oxygen demand-supply ratio, i.e. the MTAL cells. Temporarily, oliguria may protect against ARF. Renal ischaemia is not necessarily accompanied by oliguria initially. On the contrary, *a diuresis may herald olig- or anuria since the failing tubules do not absorb fluid anymore*. ***The impact of ischaemia on the vulnerable medulla can be attenuated if the oxygen content (haematocrit and SaO$_2$) is increased.***

Preoperative approach to the patient at risk to develop kidney injury
Pre-existing renal disease is the most important predictor of perioperative ARF. *Non-end-stage renal impairment* is very common in patients presenting for all types of surgery – from minor to major surgery. The anaesthetist must *identify co-morbidities* in the patient, identify kidney-damaging procedures, avoid administration of nephrotoxins, and take steps to attenuate the effects of these insults. These patients may suffer from chronic co-morbidities complicated by renal failure, e.g. the elderly, hypertension, ischaemic heart disease, cardiac failure, vasculopathy, diabetes mellitus, toxaemia of pregnancy, hyperuricaemia, autoimmune disease (rheumatoid arthritis, SLE, scleroderma, vasculitides), liver failure, obstructive jaundice, or an acute co-morbidity, e.g. trauma, dehydration, toxic (myoglobinuria, radiocontrast), etc.

All renal diseases are caused by an anatomical defect, macroscopic or microscopic (trauma with hypovolaemia, glomerular pathology, tubular lesions, infection, and obstruction). These are complicated by *pathophysiological* effects (hypertension, cardiac failure, pulmonary oedema, uraemic encephalopathy, autonomic neuropathy, anaemia, hyperkalaemia, hypocalcaemia, hyperphosphataemia, metabolic acidosis, secondary hyperparathyroidism). The patient receives some *therapy; chemical* (antihypertensives, antidiabetic, immunosuppressive) or *physical* (dialysis, nephrostomy). The extent of renal *impairment must be monitored* since it is often complicated by *impairment of endocrine disease*, e.g. hypocalcaemia (secondary and tertiary hyperparathyroidism) and anaemia (decreased erythropoietin).

Hypertension (present in up to 85% of patients with renal failure) is a major cause and complication of renal insufficiency. *Hypotension* from any cause increases the risk for the development of renal failure. *The moment you make the diagnosis of cardiovascular derangement (see Chapter 12), you imply the existence of or the possibility of renal failure.* These conditions must be recognized preoperatively and optimised to limit renal dysfunction.

The elderly are more sensitive to renal insults since they already have *decreased renal function*. Renal blood flow decreases about 10% per decade after 30 years. There is a decrease in blood supply, glomeruli, and tubules. These effects are exacerbated by cardiovascular disease and the daily exposure to renal insults (dehydration, nephrotoxic drugs). Therefore, oliguria must be prevented in the perioperative period by a low tolerance to hypovolaemia and hypotension. This must be treated before the patients are exposed to further kidney insults. The aging kidney cannot reabsorb sodium adequately and lead to sodium and volume depletion. *An adequate urinary output is therefore not indicative of kidney perfusion or plasma volume.* There is a decrease in the capacity for drug clearance.

Several mechanisms contribute to the increased risk of the geriatric patient to develop acute renal failure: Sympathetic-mediated renal vasoconstriction is increased, while the vasodilatory response to vasodilators, such as atrial natriuretic peptide and prostacyclin is decreased. The renal vasculature exhibits an increased vasoconstrictor effect to angiotensin-II. Abnormal autoregulatory mechanisms that normally preserve renal blood flow and glomerular filtration rate (increased vascular resistance) can lead to ischaemia.

The preoperative assessment enables the anaesthetist to optimize the preoperative condition, plan the

intraoperative management, and arrange for postoperative care. The *preoperative evaluation* includes:

- Clinical examination to identify the causes and complications of renal failure (cardiovascular, respiratory, endocrine, haematological, neurological, musculoskeletal, etc.)
- Haematological (anaemia, thrombocytopathy, coagulopathy)
- Chemical (electrolytes, acid-base, glucose),
- Imaging (radiological, echocardiography)
- Electrophysiological (ECG).

The preoperative preparation *of the patient at risk to develop kidney injury or with renal pathology consists of:*

- Preoperative optimization of volume status
- Cardiovascular preparation
- Review of present and recent medications and renal toxins
- *Pre-operative preparation of the patient with end-stage renal failure*
- *Preoperative optimization of volume status*
  Fluid status entails evaluation of *fluid volume, concentration, and composition*. Serum electrolytes, urea, creatinine, acid-base status, and blood gases must be assessed. Patients must have a serum K^+ $< 5.3 \ mM$. Patients can be anuric, oliguric or polyuric. Patients on dialysis are often dehydrated. Estimation of the fluid status starts with the *clinical examination*. *Clinical signs* include consciousness, breathing pattern, skin colour and turgor, peripheral oedema, quality of mucus membranes, palpating peripheral pulses (do not forget foot pulses), heart rate, blood pressure, jugular venous pressure, presence of orthostatic hypotension, auscultation of the heart and lungs, and examination of the abdomen (can you think of abdominal signs pointing to hypovolaemia?). Many patients who are at increased risk to develop perioperative renal failure, are *atherosclerotic and hypertensive*. They often have strong peripheral pulses despite relative hypovolaemia.

  Although *anaemia* is common in patients with acute and chronic renal failure, it is as deleterious and blood transfusion should be considered when indicated as in patients with normal renal function. However, blood transfusion must be avoided in patients awaiting renal transplant since isoimmunisation may occur, which jeopardizes the survival of the transplanted kidney. If blood transfusion is considered, leukodepleted blood must be used.

- *Preoperative cardiovascular preparation*
  Haemodynamic stabilization forms the *basis of renal survival*. Many patients receive cardiovascular drugs, which have cardiac, vascular, and renal effects (Table 2). *If possible*, cardiovascular function must be optimized before the induction of anaesthesia. Patients with untreated hypertension are notoriously unstable intraoperatively. They are very sensitive to vasodilators (the majority of anaesthetic drugs), volume shifts, and stimulation or suppression of the autonomic nervous system (higher highs and lower lows). Patients that start out hypotensive often need inotropes and vasotropes after the induction of anaesthesia. Therefore, preoperative blood pressure control is essential.

  Hypotension exerts the most severe acute form of stress on renal viability – especially in hypertensive patients since the autoregulation curve of the kidneys is shifted to the right. Hypotension, especially in combination with hypovolaemia, is deleterious and must be avoided and treated before induction of anaesthesia.

- *Review present and recent medications and renal toxins*
  Identify and eliminate potentially nephrotoxic drugs. Several drugs are nephrotoxic and must be avoided if possible. These include intravascular radiocontrast, *antibiotics, antihypertensive agents, NSAIDs, ACEIs, etc.* Patients with renal insufficiency have *decreased clearance of many drugs* (e.g., muscle relaxants, digoxin, aminoglycosides, vancomycin), requiring a decrease in dosage or increase in interval.

- *Pre-operative preparation of the patient with end-stage renal failure*
  Patients with *end-stage renal failure often present for diagnostic* (cystoscopy, pyelography, kidney biopsy), or *therapeutic procedures* (nephrostomy, dialysis devices, AV fistulae, parathyroidectomy, and renal transplant). If the patient is on dialysis already, he/she must have been dialysed recently, and postdialysis biochemistry must be available. The approach to these patients is to take cognisance of their disease, treatment, and complications and to avoid any factor that can decrease the already limited renal reserve.

Table 2 Cardiovascular and renal effects of cardiovascular drugs

Drug	Cardiovascular effect	Renal effect
ACE II inhibitors	$\downarrow$ AII $\rightarrow \downarrow$ AL $\rightarrow \downarrow$ BP	$\downarrow$ RBF; $\downarrow$GFR
Ca channel blockers	$\downarrow$ inotropy + $\downarrow$ AL $\rightarrow \downarrow$ BP	$\downarrow$ RBF; $\downarrow$GFR
β_1 -blockers	$\downarrow$ inotropy; $\downarrow$ HR	$\downarrow \beta_1$ effect $\rightarrow \downarrow$ renin; $\downarrow$RBF
Nitrates	$\downarrow$ PL; $\downarrow$ AL	$\downarrow$ volume $\rightarrow \downarrow$ organ perfusion
α_2 agonist (DxM)	$\downarrow$ inotropy; $\downarrow$ AL; $\downarrow$ HR	$\downarrow$ RBF; $\downarrow$ GFR
Dopamine: renal dose	1 - 3 μg kg^{-1} min^{-1} $\rightarrow$ minimal	$\uparrow$ RBF, $\uparrow$ GFR
Dopamine: β dose	3 - 10 μg kg^{-1} min^{-1} $\rightarrow \uparrow$HR, $\downarrow$AL	$\uparrow$ RBF, $\uparrow$GFR
Dopamine: α_1 dose	10 – 20 μg kg min^{-1} $\rightarrow \uparrow$ AL	$\uparrow$ RBF, $\uparrow$GFR
Mannitol	$\uparrow$ PL (initially); $\downarrow$ PL (diuresis)	Afferent VD; $\uparrow$ RBF; $\uparrow$ GFR
Furosemide	$\downarrow$ PL	$\uparrow$renin; $\uparrow$AII; Afferent + efferent VC; $\downarrow$RBF

AL afterload; HR heart rate; PL preload; VD vasodilatation; DxM dexmedetomidine; VC vasoconstriction

Factors that aggravate renal dysfunction

- *Procedures affecting renal function*
  Patients scheduled for procedures affecting renal function need special preoperative preparation. Again, adequate *prehydration* (usually overnight) and intraoperative maintenance of perfusion are essential. These include surgery causing major blood loss and/or affecting renal perfusion, e.g. trauma, major abdominal surgery, biliary surgery, aortic surgery, cardiac surgery involving cardiopulmonary bypass, burns, genitourinary surgery, obstetric surgery, and transplant surgery.

- *Hypovolaemia and hypotension (hypoperfusion states)*
  These are the most common and preventable causes of oliguria. This is called *prerenal oliguria.* Prolonged hypotension or hypovolaemia can cause ARF in patients with normal kidneys, and exacerbates the renal effects of other insults. *Patients with prerenal oliguria suffer from an absolute hypovolaemia or a relative hypovolaemia (hypervolaemic oliguria)* (see Chapters 12 and 18). During episodes of predictable renal hypoperfusion (clamping of the aorta, blood loss, hypotension) the period of hypoperfusion must be limited to a short as possible time and restored as soon as possible (< 1 h in patients with normal kidneys).

- *Sepsis, obstructive jaundice, and liver failure*
  Severe sepsis (that is sepsis plus organ failure), septic shock (that is severe sepsis plus hypotension), obstructive jaundice, and liver failure cause a *syndrome of vasomotor nephropathy.* This is considered a prerenal oliguria and is caused by circulating endotoxin, which causes intense renal vasoconstriction. This condition is *resistant to fluid therapy* and must be treated by eliminating the cause and the treatment of hypotension (inotropes and vasotropes). In patients with end-stage liver failure, this condition is known as the *hepatorenal syndrome.*

- *Nephrotoxins*
  Patients are exposed to several potentially nephrotoxic agents perioperatively. These substances are *therapeutic* (antibiotics, antihypertensives, antineoplastic agents, etc), *diagnostic* (radiocontrast), or *pathophysiological* (endogenous pigments such as free myoglobin and haemoglobin).

  Simultaneous therapy with nephrotoxic drugs increases the nephrotoxicity of the individual agents. *In sepsis, liver dysfunction, or a low cardiac output (absolute or relative hypovolaemia)*, the nephrotoxic potential of drugs and other nephrotoxins, are aggravated.

Nephrotoxins include NSAIDs, ACEIs (impairs renal autoregulation), intravenous radiocontrast, cimetidine, ranitidine (interstitial nephritis), metoclopramide (inhibits renal D_2 receptors), oncotherapeutic agents, immunosuppressants (cyclosporin A, tacrolimus, methotrexate) allopurinol, and antibiotics.

Radiocontrast agents are nephrotoxic and must be avoided when possible. Patients at risk must be prehydrated, if possible, over-night. At risk patients should also receive prophylactic oral *N*-acetyl cysteine (an antioxidant also used for paracetamol poisoning) the day before and day of contrast exposure. The dose is 600 mg orally twice daily the day before and the day of the procedure. This preserves renal function better than hydration alone. After exposure to radiocontrast, the kidneys must be allowed to recover for several days before the patient is exposed to further renal insults, i.e. further radiocontrast administration or surgery.

Several antibiotics are nephrotoxic, e.g. aminoglycosides (proximal tubule necrosis), amphotericin B (glomerulonephritis and ATN), vancomycin, and first generation cephalosporins (cefazolin). The combination of a *cephalosporin and aminoglycoside* increase their nephrotoxicities. In patients with intra-abdominal sepsis, cefoxitin alone is less toxic than clindamycin plus tobramycin, or ampicillin, gentamicin and metronidazole.

Haem pigments (myoglobin and haemoglobin) are nephrotoxic. *Myoglobinaemia* and haemoglobinaemia occur after muscle trauma and haemolysis. Toxic levels of these pigments damage the renal tubules. Therefore, *rhabdomyolysis* (crush injury, compartment syndrome, electrical shock, burns, dead bowel, malignant hyperthermia, hyponatraemia, hypokalaemia) and *haemolysis* (incompatible blood transfusion) are common causes of acute renal failure. Haem pigments cause *renal vasoconstriction* (they bind NO), *free radical-mediated* tubular injury, and *tubular obstruction* when they precipitate in acidic conditions. Steps must be taken to prevent and treat rhabdomyolysis- and haemolysis-induced renal injury (Table 3).

Table 3 Prevention and treatment of haem pigment-induced acute renal injury

Diagnosis	• Suspect release of pigment (crush injury, malignant hyperthermia, haemolysis, dark urine). Do a urine dipstick for haem pigments. • Do not wait for blood results confirming myoglobinaemia or elevated muscle or red cell enzymes. They add little to the diagnosis and management.
Management	• *The targets* are normotension, a urinary output of about 3 ml kg^{-1} h^{-1}, normal blood biochemistry and urine dipstick result negative for blood. • Early extracellular volume resuscitation; start immediately before evacuating patient. • Volume repletion: Ringer lactate (if $K^+ > 5.5$ mM, use saline) about 10 ml kg^{-1} h^{-1} (in an adult 200 to 1000 ml h^{-1} depending on the severity). • If the urine pH is < 6.5, administer sodium bicarbonate about 1 mmol kg^{-1} lean body mass or acetazolamide 3 mg kg^{-1} 6-hourly. • ↓ Ca^{2+} corrected in the presence of hyperkalaemia and symptomatic (tetany, seizures). • Mannitol does not improve outcome. If administered, the dose is 0.2 g kg^{-1} (up to 3 g kg^{-1} day^{-1}) – with the proviso that the urinary output is > 0.3 ml kg^{-1} h^{-1}. • Maintain volume repletion until myoglobinuria is cleared. • If monitoring indicates acute renal failure (hypervolaemia, persistent oliguria < 0.5 ml kg^{-1} h^{-1} for 12 hours or anuria, ↑ metabolic acidosis, ↑K^+), consider renal replacement.
Monitoring	• Blood pressure, heart rate, mucous membranes, urine output, and central venous pressure. • If you have the facilities, measure serum creatine kinase, urea, creatinine, potassium, sodium, calcium, magnesium, phosphorus, uric acid, albumin, acid–base status, blood cell count, and coagulation.* • Monitor blood electrolytes, acid-base, and myoglobin. Measure plasma potassium frequently.**

* Rhabdomyolysis release of intracellular content (K^+, H^+, Mg^{2+}, phosphate, urate), but intracellular movement of Na^+ and Ca^{2+}. The opposite happens with muscle repair.** Na^+, K^+, and Ca^{2+} is usually part of the blood gas analysis. These tests can be done on venous blood; an arterial cannula is not necessary to resuscitate these patients. Measure the urine pH.

Most causes of pigment-induced acute renal injury encountered perioperatively are accompanied by absolute or relative hypovolaemia. Therefore, correction and maintenance of renal perfusion and urine flow form the basis of the prevention and treatment of pigment-induced renal injury. These include management of trauma, increased intra-abdominal pressure, anaemia, etc.

Effects of anaesthesia and surgery on renal function (For a discussion about the renal effects of anaesthetic drugs, see Chapters 5, 6, 7, and 8)

- *Effect of the perioperative stress response*

Activation of the sympathetic nervous system as part of the peri-operative stress response leads to an increase in renal vascular resistance. That causes a reduction in renal blood flow, glomerular filtration, and urine flow. The perioperative stress response causes an increase in catecholamines (adrenaline, noradrenaline), renin, angiotensin II, aldosterone, ADH, and cortisol secretion. All these hormones cause a reduction in renal blood flow and urine production, as well as sodium and water retention.

- *Effect of anaesthetic agents on renal function*

Reversible decreases in renal blood flow and glomerular filtration rate occur during general and regional anaesthesia. This leads to decreased urine flow and sodium excretion. The most of these effects *are not direct*, *but indirect*.

All *volatile and intravenous anaesthetics* influence renal function (GFR and tubular reabsorption), *mainly indirectly by a decrease in cardiac output and/or blood pressure*. Anaesthetics alter renal function *directly* by redistribution of renal blood flow from the inner cortex to the medulla, favouring salt and water reabsorption (decreased urine production). *Fluoride production* occurs during breakdown of enflurane and sevoflurane. Prolonged administration of these drugs can *theoretically* lead to renal dysfunction, but the development of renal failure has not been proven in humans. Another breakdown product of sevoflurane, *Compound A*, has been shown to cause renal damage in laboratory animals, but clinical studies have *not detected significant renal injury in humans*.

Regional anaesthesia above level T4 reduces *sympathetic out-flow* causing hypotension (decreased renal perfusion). The sympathetic block also causes renal vasodilatation and disruption of autoregulation, which makes the kidney *directly dependent on perfusion pressure* for its perfusion. *When RBF decreases, glomerular pressure and filtration decrease, causing over-reabsorption of chloride and a decrease in chloride ion at the macula densa; this reflexively signals the afferent arterial to vasodilate, increasing RBF and GRF back to acceptable levels.*

Choice of anaesthetic technique and intraoperative considerations
If a patient has an AV fistula, that limb is a no-go zone; you do not draw blood there, don not put up an infusion in those distended veins, do not put a blood pressure cuff on that limb, and protect that limb intraoperatively. The limb must be next to the patient with no towels or drapes compressing the limb.

Most drugs used during anaesthesia are at least partly dependent on excretion by the kidneys. *Plasma protein* concentrations are decreased in renal disease. Furthermore, cardiovascular (ischaemic heart disease, hypertension, cardiac failure), neurological (increased permeability of the blood-brain barrier and autonomic neuropathy), pulmonary (pulmonary oedema, pleural effusions, pulmonary hypertension), metabolic (diabetes mellitus, electrolyte disturbances, metabolic acidosis), and haematological (anaemia) *complications of renal failure* affect *pharmacodynamics and -kinetics*. In general, *dosages of all drugs should be reduced* to prevent cardiovascular suppression and drug accumulation. Therefore, *increased perioperative vigilance* (monitoring) to determine drug effects and vital functions is necessary.

- *Premedication*

The preoperative prescription depends on the general condition of the patient. *Sedatives* are best avoided in acutely ill patients, but can be given for the stable patient with chronic renal failure. Midazolam is a good choice. *Prophylaxis for aspiration* must be given for patients with *nausea*, vomiting or gastro-intestinal bleeding (H2 antagonist, serotonin antagonist). Patients must receive their *routine medication*. If the patient receives corticosteroids and is scheduled for major surgery, an additional dose must be prescribed.

Fluid balance is important and *central venous pressure (CVP)* measurement is often necessary to guide fluid replacement. Anuric patients must receive fluid according to *blood loss* plus the *insensible loss* of about 0.3 ml kg^{-1} h^{-1}. Potassium-containing fluid may be administered in the presence of hypokalaemia. Although proof is lacking, it seems as though colloid resuscitation fluids are safe in patients with renal failure. These fluids include albumin, the gelatines, and the *low molecular mass starches* (130 kD, e.g. Voluven, Venofundin).

- *A rapid-sequence induction* is usually indicated because of the presence of nausea, vomiting and delayed gastric emptying due to the uraemia (autonomic neuropathy).

- *Regional anaesthesia* is *not contraindicated* in patients with renal failure if the following aspects are taken into account:
  - The cause of renal failure
  - Neuraxial anaesthesia causes *hypotension*, which decreases renal perfusion.
  - They often have *cardiovascular* (cardiac failure, hypertension) and *pulmonary* (pulmonary oedema) disease.
  - Uraemia decreases *platelet function* but there is no correlation between bleeding time and plasma urea concentration. Uraemic patients may actually be hypercoagulable (Study by Dr JC de Bruin and Dr G Haasbroek, Kalafong Hospital).
  - They often have an *autonomic neuropathy*, which makes them very sensitive to changes in sympathetic tone (hypotension). The autonomic neuropathy also causes gastroparesis, which increases the risk of regurgitation and aspiration.

- *Induction agents*
  - The acidosis and decrease in plasma proteins lead to decreased protein-binding and an increase in the free drug concentration. Therefore, patients with renal failure show an increased sensitivity to propofol, barbiturates, and etomidate and their doses should be reduced.
  - Although the metabolism of induction agents are not significantly affected by impaired renal function, the comorbidities, e.g. cardiovascular disease, may require a dose reduction.
  - *Ketamine* is metabolised to, amongst others, *norketamine*. This metabolite has an analgesic potency of one third of ketamine. Norketamine is cleared by the kidneys. Although little data are available regarding the use of ketamine in patients with renal failure, dose reductions are probably indicated.
  - *Benzodiazepines* are highly protein bound and increased sensitivity is seen in patients with low albumin levels. Diazepam should be used cautiously due to the potential for accumulation of active metabolites.

- *Inhalational agents*
  Inhalational agents are nearly ideal for patients with renal failure because they are independent of the kidneys for excretion. Enflurane and sevoflurane are probably safe in humans. N_2O is safe. The MAC values may be decreased in patients with severe anaemia and uraemia.

- *Opioids*
  - *Fentanyl, alfentanil, and sufentanil* are inactivated by the liver to inactive metabolites and significant accumulation does not occur. However, these drugs are highly protein bound and free fractions may increase. *Remifentanil* is metabolised by erythrocyte and tissue non-specific esterases – not choline esterases. Therefore, it is not affected by poor kidney function.
  - The active metabolites of *morphine* are *morphine-3-glucuronide and morphine-6-glucoronide*. Both these metabolites are excreted exclusively by the kidneys. *Morphine-6-glucoronide* is several times more potent than *morphine* and has a $t_{1/2}$ several times longer than that of morphine. Therefore, patients with renal failure require far less morphine.
  - The metabolite of *pethidine, norpethidine* is excreted by the kidneys and accumulates in patients with renal failure. Norpethidine is epileptogenic. It can also accumulate in patients with

normal renal function receiving high doses.

- The *muscle relaxants* (Table 4)
    o The *muscle relaxants of choice* in patients with impaired renal function are *atracurium and cisatracurium*, since their clearance is independent of renal function.
    o *Pancuronium, vecuronium, and rocuronium* are dependent on elimination by the liver and kidneys. A prolonged effect is sometimes seen in patients with severe renal failure.
    o *100% of alcuronium* and about 20% of *pancuronium and* its active metabolites are dependent on renal excretion. Therefore, their effect is significantly prolonged. They are best avoided in patients with renal failure.
    o *Mivacurium* is metabolised by pseudocholine esterase and therefore not dependent on the kidneys for elimination. Minor prolongation of the effect may be seen due to reduced plasma cholinesterase levels.
    o *Suxamethonium* is indicated for a rapid sequence induction, which is indicated in these patients (gastroparesis due to the autonomic neuropathy). *Suxamethonium* should not be used in patients with a serum potassium concentration > 5.3 mM.

- *The reversal agents* neostigmine, pyridostigmine, and edrophonium are about 50% dependent on renal excretion. Therefore, their effects are prolonged in renal failure patients. These prolonged effects protect patients from the prolonged effects of muscle relaxants. It should be clear that the intraoperative monitoring of neuromuscular function is mandatory in these patients. Atropine and glycopyrrolate are at least 50% dependent on the kidneys for excretion. Therefore, their effects are also extended in patients with renal failure.

Table 4 Kinetics of muscle relaxants

Relaxant	Clearance by kidney/liver	Metabolites
Alcuronium	100/0	-
Atracurium	Hoffmann	Inactive
Cisatracurium	Hoffmann	Inactive
Mivacurium	BuChE (PsChE)	Inactive
Pancuronium	**20/80**	**Active**
Vecuronium	**50/50**	**Active**
Rocuronium	80/20	Inactive
Suxamethonium	BuChE	Inactive

Delayed awakening is common in patients with renal failure. Can you name the reasons? Postoperative nausea and vomiting occurs commonly in these patients. Metoclopramide must be avoided since it causes renal vasoconstriction (D_2 antagonist).

To summarise intraoperative considerations:
- Co-morbidities: cardiovascular disease (cardiac failure, ischaemic heart disease, hypertension)
- Inability to excrete a fluid load
- Aspiration risk
- Abnormal clotting (increased or decreased)
- Decreased clearance of drugs
- Electrolyte disturbances: metabolic acidosis and hyperkalaemia (dysrhythmias, suxamethonium.

Perioperative monitoring of renal function
Intraoperative monitoring depends on end-organ function, the procedure, and anaesthetic technique. A reliable intraoperative monitor of renal function does not exist. Renal function monitoring includes haemodynamic monitoring (blood flow), urine flow (volume per time), and urine volume, concentration, and composition: ↓ RBF (↓ clearance of waste products) → ↓ GFR (extraction of waste products) → ↑ tubular reabsorption → ↓ urine volume + ↑ urine concentration + ↑ plasma creatinine + urea.

Monitoring urine output

Oliguria is traditionally defined as a urine flow of < 0.5 ml^{-1} kg^{-1} h^{-1}. However, in patients with acute pathology (trauma, burns, surgery), no correlation exists between histological evidence of ATN and GFR, creatinine clearance, or plasma urea and creatinine. For example, during aortic surgery, oliguria does not predict postoperative renal failure. This observation is explained by the influence of intraoperative factors influencing renal function (perfusion, glomerular filtration, tubular reabsorption and secretion, and urine off-flow), namely increased sympathetic tone, renin, AII, aldosterone, and vasopressin. These factors are profoundly affected by the stress response to surgery (Chapter 17), haemodynamic instability, anaesthetic drugs, positive pressure ventilation, etc. Therefore, intraoperative *oliguria is an unreliable sign of imminent renal failure. However, that does not mean that we should not monitor urine flow.*

Intraoperative urine flow gives an indication of intravascular volume if:
- Renal function is normal,
- Plasma osmolality is not increased (hyperglycaemia, mannitol, ethanol), and
- No diuretics have been administered.

A *rising serum urea and creatinine* (decreased clearance) are the standard indicators of worsening *renal function*. A doubling of serum creatinine represents a 50% decrease in GFR at *steady state*. Serial determinations of serum creatinine and creatinine clearance are the most sensitive tests for predicting the onset of perioperative renal dysfunction. Since steady state is not reached while large fluid shifts are occurring (dilution due to blood loss followed by resuscitation fluid), intraoperative serial creatinine is not practical.

Indirect monitors of intraoperative renal function: blood pressure and blood volume
- *Blood pressure*
  Since urine flow is an unreliable indicator of renal function, haemodynamic stability (cardiac output and blood pressure) is the most important intraoperative factor (indirect) that reflects adequate renal function. During an episode of predictable renal hypoperfusion (clamping of the aorta, blood loss, hypotension) the period of hypoperfusion must be limited to a short as possible time and restored as soon as possible (< 1 h in a patient with normal kidneys).

  Blood pressure can be monitored non-invasively (*blood pressure cuff*). However, *invasive blood pressure monitoring* (arterial cannula) is indicated in patients or procedures where large pressure and volume shifts occur, and where renal function may be compromised. Not only does it give a *continuous display* of blood pressure, but also allows repeated *blood sampling*, and allows assessment of blood *volume status* by calculating the *pulse pressure variation* (see Chapter 18).

- *Central venous pressure (CVP)*
  Central venous pressure (CVP) reflects the interaction between blood volume, venous tone, and right heart function. In the absence of pulmonary hypertension and heart disease, it also gives an indication of left ventricular preload. In the presence of pulmonary hypertension and heart dysfunction (especially left heart pathology), pulmonary artery wedge pressures (PAWP) may reflect left ventricular preload more reliably. Since CVP (and PAWP) is influenced by several intra- and extra cardiac variables, more is often learned from the *CVP trend and the relationship between the CVP trend and other trends*, e.g. blood pressure, heart rate, PPV, end-tidal PCO$_2$, and for what it is worth, urine flow. The CVP can also be used to do *pre-emptive volume loading* before critical stages when adequate RBF is essential, e.g. before unclamping of the aorta, or before releasing the arterial clamp during renal transplant.

Approach to intraoperative oliguria

The first response to oliguria should be to optimise intravascular volume and arterial blood pressure *__while__* (not after) determining the aetiology (Table 5).

- *Making the diagnosis of oliguria*

  Adequate haemodynamic function (blood pressure, fluid volume) must be evaluated before the diagnosis of oliguria is made, since the *definition of oliguria* depends on the presence of renal pathology (ability to concentrate urine) and blood osmolality (osmolal load of the kidneys). Therefore, the *definition of oliguria depends on the ability of the kidneys to concentrate the filtrate.*

  The *osmolal load* must be solved in a minimum volume of solvent (water). The maximum concentrating ability of the normal kidney is about 1200 mOsm kg^{-1}. If the kidneys can concentrate urine to this osmolality, a minimum daily urine flow of 400 ml to 500 ml is necessary (*obligatory urine flow*). In a patient with a *normal blood volume and normal kidneys*, *oliguria is defined* as in a daily urine flow of less than the obligatory flow, i.e. < 500 ml day^{-1} in a 70 kg or < 500 ml/(70 kg × 24 h) = *0.3 ml kg^{-1} h^{-1} or < 0.5 ml kg^{-1} h^{-1}. Patients with renal impairment* cannot concentrate urine sufficiently and the obligate solute load is excreted in urine volumes > 0.5 ml kg^{-1} h^{-1}.

  A patient with normal renal function may be hyperglycaemic, has received mannitol, or has had alcohol. All these substances cause an *osmotic diuresis* – even in the hypovolaemic patient. On the other hand, a patient in *cardiac failure* complicated by renal failure (absolute hypervolaemia) may be oliguric, and may require renal replacement therapy. Therefore, <u>**urine volume gives no indication of urine quality.**</u>

  The following steps should be taken when urine flow is low or absent (Table 5):
  - <u>***Is the Foley catheter working***</u>*?* Exclude kinking, clots, etc. Flush the catheter.
  - *Establishing the causes of oliguria (prerenal, intrinsic, postrenal)*
  - *Indirect measures of renal well-being* (haemodynamics) and simultaneously do a
  - *Urine analysis*, including colour, dipstick (blood, bilirubin, glucose, protein, haem pigment) and specific gravity (normal 1.010 g ml^{-1} to 1.030 g ml^{-1}).
  - *Serum and urine* electrolytes, urea, and creatinine, and fractional excretion of sodium. Prerenal oliguria results in a small volume of concentrated urine (tubular function, vasopressin) with a low [Na^+] (< 20 mM; most Na^+ has been absorbed under the influence of aldosterone) and low fractional excretion of sodium (FENa) (See appendix to this chapter – not necessary to know this information, but you must know that these tests are available).
- While the above testing is being done, *start with haemodynamic optimisation*, including fluid challenges and inotropic and/or vasotropic drugs. *While urine flow is declining, the diagnosis of oliguria must be considered*, and the *pathophysiology* determined. The first steps are to obtain a history (trauma, disease, therapy, intoxication) and to assess plasma volume and haemodynamic function. Fluid volume is evaluated using CVP, PAWP, or PPV.
- *Microscopy* of urine sediment (ATN).

Pharmacologic management of oliguria

<u>*The mainstay of the prevention and treatment of oliguria is perfusion, i.e. maintenance of cardiac output and blood pressure by optimising intravascular volume, and if necessary, inotropes and vasotropes.*</u> Thereafter, other drugs may be considered. Although several drugs, including diuretics, have shown promise in animal studies, they have not been proven to improve outcome in humans.[20] *There is one exception*, namely the use of *N-acetyl cysteine* before radiocontrast studies (see above). The use of diuretics does not improve renal outcome. On the contrary, the diuresis they cause, worsens hypovolaemia.

- *Dopamine* in diuretic doses does not prevent the onset of or improve the outcome of perioperative ARF.
- *Calcium channel blockers* are renovascular vasodilators, and reduce the vasoconstrictive action of cyclosporin and radiocontrast-associated vasoconstriction and nephrotoxicity. However, they also cause hypotension and decrease renal perfusion.
- Although diuretics such as *mannitol and furosemide* are still used to convert an oliguric to a non-oliguric ATN, there is *little evidence* that they decrease the mortality in renal failure. In animals, mannitol and furosemide protect against ischemic and toxic injury. However, evidence in humans is lacking. Decreasing the energy consumption of tubular cells by furosemide prevents medullary hypoxic injury only in isolated rat kidneys. Neither furosemide nor mannitol

confers any protection against radiocontrast-induced renal failure.

o *Anaritide* (a synthetic ANP) has been administered prospectively to critically ill patients with ATN. The benefit of anaritide in oliguria without ATN has not been studied yet, but is likely to be beneficial.

o Endothelin-1 is produced by endothelial cells and in vascular smooth muscle cells where it causes vasoconstriction. Endothelin-receptor antagonists (e.g. darusentan) can prevent experimentally induced ischaemic renal injury but human studies are still in progress.

Table 5 Diagnosis and treatment of a patient with oliguria (See also appendix)

Measurement	Response*	Diagnosis
Plumbing		
Catheter, urine bag, bladder, ureters	Fix	Postrenal
Intra-abdominal pressure > 20 mm Hg	Decompression	Prerenal
Are the ureters, bladder intact, e.g. pelvis fracture?	Ask surgeon	Postrenal
Haemodynamics		
MAP > 100 mm Hg; PPV < 8%	Hold	Prerenal
MAP > 90 mm Hg; CVP < 15 mm Hg; PPV 8 - 12 %	Bolus 200 ml (3 ml kg^{-1})	Prerenal
MAP > 70 mm Hg; CVP < 10 mmHg; PPV 8 - 12 %	Bolus 400 ml (6 ml kg^{-1})	Prerenal
MAP > 60 mm Hg, CVP < 5 mm Hg; PPV > 12%	Bolus 800 ml (12 ml kg^{-1})	Prerenal
Fluid balance		
In > out	Hold	Pre/intrinsic
In = out	Bolus 400 ml (6 ml kg^{-1})	Pre/intrinsic
In < out	Bolus 800 ml (12 ml kg^{-1})	Pre/intrinsic
Urine analysis: Urine colour, tonicity, micro, FE_{Na}		
Specific gravity < 1.010 (dilute)	Hold	Pre/intrinsic/ post-renal
Specific gravity > 1.020 (concentrated)	Bolus 400 ml (6 ml kg^{-1})	Pre/intrinsic/ post-renal
Specific gravity > 1.030 (concentrated)	Bolus 800 ml (12 ml kg^{-1})	Pre/intrinsic/ post-renal
Sediment suggestive of ATN	Bolus 200 ml (3 ml kg^{-1})	Pre/intrinsic/ post-renal
Sediment normal	Bolus 400 ml (6 ml kg^{-1})	Pre/intrinsic/ post-renal
Check FE_{Na} > 1.0% (ATN)	Hold	Pre/intrinsic/ post-renal
Check FE_{Na} < 1.0% (Prerenal)	Bolus 800 ml (12 ml kg^{-1})	Pre/intrinsic/ post-renal
Optimize volume replacement		
Monitor in/out, biochemistry, haematocrit every 30 minutes. Keep urinary flow > 0.5 ml kg^{-1} h^{-1} (controversial).	Titrate: MAP > 70 mm Hg + CVP 10 to 15 mm Hg + PPV 8 - 12% + Hct $\geq$ 25% ?Natriuretic therapy (DA, etc.)	

* According to lean body mass; DA, dopamine; CVP, central venous pressure; PPV, pulse pressure variation; MAP, mean arterial pressure

When is oliguria particularly worrisome?

Situations have been highlighted earlier where patients are at risk to develop perioperative renal failure, e.g. patients receiving nephrotoxins, diabetics, patients receiving intravascular radiocontrast, etc. There are however five perioperative situations where oliguria is an ominous sign, namely changes in urine flow, situations when urine output cannot be assessed, urological procedures, renal transplantation, and abdominal compartment syndrome. These may require surgical, haemodynamic, and pharmacological intervention (volume, vasotropes, inotropes) to rescue renal function.

- *Changes in urine flow*

  Clinicians frequently look at absolute values of physiological variables. Many forget to observe trends. The same applies to variables that reflect renal function. Although urine flow per se does not necessarily indicate normal renal function (see above), the trend in urine flow is still important. Anuria is obviously abnormal. Anuria changing to oliguria may indicate an improvement in renal function. However, normal urine production followed by a declining flow should be investigated in the context of the effect of surgery and anaesthesia. Therefore, do not forget the urine bag, monitor it every 30 minutes, and observe any trend in urine flow.

  Oliguria or anuria in the scenario of blood loss or hypotension is obviously indicative of deteriorating renal function. Correlate these changes in urine production with other changes, e.g. urine colour and blood biochemistry. Likewise, intraoperative oliguria may be replaced by a diuresis, e.g. diabetes insipidus, neurogenic salt wasting (brain pathology), and after the

administration of mannitol (brain injury). Steps must be taken to address the cause.

- *Some procedures do not allow monitoring of urine flow*
  During procedures involving the bladder and ureters, it is not possible to monitor urine production. During these procedures, the only way to monitor renal well-being, are haemodynamic function (renal perfusion) and blood biochemistry.
- *The TURP syndrome*
  One of the most common urological procedures performed is the transurethral resection of the prostate (TURP). Although TURPs are done on "easy" urology endoscopy lists, they *are not to be regarded as minor procedures*. During this procedure, hyperplasic prostate is resected using *electro-curettage*. During this endoscopic procedure, the surgeon resects the prostate under vision. The surgical field is continuously irrigated by a *non-electrolyte solution*, e.g. mannitol, sorbitol, and glycine. These electrolyte-free solutions are absorbed into the systemic circulation (up to about 200 ml min^{-1}) via the prostate venous sinuses, causing water overload with severe hyponatraemia, hypochloraemia, and a metabolic acidosis. The procedure can also be accompanied by substantial blood loss.

  Clinically, the condition reflects hypervolaemic hyponatraemia and is characterized by changes in mentation (therefore, intrathecal anaesthesia is the anaesthetic technique of choice), convulsions, hypertension followed by hypotension, bradycardia, ST segment changes, and a decrease in oxygen saturation (pulmonary oedema). The patient also becomes hypothermic. This is known as the *TURP syndrome* and can be prevented by limiting the height of the irrigation solution (< 45 cm above the bladder), intravesical pressure (< 15 cm H_2O), resection time (< 45 minutes), and mass of prostate resected.

  Regarding *renal function during a TURP*, the problems are:
  o Patients are usually older men with *comorbidities*, e.g. hypertension, ischaemic heart disease, renal impairment, and on *medications* that are potentially nephrotoxic.
  o They often receive an *aminoglycoside* intraoperatively.
  o It is difficult to assess *blood loss and urine output* intraoperatively; they may have a diuresis postoperatively.
  o Intraoperative *haemodynamic compromise* and *anaemia* aggravate renal dysfunction.

The *TURP syndrome is treated* symptomatically by cardiovascular support, oxygen, anticonvulsant if necessary, and slow (over about 24 hours) correction of the hyponatraemia (to prevent pontine myelinolysis) using hypertonic NaCl. These patients develop a diuresis, which correct the hyponatraemia over time.

- *Renal Transplantation*
  Before removal of donor kidneys (cadaver or alive) the most important aspect of renal preservation is perfusion of the kidney before the ischaemic time starts. These steps are the same as mentioned previously, namely hydration, perfusion, blood pressure, and avoidance of nephrotoxins. *During kidney transplantation*, hypotension is often observed after unclamping the iliac artery. This is caused by some renal preservation solution and ischemic blood from the leg that returns to the circulation. Therefore, crystalloid is administered to increase the CVP to about 12 mm Hg before reperfusion of the donor kidney. The mean arterial blood pressure should be above 75 to 80 mm Hg (lower limit of autoregulation). Additional crystalloid, colloid, and blood may be needed. Postoperative measures to ensure survival of the transplanted kidney are the same as for native kidneys. (Regarding renal transplant, the following advice: This is a procedure that requires a deep neuromuscular block, especially during the vascular anastomoses; if the patient would cough during this critical surgical stage, the vascular pedicle may tear, resulting in loss of the kidney. ***Therefore, monitor neuromuscular function in these patients!!***).

- *Abdominal Compartment Syndrome (ACS)*
  Abdominal compartment syndrome results from increased intra-abdominal pressure (IAP). Normal postoperative abdominal pressure is about 5 mm Hg. Hepatic perfusion decreases at an IAP > 10 mm Hg. Oliguria occurs at *15 to 20 mm Hg, and anuria at IAP of 20 mm Hg to 40 mm Hg.* Increased IAP may result from fluid in the peritoneal cavity, oedema of the intestines (massive fluid resuscitation), and distended bowel (obstruction). Increased IAP does not impair perfusion of intra-abdominal organs only, but also cause a decrease in cardiac output due to decreased venous return from the inferior vena cava. Increased IAP also impairs ventilation resulting in hypercapnia. The decreased cardiac output and increased IAP result in ischaemia of the kidneys, bowel, liver, etc. Intracranial pressure is also elevated, which decreases cerebral perfusion (hypoventilation $\rightarrow \uparrow PaCO_2 \rightarrow$ cerebral vasodilatation).

Intravesical pressure is a reliable indicator of IAP and is measured using a urinary catheter. (Empty the bladder, put 50 ml of saline back, and measure the pressure using an ordinary manometer.) An IAP > 20 mm Hg to 25 mm Hg requires *urgent decompression laparotomy* to restore renal perfusion. Decompression laparotomy results in a sudden decrease in IAP, followed by reperfusion of ischaemic organs. This may cause severe hypotension (reperfusion syndrome) and must be anticipated and treated with a vasoconstrictor if necessary.

Preparation for decompression includes administration of fluid, inotropes, vasotropes, and increased ventilation to attenuate the surge in CO_2. The value of sodium bicarbonate for the ensuing metabolic acidosis is controversial. Calcium chloride (about 10 mg kg^{-1}) may be necessary should the potassium increase.

In the perioperative preservation of renal function, the three most important principles are: perfusion, perfusion, and perfusion. The most important treatment modalities are hydration, blood pressure, and avoidance of nephrotoxins. In general, it can be stated that drugs that increase the cardiac output and/or blood pressure and maintain an acceptable blood pressure (within the autoregulatory limits), preserves renal function – IF THE PATIENT IS NOT HYPOVOLAEMIC OR DEHYDRATED. Therefore, treat a low cardiac output by correcting absolute (blood loss, dehydration) and relative hypovolaemia (cardiac failure, vasodilatation). This is probably the explanation why diuretics do not improve outcome of the oliguric patient.

ANAESTHESIA AND LIVER DISEASE (for further reading see[21] [22])

Liver failure is a multisystem disease. It affects nutrition, fluid and electrolytes, endocrine function, the central and peripheral nervous systems, cardiovascular function, lungs, gastrointestinal tract, haemopoietic system, and kidney function. Furthermore, several drugs, primary extrahepatic conditions, and perioperative factors influence hepatic function.

Liver perfusion

Splanchnic and liver blood flow
The *splanchnic circulation* refers to the hepatic, gastric, pancreatic, splenic, small intestinal, and colonic circulations. The coeliac and superior and inferior mesenteric arteries supply these viscera. Liver blood flow is closely linked to splanchnic blood flow. The liver receives about 25% of the cardiac output (100 ml 100 g^{-1} min^{-1}); 25 % from the hepatic artery, and 75% from the portal vein. It receives equal amounts of oxygen from arterial and portal blood flow. The portal vein drains blood from the stomach, pancreas, spleen, small intestine, and colon. Portal and arterial blood drain into the liver sinusoids, central veins, and finally via the hepatic veins into the inferior vena cava (IVC).

The splanchnic vasculature contains as much as 15% of the total blood volume, of which 70% is in the veins. Therefore, anatomical, physiological (including neuroendocrine), and pharmacologic factors affecting the splanchnic resistance, venous capacitance vessels, and drainage of blood into the IVC, influence the blood volume and pressure in the splanchnic reservoir. For example, vasoconstriction in the splanchnic bed shifts blood from the reservoir to the systemic circulation, while obstruction to flow from the liver to the IVC or from the portal blood to the liver (portal hypertension) increases pressure in the reservoir resulting in oedema, ascites, and loss of systemic blood volume, i.e. hypovolaemia.

Regulation of liver perfusion
As in other organs, liver perfusion is determined by extrinsic (perfusion pressure and neurohumoral factors) and intrinsic factors (hepatic arterial buffer, metabolic control, and pressure-flow autoregulation). Extrinsic and intrinsic factors work independently.

- *Extrinsic regulation*
  - *Neural control*
    Postganglionic sympathetic fibres from T6 to T11 (via the vagal, and splanchnic nerves) are carried into the liver along the hepatic arteries, portal veins, and bile ducts to end on the arterioles and venules. Increased sympathetic nervous system stimulation decreases (blood shifted to systemic circulation), while decreased sympathetic stimulation increases splanchnic reservoir volume (pooling of blood). Vagal stimulation causes vasodilatation and has the opposite effect on the splanchnic reservoir.
  - *Humoral control*
    The splanchnic and hepatic arteries have α_1-, α_2-, and β_2-adrenergic receptors, the splanchnic and sinusoid microcirculation (capacitance vessels) have α_1 and α_2 receptors, while the portal veins have only α_1 receptors. At low doses (< about 150 ng kg^{-1} min^{-1}), *adrenaline* stimulates mainly β receptors causing splanchnic and hepatic arterial vasodilatation, while high doses (> 150 ng kg^{-1} min^{-1}) also stimulate α receptors causing vasoconstriction. In splanchnic and portal veins, as well as the capacitance vessels, adrenaline causes only vasoconstriction (no β receptors).

Glucagon causes hepatic arterial vasodilatation. *Angiotensin II* cause splanchnic arterial and portal vein vasoconstriction. *Vasopressin*, increases splanchnic arterial resistance, but it decreases portal venous resistance. This decreases portal venous pressure and is useful in the *treatment of bleeding oesophageal varices.*

- *Intrinsic Regulation*
  - *Hepatic arterial buffer (HAB)*
    The HAB is the most important intrinsic mechanism and is mediated by adenosine in the periportal areas. When portal venous flow decreases, adenosine accumulates, which vasodilates periportal arterioles (from the hepatic artery), resulting in an increased contribution of arterial flow to the liver. The opposite happens with increased portal venous flow. The HAB can double hepatic arterial flow but cannot fully compensate for a decrease of > 50% in portal venous flow, but oxygen supply is restored since hepatic arterial blood oxygen content is much higher than portal venous oxygen content. *Splanchnic ischaemia and endotoxin may decrease the effectiveness of HAB to maintain liver oxygenation.*
  - *Metabolic control*
    Decreases in *portal PaO$_2$ and pH* (metabolic and respiratory) increase hepatic arterial blood flow. Metabolic and respiratory alkalosis decrease hepatic blood flow. Increased *postprandial plasma osmolality* increases hepatic arterial and portal venous blood flow:
  - *Pressure-flow autoregulation*
    Contrary to other organs where arterial autoregulation (Chapter 12) is active all the time, autoregulation in the liver is active only after meals but not in the fasting state. Autoregulation does not exist in the portal circulation. This means that, in the fasting state, including *perioperatively, autoregulation is ineffective and liver perfusion is strictly pressure dependent.* Therefore, the liver is *vulnerable to ischaemia during perioperative hypotension.*

Functions of the liver
- *The liver and intermediary metabolism*
  The liver plays a *central role* in intermediary metabolism.
  - *Protein Metabolism*
    Liver-derived proteins have an effect on all organs. The liver synthesises and degrades amino acids, peptides, and proteins. Hepatocytes change amino acids to keto acids, glutamine, and ammonia. Ammonia from the gut and from deamination of amino acids is removed by the urea cycle. Therefore, plasma ammonia increases, while urea decreases in patients with liver failure.

    Proteins produced by the liver include albumin, hormones, procoagulants, anticoagulants, mediators of inflammation (cytokines, chemokines), acute-phase proteins, binding proteins (e.g. for insulin-like growth factor 1), and transport proteins. *Albumin* production forms about 15% of the liver protein production. The total *albumin pool* is about 5 g kg^{-1} of which 40% occurs *intravascularly*, and much of the rest in the *skin* (remember the influence of burns on plasma protein). About 300 mg kg^{-1} of albumin is *degraded and replaced daily*. *Albumin levels are regulated* mainly by plasma colloid osmotic pressure (increased with excessive protein loss, such as nephrotic syndrome), the availability of amino-acids (decreased during fasting), and hormones (decreased during the stress response).

    Albumin transports several substances, including calcium, hormones, fatty acids, unconjugated bilirubin, drugs, and metals. Therefore, albumin levels influence *free fractions* (biological active), *volume of distribution* (increased in hypoalbuminaemia), and *clearance* (free fractions are filtered by the glomerulus) of the above-mentioned substances.

    In the foetus, the liver produces mainly *α-fetoprotein* (AFP). It has the same functions as albumin. It is the main plasma protein in the neonate and is replaced by *albumin by the age of about one year*. In the adult, *elevated AFP* occurs in hepatocyte proliferation, e.g. hepatitis, injury, and hepatocellular carcinoma.
  - *Carbohydrate metabolism*
    The liver is one of the most important *regulators of blood glucose concentration*. Glucose concentration in *sinusoidal blood and several hormones* (insulin, catecholamines, glucagon, and cortisol) control carbohydrate homeostasis, i.e. glucose uptake (glycogenesis) and release (glycogenolysis and gluconeogenesis).

    The liver stores glycogen. When glycogen stores are depleted, blood glucose is replenished by *liver gluconeogenesis* from lactate, glycerol (from triglycerides), and skeletal muscle amino-acids. *Endocrine modulators* of gluconeogenesis and glycogenolysis include glucagon, catecholamines, and insulin. Both glucagon and catecholamines stimulate glycogenolysis. Glucagon and cortisol also stimulate gluconeogenesis. (*Remember, catecholamines stimulate glycogenolysis and glycolysis, but not gluconeogenesis. Therefore, administration of these drugs increases lactate levels.*) *Insulin* inhibits gluconeogenesis and glycogenolysis (the path ways to glucose), but stimulates glycogenesis and glycolysis (the pathways away from glucose). Therefore, *patients with liver failure become hypoglycaemic.*

    Remember, after removal of a *phaeochromocytoma*, the abrupt decrease in catecholamines causes a decreased glycogenolysis, resulting in hypoglycaemia. An *acidosis decreases glycolysis* causing an increase in plasma glucose, while *alkalosis stimulates the tempo-determining enzyme of glycolysis* (phosphofructokinase), causing a decrease in blood glucose.
  - *Lipid metabolism*

The liver takes up (mainly as chylomicrons and lipoproteins from the blood), manufactures (lipogenesis from glucose), stores (as triglycerides), oxidizes (β oxidation of fatty acids to acetyl CoA and ketones with build-up of AcCoA), and releases fatty acids into the blood (as VLDLs).

Insulin promotes lipogenesis (and inhibits ketogenesis), while glucagon and catecholamines stimulate lipolysis and β oxidation. The liver *produces ketones* from AcCoA, but cannot revert it back to AcCoA, since it lacks the CoA transferases. However, other organs, including the brain and heart, have these enzymes and use ketones when liver (and muscle) glycogen has been depleted (starvation). Therefore, the liver supplies substrate for energy consumption in the form of glucose (in the fed state) and as fatty acids and ketones (during starvation or inability to catabolise glucose, i.e. diabetes mellitus). *Starvation-induced ketosis* is self-limiting since ketones *stimulate insulin release*, and thereby has a negative feedback on β oxidation of fatty acids to AcCoA. This explains the ketosis developing in the absence of the insulin feedback. *Therefore, patients with liver failure smell of ammonia and are alkalotic, while starving patients with normal liver function smell of ketones and are acidotic.*

- *Bile metabolism*

  Bile salts play an important role in the *absorption and excretion of lipids, as well as the regulation of plasma lipids*. They play an important role in the gastrointestinal *absorption* of lipids, including fatty acids, cholesterol, and fat-soluble vitamins (A, D, E, and K). They facilitate the *excretion* of lipophilic substances, including xenobiotics[xvii] and endogenous molecules such as bilirubin, cholesterol, and amphipathic[xviii] steroid hormonal derivatives. Bile salts *affect plasma lipid levels* by regulating the expression of lipoprotein receptors on hepatocytes that enable them to extract lipoprotein cholesterol from blood, as well as HMG-CoA reductase, which is the rate-limiting enzyme in cholesterol production.

  Hepatocellular porters regulate the uptake of bile salts from the sinusoids and their secretion into bile canaliculi. Bile and pancreatic secretions are secreted into the duodenum via the common bile duct. Bile salts are reabsorbed from the terminal ileum into the portal circulation and transported back to the liver. This is called the *enterohepatic circulation*.

  The *sphincter of Oddi* regulates flow of bile into the duodenum. Opioids can cause painful spasms of bile ducts and sphincter of Oddi. Spasm is reversed by smooth muscle relaxants (glyceryl trinitrate), antimuscarinic agents (atropine, glycopyrrolate), volatile anaesthetics, naloxone, and glucagon.

- *Electrolyte homeostasis, including acid-base regulation* (See Chapter 20)

  The liver affects water and electrolyte homeostasis through its endocrine function (secondary hyperaldosteronism, calcium, magnesium), albumin production (hypoalbuminaemia is a common cause of a metabolic alkalosis), and urea synthesis (the urea cycle is acid-forming).

- *Coagulation*

  The liver produces *procoagulants and anticoagulants*. The vitamin K-dependent proteins include *clotting factors* II, VII, IX, and X, and the *anticlotting factors* proteins C, S, and Z. Hepatocytes produce most of the *procoagulants*, except factors III (tissue thromboplastin), IV (calcium), and VIII-von Willebrand factor (from endothelium). A deficiency of procoagulants causes *hypocoagulability*. *Portal hypertension* results in hypersplenism, which is complicated by *thrombocytopaenia*. The *anticoagulants regulate coagulation and fibrinolysis*. These include protein S, protein C, protein Z, plasminogen activator inhibitor (PAI 1), and antithrombin III. *Protein Z* facilitates the degradation of factor Xa. *Activated protein C* inactivates the factor VIIIa-Va complex. *Protein S* is a cofactor of Protein C; a lack of protein S increases the risk for *hypercoagulability*. *PAI-1* blocks plasminogen activators, such as urokinase or tissue plasminogen activator, to convert plasminogen to plasmin. A lack of PAI results in *uncontrolled fibrinolysis*.

  Therefore, decreased liver function, including bile obstruction, and portal hypertension, is complicated by abnormal blood clotting (hypo- or hypercoagulability, hyperfibrinolysis, and thrombocytopaenia).

- *Haem and bilirubin metabolism*

  In adults, about 20% of the *haem portion of haemoglobin* is produced in the liver and 80% in bone marrow. Abnormal haem synthesis is responsible for the *different hepatic porphyrias* (see Chapter 11). The main source of serum bilirubin is the catabolism of haem. In adults, about 80% of *bilirubin* is derived from phagocytosis of old erythrocytes by macrophages in reticuloendothelial cells in the spleen, liver, and bone marrow. *Therefore, massive haemolysis and the breakdown of haematomas cause jaundice with an increase in unconjugated bilirubin.*

  Bilirubin is bound to plasma albumin from where it is extracted by hepatocytes, conjugated to glucuronic acid, and secreted into the bile canaliculi. Most of the bilirubin is metabolised by bacteria further to stercobilinogen in the gut and excreted, while a small portion returns to the liver and systemic blood (*bilirubin enterohepatic circulation*). Some stercobilinogen is absorbed and excreted in the urine (then known as urobilinogen). Therefore, plasma normally contains a small amount of conjugated bilirubin. *Obstruction of the flow of bile from the liver to the duodenum causes jaundice with an accumulation of conjugated bilirubin in plasma and decreased absorption of lipids, including the lipid-soluble vitamins* (remember vitamin K).

- *Erythropoiesis and thrombopoiesis*

[xvii] A *xenobiotic* is a chemical which is found in the body but which is not normally produced or expected to be present in it, e.g. drugs and environmental pollutants.

[xviii] *Amphipathic lipids* are molecules that are lipophilic (hydrophobic) substances with a polar (hydrophilic) region, e.g. phospholipids, glycolipids and steroids.

During foetal life and early infancy, the liver is the main site of erythrocyte production (extramedullary haematopoiesis). Thereafter, the bone marrow matures and is the main site of haematopoiesis. Extramedullary haematopoiesis may persist or reappear in severe haemolytic anaemias, bone marrow failure, and myeloproliferative disorders. The liver produces thrombopoietin, which stimulates stem cells to form megakaryocytes in bone marrow.

- *Endocrine function*
  Liver failure is often accompanied by several endocrine related abnormalities. The liver produces hormones (vitamin D, angiotensinogen, insulin growth factor I), activates hormones ($T_4 \rightarrow T_3$), inactivate hormones (T_3, insulin, aldosterone, vasopressin, oestrogens, androgens), and is a target of hormone action (insulin, glucagon, catecholamines, cortisol), and produces hormone-binding proteins. About 50% of insulin from the pancreas is degraded by the liver before it reaches the systemic circulation. This contributes to hypoglycaemia in patients with hepatic failure.

- *Immune and inflammatory responses*
  The liver is the largest reticulo-endothelial organ with macrophages (Kupffer cells) accounting for about 10% of its mass. *Kupffer cells are scavengers, and have pro-inflammatory and anti-inflammatory* functions.
  Kupffer cells filter blood from splanchnic organs. They remove toxins, antigens, and bacteria. By removing inciting substances from the blood, these cells are *anti-inflammatory*. Kupffer cells are also *pro-inflammatory* by releasing proinflammatory mediators and recruiting neutrophils. These mediators include prostaglandins, leukotrienes, cytokines,[xix] chemokines,[xx] proteases, nitro-radicals, and oxygen free radicals. The *pro-inflammatory substances can damage endothelial cells* and induce fibrosis, e.g. methotrexate-induced liver fibrosis.

- *Pharmacokinetics: Xenobiotic clearance* (See your pharmacology lectures)
  Hepatic biotransformation increases drug excretion, and activate, inactivate or attenuate the biologic activity of drugs. However, xenobiotic metabolism produces reactive chemicals that cause severe liver damage (either directly or indirectly by immune sensitization, as is probably involved in the pathogenesis of halothane hepatitis). Since brain and kidney functions are often compromised in patients with liver disease, pharmacodynamics (potentiated) and pharmacokinetics (prolonged action) are often markedly affected.

  There is a relationship between the inherent ability of the liver to remove (clear) a xenobiotic and liver perfusion (Q). The clearance (Cl) relative to Q is called the extraction ratio (ER = Cl/Q). The ER reflects the efficiency of the liver to extract or eliminate a drug. The amount of xenobiotic removed by the liver is also affected by the amount of free drug (plasma protein binding; PPB).

  If the liver has a *poor capacity to clear a drug* (low Cl), it does not matter how high Q is because its capacity is limited. Therefore, *Cl it is flow insensitive*. It can also only degrade free drug. Therefore, drugs with a low ER are sensitive to the PPB. The elimination of these drugs is *dose-dependent, nonlinear, saturable, and follow zero-order elimination*. When the capacity of the liver to eliminate a drug is less than the dosing rate, plasma levels of drug will continue to rise and a steady state will not be reached, unless the dosing rate is decreased. Therefore, the term "drug clearance" is not applicable for those drugs.

  On the other hand, if the liver has a *high capacity to clear a drug*, it does matter how high Q is since it extracts all drug presented to it; it will extract more drug with higher flow en is therefore *flow sensitive*. It can also remove drugs with a high PPB. Therefore, drugs with a high ER are insensitive to the PPB (Table 6). *However, loss of liver mass and decreased blood flow decreases the clearance of both drugs with a high and a low ER; it does not help if only a small number of hepatocytes with normal perfusion are left to extract a certain amount of drug.*

Table 6 Extraction ratio, liver perfusion and protein binding

	Low ER drugs	**High ER drug**
Clearance	Low	High
Capacity limited	Yes. Hepatic elimination of these drugs is determined by their plasma concentration.	No. Because drugs with a high ER are metabolized rapidly, their clearances are about equal to their rates of transport to the liver, i.e. the hepatic blood flow.
Perfusion limited	No. Removal of drug from the blood is dose-dependent (concentration-dependent).	Yes. At clinically relevant concentrations, most of the drug in the afferent hepatic blood is eliminated on first pass through the liver.
PPB sensitive	Yes	No
Kinetics	Zero order	First order
Examples	*Paracetamol, aspirin, phenytoin, diazepam, clindamycin, warfarin, heparin, ethanol, thiopental	Propofol, etomidate, ketamine, morphine, pethidine, pentazocine, lignocaine, labetolol, vecuronium, rocuronium, pancuronium.

* **Peas** & **WHEATS:' P**henytoin, **P**henylbutazone, **W**arfarin, **H**eparin, **E**thanol, **A**spirin, **T**heophylline, **T**olbutamide, **S**alicylates

---

[xix] *Cytokines* are immune-modulating substances, such as interleukins and interferons.
[xx] *Chemokines* are chemotactic cytokines or proteins with the ability to direct chemotaxis in nearby cells.

Multisystem complications of liver disease
The effects differ in the three main groups of liver disease: obstructive jaundice and in acute and chronic hepatocyte loss.

- *Central nervous system manifestations of liver dysfunction*
  Hepatic dysfunction is often complicated by neurological deficits; central (encephalopathy) and peripheral (sensory and autonomic neuropathy; see Chapter 12).

  These complications often overlap with the neurological complications of the causes of liver disease, e.g. alcoholic abuse complicated by a Korsakov psychosis and Wernicke encephalopathy. *Hepatic encephalopathy* is more common in acute liver failure and is ascribed to the accumulation of neurotoxins, e.g. ammonia (not cleared by the urea cycle). The increased ammonia levels in the brain disrupts glucose, glutamate, and glutamine metabolism. It exerts an osmotic effect on glial cells, which leads to cerebral oedema. In addition, abnormal function of endogenous neurotransmitters such as GABA, glutamate, and nitric oxide play a significant role. *Therefore, GABA agonists such as the benzodiazepines must be used sparingly in patients with liver failure.* In patients with liver failure, other metabolic abnormalities also cause decreased consciousness and must also be attended to, e.g. electrolyte disturbances and hypoglycaemia.

- *Cardiovascular manifestations of liver disease*
  The profound disturbances in systemic haemodynamics lie central to the development of *multi-organ failure* in cirrhotic patients. The cardiac output is increased or decreased, and the peripheral circulation is vasodilated and hyporesponsive to vasoconstrictors (hyperdynamic circulation). The cause of liver disease may cause a *cardiomyopathy*, e.g. due to ethanol and haemochromatosis.

  There are microvascular changes in cirrhotic patients, including *arteriolo-venous fistulae* and disseminated intravascular coagulation. The haemodynamic changes are due to decreased clearance of vasoactive substances such as nitric oxide and the development of *arterio-venous fistulae* in the microcirculation. An *acute liver insult*, e.g. hypotension, produces an *inflammatory state* in patients with chronic liver failure, which exacerbates these circulatory changes and *multiorgan failure*.

  Patients with cirrhosis or liver fibrosis often develop *portal hypertension* (PH). The portal circulation is vasodilated by NO and several intestinal hormones, including vasoactive intestinal polypeptide and glucagon. This results in accumulation of blood volume in the portal circulation with hypovolaemia in the central circulation. The congestion caused by PH may contribute to the formation of *protein rich ascites* resulting in intravascular *hypovolaemia*. PH causes the opening of *porto-systemic shunts*, e.g. oesophageal varices. Patients with oesophageal varices may present with *massive haematemesis*. In the gut, the swallowed blood proteins are digested to amino acids, which are deaminated in the liver forming ammonia. The liver cannot clear ammonia since the urea cycle does not work. Therefore, haematemesis is often followed by increased ammonia levels and a *liver encephalopathy*.

- *Haematological manifestation of liver failure*
  These patients are often *anaemic* due to bleeding and malnutrition. *Thrombocytopaenia* is caused by hypersplenism and the decreased production of thrombopoietin. The thrombocytopaenia aggravates the *hypocoagulability* due to decreased production of clotting factors.

- *Pulmonary manifestations of liver dysfunction*
  Pulmonary complications often occur in patients with chronic liver failure. The lung complications usually take the form of low V/Q ratios (see Chapter 13): *Ascites* increases intra-abdominal pressure resulting in lung restriction. *Arterio-venous fistulae* also form on the lungs. These fistulae tend to open in the sitting or standing position resulting shunting of blood through them. Since blood entering the AV fistulae is not oxygenated, patients become hypoxic in the upright position. This is called *platypnoeia* (dyspnoeic) *or orthodeoxia (low PaO_2)*. About 2% of patients with portal hypertension develop pulmonary fibrosis complicated by *pulmonary hypertension (portopulmonary syndrome)*. Severe *portopulmonary syndrome* may cause right cardiac failure and is treated with pulmonary vasodilators such as prostacyclin (epoprostanol).

- *Renal Manifestations of Hepatic Dysfunction*
  The relative hypovolaemia causes hypotension and renal hypoperfusion resulting in the activation of the renin-angiotensin-aldosterone and vasopressin causing constriction of the afferent and efferent arterioles and a decreased GFR. The secondary hyperaldosteronism (increased aldosterone and vasopressin) causes a dilutional hyponatraemia, hypokalaemia, and a metabolic alkalosis). *This is called the hepatorenal syndrome (HRS).* Renal failure occurs commonly in liver disease, takes the form of prerenal oliguria, and is ascribed to hypotension. Thromboxanes and endothelin aggravate renal vasoconstriction. The HRS resembles *prerenal oliguria*, namely increased serum urea and creatinine, increased urine osmolality, and a low FENa (see Appendix). Once this develops, patients need renal replacement therapy and are candidates for liver transplantation. The systemic inflammatory response syndrome (SIRS) plays a role in the development of renal failure in cirrhotic patients. It is ascribed to rightward shift in the renal autoregulation curve (more pressure dependent).

- *Endocrine and metabolic complications*
  Patients with advanced liver impairment are *hypovolaemi*c (vasodilated) and suffer from *secondary hyperaldosteronism* (hyponatraemia, hypokalaemia, metabolic alkalosis). They may be *hypoglycaemic* due to decreased degradation of insulin or *hyperglycaemic* (insulin resistance due to increased glucagon and somatotropin). Decreased sex hormones are common in men and women causing feminisation in men (gynaecomastia, testicular atrophy, impotence) and amenorrhoea and infertility in women. *Hypoglycaemia is important in acute and chronic liver failure, but not in obstructive jaundice.*

Assessment of liver dysfunction (For a complete discussion of liver function tests, please see your Chemical Pathology notes.)

Hepatic function must be assessed preoperatively. The Child-Turcotte-Pugh classification is one of several grading systems used to stratify liver dysfunction and predict postoperative outcome; the higher the score, the worse is the outcome. The variables are encephalopathy, nutritional state, ascites, serum bilirubin, serum albumin, and prothrombin time. These variables reflect the complications of liver disease, synthetic function, and excretory function of the liver. You must know the variables evaluated in liver failure, but you need not know the classification (see Appendix).

The most common perioperative complications are haemorrhage, infection, cardiac failure, pulmonary dysfunction, and renal failure. As is the case with perioperative renal dysfunction, the aim of the history and physical examination is to identify the patients that run the risk to develop perioperative liver failure and initiate steps to prevent further deterioration of liver function (*acute on chronic liver failure*).

- *History and symptoms*
  Since the risk for *perioperative complications increases two- to three-fold* in these patients, it is important to identify liver disease from the history, clinical examination, and special investigations. The liver has a *large physiological reserve. Therefore,* symptoms and signs of chronic liver disease tend to appear late and are often subtle. *The history* may reveal alcohol abuse, use of recreational drugs, sexual promiscuity, blood transfusions, occupational exposure to hepatotoxins, previous jaundice (especially anaesthetic-related), and a family history of liver disease (α_1-antitrypsin deficiency and haemochromatosis). *Symptoms* include anorexia, fatigue, malaise, sleep disturbances, abdominal distension and pain, nausea, vomiting (especially haematemesis), pruritus, bleeding diathesis, and changes in the colour of urine and stools. Relatives may note changes in mood, cognition, and personality.

- *Clinical assessment*
  Signs that may indicate hepatic disease include fetor hepaticus, encephalopathy (decreased consciousness, apraxia, and asterixis), jaundice, pruritus with scratch marks on the skin, spider angiomata, xanthelasma, palmar erythema, gynaecomastia, ascites, caput medusae, a small, large or irregular liver, splenomegaly, and peripheral oedema. However, the possibility of hepatic involvement may only transpire from the *history*.

- *Factors that aggravate perioperative liver dysfunction include*:
  - *Co-morbidities*
    Patients with a history of *alcoholism* usually *smoke,* while *recreational dru*g use is associated with *viral hepatitis and HIV*. Poor *nutritional status* is an independent predictor of postoperative liver failure. In patients with acute *hepatitis*, elective surgery should be postponed until liver function tests have normalized. Depression of hepatocellular function occurs early after *trauma* and severe haemorrhage and persists despite fluid resuscitation. Therefore, trauma in patients with liver disease has a higher mortality.
  - *The elderly*
    Liver *size and perfusion decline* with about 40% between the ages of 20 years and 90 years. *Drug clearance decreases in parallel* with a decrease in liver perfusion. These patients have a decreased liver *enzyme function*, especially P450 cytochrome and metabolite conjugation, with a consequent *increase bioavailability and* $t_{1/2}$. Since geriatric patients are very high consumers of medication, they are more exposed to *drug-related liver damage*. Liver function is also affected by age-related changes in diet and nutritional status (*malnutrition*), alcohol consumption (about 10% elderly patients have *alcohol related* problems), smoking, and co-existent disease. Hepatocellular *carcinoma* is the most common complication of liver cirrhosis in the elderly people.

    Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver abnormalities. NAFLD is mainly related to metabolic disorders including obesity, insulin-resistance, hyperlipidaemia, nutritional disorders, drug use, and hepatotoxins. In Italy, the prevalence of fatty liver increases with age with a peak incidence of about 60% in patients aged between 46 years and 75 years.

- o *Procedures affecting liver function*
  Cardiac, vascular, and pancreatic surgery is associated with an increased incidence of hepatic failure.
- o *Hypovolaemia, hypotension, and increased intraabdominal pressure*
  All hypotensive patients (low cardiac output, absolute or relative hypovolaemia) have decreased liver perfusion and are more susceptible to subsequent toxic and ischaemic insults. Increased intraabdominal pressure decreases perfusion to all intraabdominal organs, except the adrenal glands.
- o *Sepsis*
  Bacterial infection is the *major cause of death in patients with decompensated liver cirrhosis*.
  There is a *cyclical interaction between the SIRS response and infection*: SIRS causes immune deregulation, which predisposes to infection, while infection causes a pro-inflammatory response resulting in SIRS. *SIRS predicts PH-related morbidity*, including bleeding, hepatic encephalopathy, and hepatorenal syndrome. All these complications lead to an increased mortality. Therefore, *septic patients* are more prone to develop liver dysfunction – especially patients with premorbid liver dysfunction.
- o *Patients with established liver dysfunction presenting for diagnostic and therapeutic interventions. Diagnostic procedures* include liver biopsies and endoscopic retrograde cholangiopancreatography (ERCP). *Surgical procedures* include bile duct surgery, hepatectomy, pancreatectomy, porta-caval shunts, and liver transplant. *Surgery involving the hepato-biliary system* is often associated with *substantial fluid shifts* (drainage of ascites, blood loss, air embolism, vena cava clamping, etc.), *metabolic changes* (anaemia, hyper- or hypoglycaemia, metabolic acidosis or alkalosis, hypokalaemia, hypocalcaemia, etc.), and *hypocoagulability*. These are often accompanied by *circulatory compromise* with decreased liver perfusion.
- o *Hepatotoxins*
  A drug history may reveal hepatotoxins, e.g. a history of postoperative jaundice (halothane; see Chapter 6), analgesics (paracetamol), antimicrobial drugs (imidazoles, isoniaside), antineoplastic drugs (anthracyclines), anticonvulsants (sodium valproate), antihypertensives (alpha-methyl-dopa), and recreational substances (cocaine, ethanol, anabolic steroids). Traditional remedies (herbal medicine) may be hepatotoxic. Herbal hepatotoxicity presents with acute hepatic necrosis with liver failure, fatty liver (steatosis), acute and chronic hepatitis, liver fibrosis, bile duct fibrosis, and veno-occlusive disease.

- *Special investigations*
  Since increased enzyme levels also occur in non-hepatic disease, e.g. erythrocyte and muscle disorders, enzyme studies are poor indicators of hepatic function (coagulation, albumin, and bilirubin). *Better indicators of liver function are:*
  - o *Clotting factors*
    Since most clotting factors are synthesized in the liver, the *clotting profile* (PT, PTT, and INR) is the most valuable test for hepatic dysfunction.
    Factor VII has a short $t_{1/2}$ (4 hours to 6 hours), which makes the *prothrombin time* (dependent on factors II, V, VII, and X) a sensitive test for *acute liver failure*. However, vitamin K-dependent factors (II, VII, IX, and X) are also decreased in malnutrition and obstructive jaundice. *Fibrinogen* has a $t_{1/2}$ of 5 days and is not decreased in acute liver failure. *Hyperfibrinolysis* is common in liver failure (treated with cryoprecipitate or fibrinogen). These patients present with a bleeding diathesis, normal fibrinogen levels but increased fibrinogen degradation products (D-dimers). *Disseminated intravascular coagulation* often points to an *underlying endotoxaemia*.
  - o *Serum albumin*
    Serum albumin indicates synthetic liver function, but hypoalbuminaemia also occurs in kidney failure, malnutrition, surgical stress, severe sepsis, burns, etc. Albumin has a $t_{1/2}$ of about 2 weeks and may still be within normal limits in acute liver failure.
  - o *Serum and urine bilirubin* are used to differentiate between pre-, intra, and post-hepatic jaundice.
  - o *Pseudocholine esterase* has a $t_{1/2}$ of about 14 days and is not decreased in acute liver failure. In chronic liver failure, pseudocholine esterase levels parallel albumin levels.
  - o Although *serum ammonia* increases with end-stage liver disease and is implicated in hepatic encephalopathy, it correlates poorly with liver function.
  - o *Other investigations in the patient with liver disease*
    Full blood count: anaemia and thrombocytopenia
    Urea, creatinine, electrolytes, and *acid-base* status
    Electrocardiogram and *evaluation of cardiac reserve as necessary*, e.g. echocardiography (cardiomyopathy, pulmonary hypertension), and stress testing
    Chest radiograph (effusions)

Intraoperative management of patients with liver failure

- *General considerations*
  Preservation of hepatic blood flow is very important. Patients with compensated or marginal organ function may develop frank hepatic failure. Therefore, *hypotension should be avoided*. Intraoperative management is complicated by the multisystem complications of liver disease, particularly cardiovascular (hyperdynamic circulation, hypotension, cardiomyopathy), hepatorenal syndrome, metabolic disturbances, and coagulopathy. These changes affect already decreased organ perfusion (brain, heart, liver, kidney), pharmacokinetics, and pharmacodynamics.

  These patients are very susceptible to the *vasodilatory effect of anaesthetic agents*. Since their haemodynamic state is often characterized by hypotension with an *increased* cardiac output, *positive inotropes are ineffective*. Therefore, *drugs with α_1 properties* should be used, e.g. phenylephrine, noradrenalin, adrenaline, or α doses of dopamine (> 10 μg kg^{-1} min^{-1}).

  In patients with well-compensated liver disease presenting for small procedures with a small risk of significant volume shifts (clamping of large arteries and veins, blood loss), a peripheral intravenous cannula usually suffices. However, in *sick patients* (renal, pulmonary, heart, haematological dysfunction) presenting for *major surgery*, larger venous access and *invasive monitoring* are necessary, e.g. intra-arterial blood pressure, central venous pressure (CVP), and pulmonary artery wedge pressure. These intravascular monitoring catheters are also necessary to detect *sudden haemodynamic changes* and to obtain *blood samples* for haematological (haematocrit, coagulation) and metabolic monitoring (electrolytes, glucose, acid-base). *Blood glucose* must be monitored since patients with advanced liver disease may become hypoglycaemic.

  Since patients with portal hypertension may have *oesophageal varices*, the insertion of a nasogastric tube and monitors such as a transoesophageal echocardiograph probe may cause major bleeding.

  Blood loss during liver surgery can be decreased by putting the patient in a slight *Trendelenburg position* and be keeping the CVP relatively low (below 5 cm H_2O). However, both these measures predispose to *venous air embolism*.

  Liver surgery is often accompanied by *extensive surgical exposure* and *blood loss. Therefore, conservation of body temperature* is important. The patient must be covered with warming convection blankets (Bair Hugger). Warm *intravenous fluids* must be available, i.e. crystalloids, colloids, and blood components (red cells, plasma, clotting factors, platelets). Arrangements must also be made for *red cell salvage*.

  Buffers in intravenous fluids include *lactate (Ringer lactate), acetate (Ringer acetate), and citrate (in blood products)*. It is safer to administer a bicarbonate-containing crystalloid, e.g. *Balsol*. Any cause of decreased liver function, i.e. hypoperfusion (including cardiac failure, hypovolaemia) intrinsic liver failure, and hypothermia decreases the citrate clearance by the liver, causing *citrate toxicity*. Citrate binds calcium. Therefore, *plasma calcium must be monitored* in patients with decreased liver function receiving large quantities of blood products.

  Since patients with chronic hepatitis may be *carriers of the hepatitis B or C viruses* and may be infective, extra caution is indicated in preventing contact with blood and body fluids.

- *Intraoperative drug administration*
  Patients are usually more sensitive to drugs – both regarding *drug effect and duration* of action.
  - *Pharmacokinetics*
    Patients have a decreased ability to clear a wide variety of drugs. They are often hypovolaemic, have a decreased albumin level, while globulins may be elevated. These factors usually lead to an increased volume of distribution, increased free fractions, and therefore, increased drug

effects – but often unpredictable.

- o *Induction agents and sedatives*
  The *induction agents* (to a lesser extent ketamine) have a high plasma protein binding. Therefore, induction doses must be decreased to prevent severe cardiovascular depression and hypotension (particularly propofol and benzodiazepines). All induction agents are metabolised by the liver and have prolonged effects – mainly due to an increased volume of distribution. Therefore, maintenance doses of intravenous anaesthesia, including *propofol*, must be lowered. GABA$_A$ agonists, such as *midazolam,* have an increased and prolonged effect in hepatic failure and must be administered with circumspection during the perioperative period, especially in patients with encephalopathy.

- o *Maintenance of anaesthesia*
  The anaesthetic vapours isoflurane, sevoflurane, and desflurane decrease portal blood flow. However, this decrease is compensated for by a reflex increase in arterial blood flow. *Halothane is contraindicated* in patients with liver disease, it is metabolised to a large extent by the liver and since it decreases both the portal and arterial blood flow.

- o *Opioids*
  Opioids are metabolised by the liver and are highly protein bound. Doses must be decreased and dosage intervals increased. The liver extensively clears *morphine and pethidine*. The pharmacokinetics of *fentanyl, alfentanil, and sufentanil* are affected less. However, the sympatholytic effect of these agents often causes severe *hypotension* – even in normal patients. *Remifentanil* is independent of liver metabolism and is the opioid of choice in patients with liver failure. Opioids can cause *spasm of the sphincter of Oddi*, which may increase biliary pressure. Therefore, opioids may be withheld when intraoperative cholangiography is planned and given if bile duct occlusion has been excluded. I think that the newer opioids may be used safely in this regard.

- o *Muscle relaxants*
  In patients with chronic liver disease, pseudocholine esterase is decreased. Therefore, the duration of action of *suxamethonium and mivacurium* is prolonged. The elimination of the *aminosteroids* pancuronium, vecuronium, and rocuronium is decreased. *Atracurium and cisatracurium* are the muscle relaxants of choice in patients with liver failure since their clearance is organ-independent.

- o *Regional anaesthesia*
  Regional anaesthesia is not contra-indicated in these patients but remember the changed pharmacokinetics (slower clearance), coagulopathy, and neuropathy.

- o Stay away from *NSAIDS* since they can aggravate platelet dysfunction. *Paracetamol* should be avoided or the doses must be decreased.

Postoperative management of the patient with liver failure

Patients who have undergone major hepato-biliary surgery *need intensive care postoperatively*, due to the impact of *extensive surgery* on *organ systems*. This is often complicated by haemodynamic instability, pulmonary dysfunction, blood loss, massive blood transfusion, oliguria, coagulopathy, hypothermia, metabolic disturbances, and the *prolonged effect of anaesthetic drugs*.

Post-operative jaundice

Causes of post-operative jaundice can be divided into pre-, intra-, and post-hepatic.

- *Pre-hepatic (increased bilirubin production)*
  - o Large haematomas
  - o Incompatible blood transfusion with haemolysis
- *Hepatic (hepatocellular dysfunction)*
  - o Underlying liver disease
  - o Ischaemic or hypoxic liver injury
  - o Drugs (e.g. halothane)
- *Post-hepatic (biliary obstruction)*
  - o Post-operative cholecystitis

- o Post-operative pancreatitis
- o Retained bile duct stone

Summary

__The most important aspect op perioperative liver preservation is, as with all vital organs, to recognize disease and prevent further insults. The most important aspect of perioperative liver preservation is perfusion, perfusion, and perfusion__.

APPENDIX

KIDNEY FUNCTION TESTS

Creatinine clearance = $\dfrac{(\text{Urine creatinine} \times \text{Urine volume})}{(\text{Plasma creatinine} \times \text{collection time in minutes})}$

Or Creatinine clearance = $\dfrac{\text{mass}(140 - \text{age})}{\text{asma creatinine } \mu M}$

Fractional excretion of Na$^+$ (FENa)
Measures tubular function, namely ability to concentrate the filtrate.
↑↑UNa can be the result of ↑↑ reabsorption of H_2O
FENa = (UNa × Uvol)/(PNa × GFR) = (UNa × ~~Uvol~~)/[(PNa × (Ukr/Pkr) x ~~Uvol~~)
  = (UNa × Pkr)/(PNa × Ukr)
FENa% = (UNa × Pkr)/(PNa × Ukr) x 100 %
Prerenal uraemia: (↓UNa × ↑Pkr)/↑PNa × ↓Ukr) → FENa < 1%
ATN: (↑UNa × ↑Pkr)/↑PNa × ↑Ukr) → FENa > 1%

Test	Prerenal oliguria	ATN
UNa mM	< 20	> 40
FENa %	< 1%	> 1%
U:P osmol	> 1,3	< 1.3
U:P ureum	> 14	< 14

THE CHILD-TURCOTTE-PUGH CLASSIFICATION

Each of the five variables receives a count form 1 to 3. The minimum score is 5 (5 × 1) and the maximum score is 15 (5 × 3). The total score gives an indication of the postoperative mortality.
Score of ≤ 6 = Child A,
Score 7 to 9 = Child B, and
Score 10 to 15 = Child C

Variable	1	2	3
Serum bilirubin (μM)	< 34	34 – 51	> 51
Serum albumin (g L^{-1})	> 35	30 – 35	< 30
Prothrombin time (s), or INR	0 – 4 < 1.7	> 4 – 6 1.7 – 2.3	> 6 > 2.3
Ascites	Absent	Easily controlled	Poorly controlled
Encephalopathy	Absent	Minimal	Severe

CHAPTER 17

PERI-OPERATIVE APPROACH OF THE PATIENT WITH ENDOCRINE DISORDERS, INCLUDING OBESITY

Key points
- The objective of the Chapter 9s to illustrate the perioperative impact of *endocrine* disorders and *obesity*.
- Endocrine dysfunction has anatomical, physiological, pharmacological implications.
- Disorders must be evaluated and optimised preoperatively.
- Intraoperatively, the primary disease, its complications, and treatment must be considered (monitored and treated).
- Postoperatively, the anatomical, physiological, pharmacological aspects and complications must be diagnosed (monitored) and treated early and appropriately.
- The perioperative management of the obese patient is discussed briefly.

Endocrinology encompasses the study of endocrine organs and the substances they secrete. These organs and their secretions should however not be regarded as separate entities. Their functions are intimately linked and have a wide range of *multisystemic effects*.

The endocrine organs do not only include the *classic endocrine organs*, namely the pituitary gland, thyroid, parathyroid glands, endocrine pancreas, adrenal glands, and gonads. Several *other organs are now regarded as endocrine organs*, including the central nervous system, heart, kidney, gastrointestinal tract, endothelium, etc.

*The aim of this Chapter 9*s not to address endocrine diseases separately, but to give an overview of endocrine disease, particularly endocrine interactions, their significance, and management in the peri-operative setting, i.e. pre-, intra- and postoperatively. A disease that often causes endocrine abnormalities, but is not addressed in this lecture, is *HIV and AIDS. Pregnancy* is addressed elsewhere.

Patients presenting for surgery may:
- need *anaesthesia for the removal of endocrine organs or hormone secreting tumours*, e.g. phaeochromocytoma, hyperthyroidism, Cushing syndrome, acromegaly, etc.
- present for unrelated procedures or *treatment of complications* of the disorder, e.g. vascular surgery in a diabetic, or parathyroidectomy in a patient with renal failure complicated by secondary or tertiary hyperparathyroidism.
- be on *hormonal replacement* after removal of hormone-secreting organs, e.g. hypophysectomy, thyroidectomy, adrenalectomy, or pancreatectomy.
- receive hormones to treat *non-endocrine diseases*, e.g. glucocorticosteroids for autoimmune diseases, asthma, or malignancies.
- be on an *anabolic steroid* or *oral contraceptive*.

Peri-operative interventions, including anaesthesia, or mere *hospitalisation* often illustrate the close relationship between endocrine functions (stress response). These interactions often complicate the peri-operative course of patients suffering from endocrine disease.

FUNCTIONS OF HORMONES

Hormones are multi-tasking communication substances with a wide range of effects. Hormones exert their effects in the following ways:
- *autocrine* (effect receptors on the cell secreting the hormone),
- *paracrine* (effect receptors on cells in the vicinity of the secreting cell),
- *endocrine* (hormones are secreted into the blood stream and have effects on receptors in distant organs),
- *neural*. In *neural communication*, a nerve ending secretes a hormone (neurotransmitter), the hormones diffuse to the postsynaptic receptors on their effector organs. The latter mode of

communication is found, for example, in the hypothalamus-hypophysis communication (trophic hormones, vasopressin, and oxytocin), the preganglionic sympathetic-adrenal medulla stimulation (adrenaline), and postganglionic sympathetic nerve-juxta-glomerular cells (renin).

Endocrine organs communicate with other organs via the nervous system, hormones, cytokines, and growth factors. *Visa versa*, each of these means of communication affects several endocrine organs. Moreover, hormones, growth factors, and cytokines may share the same receptors, e.g. growth hormone (GH) and cytokines, insulin and insulin-like growth factors (IGF), etc.

The *close interplay of hormonal function makes classification of their effects highly artificial*. Examples include the following:
- The central nervous system has a large influence on pituitary function.
- The autonomic nervous system affects the function of several organs, including the heart, gastrointestinal tract, adrenal medulla, kidneys (juxta-glomerular apparatus), and pancreatic islets.
- The adrenal glucocorticosteroid, cortisol, is a potent immunosuppressant.
- Cytokines exert profound effects on endocrine function.
- Endocrine disease may also be caused by dysregulation of immune surveillance and tolerance, e.g. thyroiditis and type I diabetes mellitus.

From a perioperative perspective (pre-, intra-, and postoperative), hormone function can roughly be divided into four general functional areas. These endocrine functions will usually have the following *peri-operative* implications, which must always be kept in mind. Most of the time, endocrine dysfunction involves several of the following entities (m*ulti-system involvement) (Table 1)*:
- *Anatomical*
- *Pathophysiological*
- *Pharmacological*
- *Monitoring*

Anatomical effects
External features often reveal abnormal endocrine function and interactions between hormones, growth factors, immunological function, and the nervous system. Take note of external features, mentation, growth, development, anatomical abnormalities, body mass, height, and pigmentation.

Some hormones (sex hormones) cause closure of epiphyseal growth plates, while others GH, insulin-like growth factor (IGF), and thyroid hormone] stimulate growth. Patients may be *very tall* due to low levels of sex steroids in the presence of growth hormone. Of great interest to the anaesthetist are increased levels of GH after closure of epiphyseal plates. These give rise to facial deformities (*airway; see intraoperative management*), tall stature, and glucose intolerance. *Short stature* is caused by early closure of growth plates (precocious puberty), GH deficiency, hypothyroidism, Cushing syndrome, and diabetes mellitus.

Obesity occurs in Cushing syndrome, hypothyroidism, and diabetes mellitus. Diabetes mellitus with poorly controlled glycaemic control affects growth, as well as abnormal connective tissue with stiffening of joints (spine, airway, thoracic cage compliance). *Weight loss* may occurs in Addison disease, hyperthyroidism, phaeochromocytoma, and diabetes mellitus.

Abnormal pigmentation of the skin and mucus membranes may indicate underlying endocrine disease or hormonal treatment, e.g. *hypopigmentation* in Cushing *syndrome* [high cortisol + low adrenocorticotrophic hormone (ACTH)] and treatment with glucocorticosteroids (low ACTH); *hyperpigmentation* in Addison disease (low cortisol + high ACTH), or Cushing *disease* or ectopic secretion of ACTH by a bronchial carcinoma (high cortisol + high ACTH). *Focal pigmentation* may indicate the presence of neurofibromatosis (café au lait spots), which may be associated with phaeochromocytoma.

Patients may present with *multiple endocrine neoplasias (MEN syndromes)* causing multiple endocrine abnormalities. These diseases often involve other organs, e.g. intracranial, pituitary, parathyroid, thyroid, adrenal medulla, pancreatic, and renal.

Physiological effects: Maintenance of homeostasis

Endocrine disorders affect several physiological functions, e.g. intermediary metabolism (carbohydrates, lipids, and proteins), fluid and electrolytes, acid-base state, reproduction, immunological function, etc. All hormones, growth factors, cytokines, and the nervous system have some effect on homeostasis.

- Several endocrine diseases are complicated by abnormal *intelligence and/or mentation, ranging from coma, delirium, and psychosis*. These conditions include Cushing syndrome, Addison disease, phaeochromocytoma, hyperthyroidism, cretinism, myxoedema, and diabetes mellitus.
- *Thyroid hormone* controls about 25% of basal metabolic rate in most tissues and sensitises β adrenergic receptors. Hyper- and hypothyroidism cause hyper- and hypometabolic states, respectively.
- Apart from its own effect, *cortisol* has a permissive effect on the actions of several hormones, e.g. thyroid hormone, glucagon, aldosterone.
- *Parathyroid hormone* (PTH) and *vitamin D* regulate calcium and phosphate levels as well as bone physiology. Hyperparathyroidism may be primary (parathyroid adenoma, bronchial carcinoma), secondary (hypocalcaemia complicating renal failure), or tertiary (following secondary hyperparathyroidism). Hypoparathyroidism may result from inadvertent removal of the parathyroid glands during thyroidectomy.
- *Vasopressin (antidiuretic hormone)* is secreted by the neurohypophysis. It regulates plasma *osmolality* and *volume* through its effect on water intake (thirst) and tubular reabsorption of water. The effect of vasopressin on absorption of water is facilitated by cortisol and thyroid hormone. Vasopressin is a *stress hormone* and is secreted during hypotension and hyperosmotic states (appropriate secretion). The *syndrome of inappropriate secretion of vasopressin (SIADH)* may be caused by intracranial tumours, porphyria, hypothyroidism, and drugs. Several drugs are associated with SIADH but the three drug classes most commonly implicated in inappropriate secretion of vasopressin are psychotropic agents (haloperidol, fluoxetine, tricyclic antidepressants), sulfonylureas, and Vinca alkaloids (vincristine and vinblastine). A vasopressin deficiency may follow injury or surgery of the hypophysis. This is complicated by diabetes insipidus (water diuresis and hypernatraemia).
- *The mineralocorticosteroid aldosterone* controls plasma volume, potassium, and sodium concentrations. One of the most common endocrine abnormalities is *secondary hyperaldosteronism*. All conditions that stimulate renin secretion, increase angiotensin II and aldosterone levels, as well as hypotension-induced increased levels of *vasopressin*. This condition is characterised by hyper- (cardiac failure, liver failure, renal failure, lung disease) or hypovolaemia (dehydration, haemorrhage, diuresis), hyponatraemia, hypokalaemia, and a metabolic alkalosis.
- *Insulin* is one of the main anabolic hormones, which control carbohydrate, protein, and fat metabolism (anabolism) as well as intracellular movement of glucose and amino acids. The *hypoglycaemic effect of insulin is immediately counteracted* by glucagon and adrenaline and *over the long term,* by cortisol and GH. Type I diabetes mellitus is caused by an absolute insulin deficiency due to autoimmune destruction of β cells, while Type II is caused by insulin resistance. Metabolic complications of diabetes mellitus include hypoglycaemia, diabetic keto-acidosis, non-ketotic hyperosmolar crisis, and lactic acidosis. Over production of insulin (*insulinoma*) and an insulin overdose cause hypoglycaemia and hypokalaemia.
- *Reproduction* is often affected by endocrine disease. A wide range of hormones, growth factors, cytokines, and prostaglandins influence all the stages of reproduction (sex determination, sexual maturation, conception, pregnancy, lactation, and cessation of reproductive capability). The anaesthetist must take note of changes in, or *abnormal secondary sexual features*, abnormal hair growth, muscle mass, and gynaecomastia. These findings may indicate *abnormal levels of sex*

hormones, e.g. hormonal treatment (treatment with sex hormones, glucocorticosteroids, or anabolic steroids), and liver cirrhosis (alcoholism). Abnormalities in sexual development may be accompanied by abnormal *electrolytes and hypertension*, e.g. congenital adrenal hyperplasia.

- *Paraneoplastic secretion of hormones* may cause endocrine disease, e.g. bronchial carcinoma may secrete ACTH, vasopressin, and PTH.
- *The stress response* is evoked by psychological and physical stress (environmental exposure, exercise, surgery, and trauma). This response *activates multiple* endocrine and cytokine pathways, which mount the physiological response to stress. Stress activates the *sympathetic nervous system* and the *hypothalamus.* The hypothalamus secretes vasopressin, and several releasing hormones (liberins). These releasing hormones and cytokines increase the production of trophic hormones (ACTH, GH, TSH, and prolactin). This is followed by an increase in adrenaline, cortisol, thyroxin, glucagon, as well as the renin-angiotensin-aldosterone system. The stress response results in the activation of survival mechanisms, including cardiovascular stimulation, catabolism (gluconeogenesis, glycogenolysis, lipolysis) sodium and water retention, and very importantly, an increase in oxygen consumption.

  Although the stress response may have deleterious effects, it is essential for survival. *Inability* to mount a stress response (*stress hormones and adequate oxygen flux*) is complicated by severe inability to maintain homeostasis. This may, for example occur in patients with low levels of ACTH (during or after glucocorticoid therapy), hypothyroidism, any cause that impedes the ability to increase oxygen flux.

Pharmacological aspects

Patients suffering from endocrine disorders often receive *pharmacotherapy* to *suppress* over-production of hormones and to treat the *complications* of the particular disease. After removal of endocrine organs, patients often need *replacement therapy.* Hormones are also used for *contraception* and in *recreation*:

- After *hypophysectomy,* patients receive several replacement hormones, including arginin vasopressin (vasopressin) for *diabetes insipidus*. *SIADH* is treated with water restriction, hypertonic saline, and demeclocycline.
- *Diabetics* are on insulin and/or oral treatment for *glycaemic control*, as well as on *treatment of complications* of DM, including hypertension, ischaemic heart disease, and renal failure.
- *Hyperthyroid* patients are on antithyroid drugs and/or β-blockers.
- *Hypothyroid* patients receive thyroxin.
- Patients with *adrenocortical failure* receive gluco- and mineralocorticosteroid replacement therapy.
- *Phaeochromocytoma* is treated with α-, and often, β-blockers.
- *Acromegaly* may be complicated by diabetes mellitus wherefore they receive treatment.
- Patients with *ovarian failure* receive hormonal replacement therapy. *Oral contraception* is one of the most commonly prescribed hormonal drugs. Both these groups of patients may suffer from complications, including hypercoagulability.
- A very common endocrine manipulation, which is rarely regarded as an endocrine disorder, is the prescription of *angiotensin converting enzyme inhibitors and angiotensin II antagonists*. Both these groups of drugs have profound physiological effects characterised by blunting of the sympathetic cardiovascular as well as volume and electrolyte response to a cardiovascular suppression and blood loss.
- *Non-endocrine disease may be treated with hormones*, e.g. *glucocorticosteroids* are used in the treatment of autoimmune diseases, malignancies, asthma, inflammatory bowel disease, etc. Corticosteroids affect glucose tolerance (hyperglycaemia) and water and electrolyte homeostasis (hypokalaemia, hypertension). These drugs cause prolonged suppression of the hypothalamo-pituitary-adrenal axis. This axis is essential for the stress response during the peri-operative period. If the adrenal cortex fails to respond during stress, the relative cortisol deficiency is complicated by hypovolaemia, hyponatraemia, hyperkalaemia, hypoglycaemia and suppression of

consciousness (Addison crisis).

- *Anabolic steroids* cause aggression, gynaecomastia, cardiovascular diseases (dyslipidaemia, atherosclerosis, hypertension, cardiomegaly, and ischaemic heart disease), erythrocytosis, hypercoagulability, and liver failure.

Table 1 Complications of endocrine disease include

Complication	Disease	Effect
Mass effects	Thyroid, hypophysis	Thyroid goitre causing displacement of the trachea, mediastinal mass, pituitary tumour causing bitemporal blindness
Central nervous system	DM, hyper- and hypothyroidism, Cushing, Addison, anabolic steroids	Altered consciousness, psychosis
Neuropathy	DM, hyper- and hypothyroidism, acromegaly	Autonomic neuropathy of diabetes mellitus (gastroparesis, postural hypotension,), Carpal tunnel syndrome
Eyes	DM, hyperthyroidism	Exophthalmos, retinopathy, cataracts.
Cardiovascular	DM, Cushing, Conn, Addison, hyper- and hypothyroidism	Hypertension, hypotension, cardiac dysrhythmias, atherosclerosis, ischaemic heart disease, sudden death, peripheral vascular disease, impotence
Gastrointestinal	DM, Thyroid	Gastroparesis, diarrhoea, constipation
Renal failure	DM, phaeochromocytoma	Hypertension, water and electrolyte disturbances
Musculoskeletal	DM, acromegaly	Muscle atrophy, joint stiffening (airway, atlanto-occipital joints, fingers), osteoporosis
Reticulo-endothelial	DM, Cushing	Anaemia, polycythaemia, immunoparesis, thrombocytopathy
Homeostatic	All endocrine diseases	Glucose, lipids, protein, electrolytes, acid-base, and water.
Temperature	Thyroid	Hyperthermia (high T_4), hypothermia (low T_4)

Monitoring of endocrine disease

Due to the anatomic, physiological, and pharmacological effects of these diseases, their effects must be assessed peri-operatively. Special investigations are often indicated to assess complications (anatomical and pathophysiological) and therapy. Patients must be *adequately evaluated, including* haematological, chemical, radiological (chest X ray, CT, MRI, angiography, isotope imaging, echographic) regarding complications, tumour location, size, mass effects, involvement of the upper airway, lungs, mediastinum (lower airways, heart, large vessels), vascular involvement in the abdomen, multicentricity and function (physiological effects) of tumours. This is particularly true regarding intracranial masses, thyroid, acromegaly, mediastinal tumours, multiple endocrine neoplasia, and paraneoplastic syndromes.

PREOPERATIVE MANAGEMENT OF THE PATIENT WITH ENDOCRINE DISEASE

Cognisance of *anatomical (mass effects), physiological (homeostasis), and pharmacological aspects (treatment) endocrine disease is* essential preoperatively. For all but immediately lifesaving procedures, *homeostatic control and treatment of complications must be optimised*. The conditions must be stabilized on the treatment for *the primary diseases and their complications*. The results of *special investigations* must be available and acted on appropriately.

During the preoperative consultation the surgical plan, foreseen complications, and *intra- and postoperative course must be discussed*, e.g. blood loss, blood salvage, and availability of high care facilities postoperatively.

Patients must as far as practically possible:

- Be adequately *evaluated*.
- Be *normoglycaemic* (DM, Cushing syndrome, Addison disease, acromegaly, phaeo-chromocytoma).
- Be *normovolaemic* (DM, Conn syndrome, Addison disease, phaeochromocytoma, diabetes insipidus, hyperparathyroidism, hypertension).
- Have a *normal electrolyte and acid-base profile* (DM, Cushing syndrome, Addison disease, acromegaly, phaeochromocytoma, hyperparathyroidism, and hypertension).
- Be *chemically and clinically euthyroid* (hyper- and hypothyroidism, panhypopituitarism).
- Be *cardiovascularly stable* (phaeochromocytoma, DM, Cushing syndrome, Conn syndrome, Addison disease, hyper- and hypothyroidism).
- have an acceptable *haematocrit*.

The preoperative prescription

In general, patients *remain on their routine medication*. Two notable *exceptions* are *DM and patients taking glucocorticosteroids*. Due to the increased requirements for insulin and cortisol during physiological stress and the nil *per os* period peri-operatively, therapy must be revised. This applies in particular to patients undergoing major or emergency procedures (preoperative fasting, bowel preparation, dehydration, blood loss, sepsis, hypothermia).

- Regarding *diabetes mellitus* presenting for *major surgery*, *oral hypoglycaemic* drugs must be stopped and glycaemic control (blood glucose 5 mM to 10 mM) must be established with insulin at least one day before surgery. Surgery on diabetics should be scheduled in the morning. The oral hypoglycaemic agents are detrimental; the sulfonylureas may cause hypoglycaemia, while the biguanides (metformin) may cause a lactic acidosis. Long acting insulin must be replaced by *short-acting insulin*, ideally intravenously. Short-acting insulin is administered according to a sliding scale to maintain blood glucose within the normal range. The sliding scale is necessitated by the unpredictable insulin requirements characteristic of the peri-operative period (Table 3). The continuous intravenous sliding scale is more physiological and preferred method.

Table 2 Insulin sliding scales

Route	Dose	Monitor
Intravenous (mU/mM/kg/h)*	4 mU mM^{-1} kg^{-1} h^{-1}× glucose mM - 20 mU mM^{-1} kg^{-1} h^{-1}	Hourly
or*	1,8 mU mM^{-1} kg^{-1} h^{-1}× glucose mM	Hourly
Subcutaneous (mU/kg/6h^{-1})*	20 mU mM^{-1} kg^{-1} 6h^{-1}× glucose mM - 100 mM^{-1} kg^{-1} 6h^{-1}	6-hourly
or*	9 mU mM^{-1} kg^{-1} 6h^{-1}× glucose (mM)	6-hourly

*No insulin given if the plasma glucose is ≤ 5 mM; mM is mmol/l; 1 mU = 1 milli-unit; 1000 mU = 1 U

Example:
A plasma glucose of 15 mM in a patient with a body mass of 60 kg.
IV insulin dose (mU/kg/h) = 4 mU mM^{-1} kg^{-1} h^{-1}× glucose (mM) – 20 mU kg^{-1} h^{-1}
$$= 4 \times 15 \text{ mU kg}^{-1} \text{ h}^{-1} – 20 \text{ mU kg}^{-1} \text{ h}^{-1} = 60 – 20 \text{ mU kg}^{-1} \text{ h}^{-1}$$
$$= 40 \text{ mUkg}^{-1} \text{ h}^{-1}$$
Therefore, for 60 kg = 40 mUkg^{-1} h^{-1} × 60 kg = 2400 mU h^{-1} = 2.4 U h^{-1} IVI (1000 mU = 1.0 U)

The insulin is stopped if the plasma glucose decreases to below 5 mM. In the case of intermittent subcutaneous insulin, one dose is skipped and the next dose decreased by 25%. If the slicing scale does not control the hyperglycaemia, the sliding scale is adjusted 25% upward.

- *The healthy human needs about 0.3 mg kg^{-1} cortisol daily*. Due to the peri-operative stress response, *cortisol requirements increase three- to four-fold*. This increase is absent in patients with suppressed hypothalamo-pituitary-adrenal axes, namely Cushing syndrome and patients receiving glucocorticosteroid therapy. These patients receive their normal dose on the morning before surgery. In addition they receive about three times the normal cortisol requirement, i.e. 1 mg kg^{-}

[1]daily intravenously, usually, about 0,3 mg kg^{-1}8-hourly. Patients must be monitored for any signs of a cortisol deficiency (Addison crisis, namely altered consciousness, hypotension, hyponatraemia, hyperkalaemia, and hypoglycaemia).

INTRAOPERATIVE MANAGEMENT

The primary endocrine disease, its complications, other co-existing disease, and current treatment determine the intraoperative management. Particular attention is given to anatomical, physiological, pharmacological, and monitoring aspects of the diseases.

Anatomical aspects

The position of the tumour *per se* may result in considerable *cardiovascular instability*, e.g. tumours in the head, neck (carotid reflexes), mediastinum, and proximity to, or involvement of large vessels such as the aorta and the venae cavae (major blood loss or kinking of vessels).

Preoperative airway evaluation is of the utmost importance. Depending on these findings, normal endotracheal intubation may be safe. However, an awake fibreoptic intubation may be required if the trachea is pushed to the side, or if the thyroid presents as a mediastinal mass. A *mediastinal mass* may result in life-threatening cardiovascular and respiratory collapse during induction of anaesthesia. All patients with airway involvement must be *extubated **only** when they are fully awake*, muscle relaxation properly reversed, and they are able to maintain and clear their airways.

Airway management may be complicated by direct airway involvement (obesity, large thyroid, stiff joint syndrome of DM, acromegaly) or due to an increased risk to regurgitation and aspiration during induction and intubation (obesity, diabetic autonomic neuropathy with gastroparesis).

A patient may present for a thyroidectomy to treat hyperthyroidism, or to remove a thyroid tumour or large goitre. This *procedure may be complicated* by the *position and size of the gland* (in the neck, extending retrosternally, or intrathoracic). When the airway is narrowed or displaced, a *reinforced thinner endotracheal tube* should be considered.

The possibility of *tracheomalacia* due to long-standing pressure of a large thyroid on the trachea must always be considered when a patient is extubated postoperatively. Furthermore, injury to the recurrent laryngeal nerves may result in *adductor spasm* of the vocal cords. Both these complications may necessitate re-intubation. (Remember, injury of the recurrent laryngeal nerves cause adduction, while transection causes abduction of the vocal cords.

Physiological aspects

The *physiological effects* of the endocrine condition have intraoperative implications. The *release of large amounts of thyroxin* may result in a thyroid storm. The removal of a phaeochromocytoma is accompanied by the release of large amounts of catecholamines, and subsequent haemodynamic instability.

Pharmacological aspects

Patients may receive drugs to control the endocrine condition or its complications, e.g. hypertension, ischaemic heart disease. The interactions between these drugs and the effect of the procedure and the anaesthetic technique must be borne in mind.

Apart from hyperglycaemia, *diabetes mellitus* is often complicated by hypertension, ischaemic heart disease, renal impairment, and autonomic neuropathy (resting tachycardia, painless myocardial ischaemia, gastroparesis, diarrhoea). All these aspects must be attended to intraoperatively. The fluid of choice is a balanced electrolyte solution, e.g. Ringer lactate or Balsol[R]; *normal saline is not used in diabetic patients* because it causes a hyperchloraemic acidosis. Other resuscitation fluids (artificial colloid, blood, plasma, platelets) are used as necessary. An electrolyte solution containing 10% glucose is given at 1 ml kg^{-1} h^{-1}.

The intraoperative course of resection of a *phaeochromocytoma* can be very stormy. Patients often receive sympatholytic (esmolol) or sympathomimetic (adrenaline, phenylephrine) drugs, vasodilators (glyceryl trinitrate, magnesium sulphate), and often, large volumes of fluid.

Since ketamine is an indirect sympathomimetic, it should be avoided in hyperthyroidism and phaeochromocytoma. Avoid *droperidol* in patients with a phaeochromocytoma. *Hypothyroid patients* are more sensitive for anaesthetic drugs, become hypothermic more often, and emergence from anaesthesia may be slow. Even a single dose of *etomidate* suppresses cortisol secretion and is contraindicated in patients with adrenocortical insufficiency.

Intra-operative monitoring

The anatomical and physiological effects, the pharmacotherapy of the disease, as well as the surgical approach dictate the extent of *monitoring*. For example, phaeochromocytoma patients are renowned for their cardiovascular instability. *Invasive cardiovascular monitoring* is necessary to monitor cardiovascular function during stressful episodes (induction, intubation, and tumour resection), and control thereof (vasodilators, adrenaline, magnesium). Patients with complicated endocrine disease often suffer from numerous complications, particularly cardiovascular, neurological (autonomic neuropathy), renal, and homeostatic (biochemical). These patients are therefore prone physiological instability, which justifies invasive cardiovascular monitoring and regular assessment of homeostatic function (acid-base, electrolytes, haematocrit, glucose, urinary output, temperature).

In diabetic patients, homeostasis is monitored at least hourly. The plasma glucose must be kept within normal limits, or at least < 11 mM. Insulin resistance is often observed during major surgery and is treated with an insulin infusion according to a sliding scale (see above). Often, this sliding scale must be adjusted upwards to control hyperglycaemia.

POSTOPERATIVE MANAGEMENT

Anatomical aspects

Airway obstruction may occur in the postoperative period. *After thyroidectomy*, airway obstruction may occur due to tracheomalacia, haematoma, or tetany (acute hypocalcaemia).

Physiological aspects

After removal of hormone secreting organs or tumours the opposite of preoperative abnormalities may ensue, e.g. hypotension and hypoglycaemia after removal of a phaeochromocytoma, hypothyroidism after thyroidectomy, hypocalcaemia after thyroidectomy or parathyroidectomy, panhypopituitarism after hypophysectomy, and cortisol deficiency after adrenalectomy.

Prolonged emergence may be caused by hyper- or hypoglycaemia, ketoacidosis, myxoedema, hyponatraemia, or hypothermia. A *myxoedema crisis* must be kept in mind in hypothyroid patients who do not wake up postoperatively. They present with coma, hypothermia, hypotension, bradycardia, and severe hyponatraemia and hypochloraemia. It is treated with T_3, cortisol, and passive warming.

Large amounts of thyroxin may be released during thyroidectomy. This causes the sudden onset of severe hyperthyroidism (*thyroid storm, thyrotoxic crisis*). This may occur intraoperatively in inadequately prepared patients, but usually manifest six to eighteen hours postoperatively. It is a medical emergency and is characterised by agitation, hyperthermia, tachycardia, dehydration, cardiac failure and eventually circulatory shock. *Thyroid storm* is treated as follows:
- rehydration with cooled intravenous fluid, e.g. Ringer lactate. You must monitor the central venous pressure in the presence of cardiac failure.
- the short-acting intravenous β blocker esmolol 0.5 mg kg^{-1} to 1 mg kg^{-1} , or oral (nasogastric) propranolol 1 mg kg^{-1} to 2 mg kg^{-1} six-hourly. Propranolol inhibits the conversion of T_4 to the active hormone T_3.

- cortisol, about 1.5 mg kg^{-1} intravenously eight-hourly.

As pointed out earlier, *the stress response* to surgery increases the need for stress hormones and insulin. A relative T$_3$ deficiency may occur during stress. The diagnosis a *sick euthyroid syndrome (SETS)* is challenging. SETS usually occur during critical illness in patients with a history of hypothyroidism who present with the clinical picture of cardiac failure. The hormone profile may vary but is usually characterised by a *low* TSH, and a normal, high or low total T$_4$. T$_4$ is de-iodated to the inactive reverse T$_3$ (rT$_3$) and T$_3$ sulphate, instead of to T$_3$. Therefore, thyroid function tests may be misleading. These patients must receive T$_3$.

Pharmacological aspects
Patients from whom hormone-secreting tumours have been removed, often need *hormone replacement,* e.g. multiple hormones after hypophysectomy, catecholamines after removal of a phaeochromocytoma, thyroxin after a thyroidectomy, and corticosteroids after adrenalectomy. *Diabetic patients* are more susceptible to the respiratory suppression of sedatives and opioids. *Patients who received hormones preoperatively* will probably need larger doses postoperatively, e.g. diabetics, patients on corticosteroids, and hypothyroid patients. It is important that patients receive all their *non-endocrine treatment* postoperatively, e.g. antihypertensive drugs and cholesterol-lowering agents (statins). *As healing progresses* postoperatively, the stress response fades and the requirements of endocrine therapy return to preoperative doses.

Postoperative monitoring
From the above it should be clear that patients suffering from endocrine disease or those that had hormone-secreting tumours removed, must be cared for in *high-care units* postoperatively. Here, anatomical and physiological function can be monitored, and complications observed early and treated appropriately.

OBESITY

Obesity is defined in terms of *Body Mass Index (BMI)* (Table 3). While obesity may occur as an entity on its own (over-eating, lack of exercise), is commonly a component of an underlying disease of disease complex. *Obesity often has an endocrine component*, the influence of leptin, hypothyroidism, apathetic hyperthyroidism in the elderly, Cushing syndrome and disease, glucocorticosteroid treatment, diabetes mellitus (especially Type II), the *metabolic syndrome* (truncal obesity, dyslipidaemia, hypertension, and insulin resistance), polycystic ovarian syndrome (polycystic ovaries, obesity, hirsutism, and insulin resistance), and more uncommon diseases such as the Prader-Willey syndrome.

As was illustrated with the endocrine disorders, obesity has *anatomical, physiological, pharmacological, and monitoring components*. Obesity may be a *consequence* of an underlying disease but is also complicated *by several multisystem disorders*.

Table 3 Body mass index

BMI (kg m^{-1})	Classification
< 25	Normal
25 to < 30	Overweight
30 to < 35	Obesity
< 35 to < 50	Morbid obesity
> 50	Super morbid obesity

BMI = Body mass in kg/(Height in m)^2

Anatomical considerations

- *Airway management may be problematic*. Mask ventilation may be difficult and laryngoscopy may be challenging. It is often difficult to insert the laryngoscope in the presence of large breasts. Visibility of airway structures during laryngoscopy may also be impeded by a short thick neck, excessive pharyngeal soft tissue, large tongue, anterior larynx, and limited atlanto-occipital extension and neck flexion (sniffing position) due to the accumulation of fat on the back (buffalo hump).

  These problems can, to some degree be overcome by *positioning* the patient on a ramp of pillows beneath the thorax and head. This position allows abdominal and breast fat to fall to the sides and caudally. It opens up the angle between the chin and the thorax and may facilitate atlanto-occipital extension and neck flexion. The anaesthetist must always have *devices available to manage a difficult airway*. He will also need at least two assistants to manage the airway. These patients must be extubated postoperatively only once they are fully awake and have regained their muscle tone.
- All the above anatomical features contribute to *obstructive sleep apnoea (OSA)*.
- There is an increased risk for *aspiration* due to hiatus hernia. A *rapid sequence induction* with suxamethonium is therefore preferred.
- Putting up *intravenous lines* is often challenging.
- *Blood pressure measurement* can be problematic, as the cuff may too small. Therefore, direct (intra-arterial) blood pressure measurement may be prudent before induction of anaesthesia.
- They have a decrease in *chest wall compliance, resulting in restrictive lung mechanics* similar to restrictive lung disease.
- They have a decrease in *functional residual capacity* (FRC).
- *Intraoperative positioning* may be challenging. Attend to ventilation (avoid the Trendelenburg position) and pressure points. Support the limbs on pillows. Two theatre tables may be necessary.

Physiological aspects

- The obesity may be part of an *endocrine disease*.
- Patients have an increased *blood volume* and an increased *cardiac output*.
- They are often *hypertensive*.
- *Cardiomegaly* is common (cardiomyopathy of obesity).
- Patients have an increased incidence of *ischaemic heart disease, diabetes hypertension, high cholesterol*.
- Hypoventilation, including OSA, is often complicated by hypoxia, hypercapnia, day-time somnolence, pulmonary hypertension, and eventually, cor pulmonale (*Pickwick syndrome*). See also Chapter 3 for a discussion about OSA.
- Obese patients have an increased *oxygen consumption and CO_2 production*.
- As they do not tolerate a *period of apnoea* (low FRC), *oxygenation* before induction of anaesthesia is essential.
- They have an increase in minute volume and work of breathing. Therefore, they need *controlled ventilation*. For mechanical ventilation, *tidal volume* is *calculated* according to *ideal body mass (IBM)[xxi] in kg, i.e.* height (cm) – 100 in men and height (cm) – 105 in women, while *minute volume* is calculated according to *a mass corrected for obesity. i.e. the obesity-derived dose mass (see below)*. Body mass with a normal amount of fat (about 15%) can also be calculated according to the following formula: The % of fat body mass that is lean = $100/\sqrt{(BMI/22)}$

  Why the distinction between ideal and lean body mass? Remember, the lungs and thorax do not grow bigger the fatter a person gets. Therefore, the tidal volume is calculated according to the mass he/she would be if not fat, i.e. IBM. However, the fatter one gets, the more muscle one needs

---

[xxi] IBM (kg) = height in cm – 100 for men and height in cm – 105 for women or $22(m^2)$

to carry the fat and the more blood you need to perfuse the extra muscle and fat. ***Therefore, the lean body mass (mass without fat, i.e. muscle + organs + bone + extracellular fluid) of an obese patient is more than the lean body mass of a person with a normal IBM.*** Since the obese patient has more metabolically active tissue, especially muscle, they consume more oxygen per minute and produce more CO_2. *Therefore, the minute ventilation is set according to a body mass with a normal amount of fat, and not ideal body mass.*

An alternative and easier way to calculate doses in obese patients, is the *obese dose-determining mass (ODDM)*:

$$ODDM = IBM + 0.4(\text{total body mass} - IBM)$$

Example: What is the ODDM of a man 1.5 m (150 cm) tall and weighing 80 kg?

$$ODDM = (150 - 100) + 0.4[80 - (150 - 100)] = 50 + 0.4(80 - 50) = 50 + 12 = 62 \text{ kg}$$

Pharmacological considerations

- Take into account the treatment of all their *co-morbid conditions*, e.g. hypertension, diabetes mellitus, ischaemic heart disease, etc.
- Prophylaxis against deep venous thrombosis is essential.
- Obese patients have an increased central volume of distribution (larger blood volume and muscle mass). These patients, especially when they are *morbidly obese*, also have an increased *volume of distribution* for *fat-soluble* drugs; *water-soluble* drugs are affected less. Although lipophilic drugs have a large volume of distribution in these patients, and while the central volume of distribution (blood, lungs, heart, and brain) is increased, fat is not well perfused. Thus, even *lipophilic drugs* should be administered in doses calculated according .to the *ODDM*. The doses of *hydrophilic drugs*, such as *muscle relaxants* and drugs that work in the distribution phase (*induction agents*) are calculated according to the *ODDM*.
- Regarding *induction agents*, it should be kept in mind that redistribution of the induction agents may be rapid, resulting in rapid emergence. Therefore, both *loading doses* of total intravenous anaesthesia as well as maintenance doses are calculated according to *ODDM*. However, studies are needed to confirm this statement. Computer models describing total intravenous anaesthesia often exclude severe obesity. It is however safer to start with doses according to ODDM.
- The *anaesthetic vapours* are lipophilic and accumulate in the fatty tissue with time, resulting in prolonged emergence postoperatively. Therefore, anaesthetic drugs (inhalational and intravenous) are stopped earlier.
- Since drug *effect in these patients are less predictable*, *drugs with short $t_{1/2}$s should be used and titrated to effect* using *monitors* such as neuromuscular stimulation, spectral entropy or bispectral index (BIS) of the EEG.
- Drugs used in *acute management of cardiovascular disorders have a small volume of distribution* and have a small therapeutic index. Therefore, drugs such as adrenaline, phenylephrine, and glyceryl trinitrate are administered according to ODDM. Again, these drugs have short $t_{1/2}$s and should be titrated to effect. Generally, morbidly obese patients should receive dosages calculated according to a mass nearer to the IBM or ODDM than fat body mass and titrated to monitored effect. This approach applies to both lipophilic and hydrophilic drugs.
- *Prevent aspiration* of acid stomach content by the preoperative prescription of sodium citrate and a H_2 antagonist such as ranitidine.
- *Regarding analgesia*, bioavailability of drugs administered subcutaneously is poor, while the uptake from the intramuscular rout is at best unpredictable. Intravenous analgesia, preferably as patient-controlled analgesia, is recommended. Since obese patients are more susceptible to the respiratory complications, epidural analgesia and nerve blocks should be attempted. Since these techniques may be difficult to perform in obese patients, they often fail.

Monitoring

- *Preoperative special investigations* regarding the anatomical, physiological, and pharmacological aspects of the surgical disease, co-morbid disease and therapy are essential to plan intra- and postoperative management.

- *Invasive blood pressure monitoring* is often necessary. The cardiovascular and pulmonary involvement necessitates insertion of an arterial cannula. The arterial cannula is used to measure *blood pressure measurement and for blood gas analysis*.
- Obese patient often suffer from several *co-morbid conditions*. These must be monitored *intraoperatively as well as postoperatively*. Therefore, admission to a *high care facility* postoperatively is justified. *Postoperative mechanical ventilatory support* is often indicated until ventilatory function has returned.

CONCLUSION

Endocrine dysfunction has anatomical, physiological, pharmacological implications (external features, maintenance of homeostasis, and reproduction). Endocrine disorders must be evaluated and optimised during the preoperative period. Intraoperatively, the primary endocrine disease, its complications, other co-existing disease, and treatment must be managed. Particular attention must be given to homeostasis, cardiovascular, and respiratory function, including airway management. Postoperatively homeostasis, cardiovascular, respiratory, and neurological function must be monitored. Complications must be treated early and appropriately.

APPENDIX

Example**:**
A male patient with a body mass of 80 kg is 1.5 m (150 cm) tall. What is the body mass corrected for obesity?
The BMI = $80 \text{ kg}/(1.5)^2 = 35.3 \text{ kg m}^{-2} \approx 35 \text{ kg m}^{-2}$

Corrected body mass (%) = $100/\sqrt{(BMI/22)} = 100/\sqrt{(35/22)} = 79\%$

$35.3 \approx 35\%$ and corresponds to 79%
Therefore, the corrected body mass of the patient = 79% of 80 kg = 63.2 kg $\approx$ 63 kg.

The *obese dose-determining mass* (ODDM) is easier:
IBM = 150 − 100 = 50 kg.
ODDM = 50 + 0.4(80 − 50) = 50 + 0.4(30) = 50 + 12 = 62 kg.

CHAPTER 18

FLUID MANAGEMENT AND BLOOD TRANSFUSION

Key points:

- *Hypovolaemia* is the most common cause of peri-operative hypotension. It is essential to recognize and immediately correct hypovolaemia of any cause.
- *Intra-operative fluid requirements* include the sum of the following : maintenance requirements, replacement of the losses during the nil per os period and replacement of any third space losses or blood loss occurring during surgery.
- *Perioperative evaluation and correction of fluid disturbances*
- *The contents , advantages*, disadvantages and uses of the various crystalloid and colloid solutions
- *Fluid replacement depends on* the volume, concentration and composition of the fluid lost. In general isotonic fluids are used for resuscitation and hypotonic fluids are used as maintenance fluids.
- *Guidelines for the use of blood products* have been laid down and should be followed.
- *Changes in stored blood*
- *Metabolic derangements* after a massive blood transfusion.
- *Complications* of blood product transfusion
- Anaesthetic implications of *electrolyte disturbances* including sodium, potassium and calcium

All chemical reactions in the body occur in water as solvent. The reactions occur intracellularly and extracellularly. These reactions are facilitated by enzymes and membrane function (channels, ion pumps) and require a particular osmolality (mmol dissolved particles per kg of water), electrolyte composition (concentration and ratios between solutes), pH, and temperature. Water forms the largest part of the body (Tables 1 and 2). The student must reread this paragraph. Every aspect mentioned is of the utmost importance. The impact of inappropriate fluid therapy on perioperative morbidity and mortality is probably gravely underestimated. The British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients is worth reading.[23]

Remember, intravenous fluids must be regarded as pharmacological agents (drugs); they have particular indications, contraindications, dosages, side effects, toxicities, and antidotes. However, as is the case with many important aspects of medicine: the greater the impact, the more the controversy. Many of our current (and well-intended) management protocols are based on misperceptions or sheer lack of knowledge of sound physiological principles.

Table 1 Body water and blood volume

Age	% of body mass	Blood volume (ml kg^{-1})
Premature	85	100
Term neonate	80	90
Infant	75	85
1 to 9 years	60	70
Young men	62	70
Young women	52	65
Elderly men	53	65

Table 2 Water distribution in body compartments in an adult of about 70 kg

Compartment	% of body mass	Amount (L)
Total	60	44
Intracellular	45	33 (including 2.3 L in red blood cells)
Extracellular	15	11
= Interstitial	11	8
+ Intravascular	3.97	2.7 (blood plasma)
+ Transcellular	0.03	0.21
Blood volume (cells + plasma)	7	5

In neonates, the fractions of body water and extracellular fluid (ECF) are increased. In neonates the ECF makes out about 40% of body mass as compared to 15% in adults. By 24 months of age, the ECF volume relative to body weight is similar to that in adults.

What is the blood volume in obese patients?
Obesity has become endemic and poses several challenges to the anaesthetist, including pharmacokinetic differences. Remember, intravenous fluids must be regarded as drugs and should always be administered in doses according to body composition and mass. The fatter the patient, the larger the part of the body consisting of fat (waterless) and the smaller the fraction made out by water – especially intravascular. Remember, body mass is indexed according to body height, namely
$$\text{Body mass index (BMI)} = \text{mass in kg}/(\text{height in m})^2$$

The normal is between 20 kg m^{-2} and 25 kg m^2

The blood volume per kg body mass is given by the following volume (you must remember this formula; it is also used when calculating the doses of induction agents, opioids, and muscle relaxants):
$$\text{Blood volume (ml kg}^{-1}) = 70 \text{ ml kg}^{-1}/\sqrt{(\text{BMI}/22 \text{ kg m}^{-2})}$$

Example:
What is the blood volume in a person of 70 kg with a height of 1.78 m?
Blood volume (ml kg^{-1}) = 70 ml kg^{-1}/(BMI/22)$^{0.5}$ = 70 ml kg^{-1}/(22/22)$^{0.5}$ = 70 ml kg^{-1}

What is the blood volume in a person with a mass of 70 kg and height of 1.5 m?
Body mass index (BMI) = mass in kg/(height in m)^2
$\qquad\qquad\qquad\qquad$ = 70 kg/(1.5 m)^2 = 31 kg m^{-2}
Blood volume = 70 ml kg^{-1}/(BMI/22)$^{0.5}$ = 70 ml kg^{-1}/(31/22)$^{0.5}$ = 59 ml kg^{-1}

What is this fat patient's *lean* body mass (LBM)?
This is the mass of muscle + organs + bone + extracellular fluid. If one assumes that the total body water component <u>*increases*</u> to the same extent as blood volume, the lean body mass percentage (LBM%) should be about:
LBM% = 100%/$\sqrt{(\text{BMI}/22 \text{ kg m}^{-2})}$

Example:
What is the LBM% of a patient with a body mass of 80 kg and height of 1.5 m?
BMI = 35.5 kg m^{-2}
Therefore, the LBM% = 100%/(35.5/22)$^{0.5}$ = 84%
Therefore, the lean body mass = 84% × 80 kg = 63 kg.

What is this patients *ideal* body mass *(IBM)*, i.e. his body mass if he was not obese?
$$\text{IBM of men in kg} = \text{height in cm} - 100 \text{ cm, and}$$
$$\text{IBM of women in kg} = \text{height in cm} - 105 \text{ cm.}$$

Therefore, the ideal body mass of the above patient is 150 – 100 = 50 kg if a man, and 45 kg if a women. Can you see that in obese patients, IBM < LBM (50 kg vs. 64 kg)? Since *active obese people* need muscle to carry their fat burden, they *have larger LBMs than thin people* with the same height. In *sedentary obese people*, muscle atrophy. *Then, LMB and IBM should be similar – as is in non-obese people*.

An easier way to take obesity into account when calculate doses, is the obese-determining dose mass (ODDM). It is a compromise between IBM and total body mass and is probably safe to use:
$$\text{ODDM} = \text{IBM} + 0.4(\text{total body mass} - \text{IBM})$$

Evaluation of perioperative fluid status
Fluid therapy is based on the evaluation of the fluid status, which is determined by the following components:
- Volume
- Composition (electrolytes, glucose, colloid substances, pH)
- Concentration (hyper-, iso-, or hypotonic) of body fluids
- What has been lost or gained from where

Remember, each of the fluid *compartments has a different volume, composition, and concentration*. The evaluation of fluid status must always establish *the cause* of the abnormal fluid status, namely
Abnormal *anatomy*, e.g. blood loss, bowel obstruction, diarrhoea, burns, renal failure, etc.
Abnormal *physiology*, e.g. endocrine defects, hyperthermia, hypothermia, sepsis, etc.

Pharmacological factors, e.g. diuretics, antihypertensive agents, anti-diabetic agents, etc.

The evaluation, i.e. monitoring of fluid status (what has happened and what is happening to the patient) includes:
- *the aetiology* of an abnormal fluid status (anatomy, physiology, and pharmacology),
- *the components* of the fluid status (composition, concentration, and volume),
- *the history, clinical examination, and special investigations* regarding each of these six aspects, and
- the pre-, intra-, and postoperative periods (Table 3)

Table 3 Perioperative monitoring of fluid status

Monitoring	Aspect	Preoperative	Intraoperative	Postoperative
History	Anatomy Physiology Pharmacology	Volume Composition Concentration	Volume Composition Concentration	Volume Composition Concentration
Clinical examination	Anatomy Physiology Pharmacology	Volume Composition Concentration	Volume Composition Concentration	Volume Composition Concentration
Special investigations	Anatomy Physiology Pharmacology	Volume Composition Concentration	Volume Composition Concentration	Volume Composition Concentration

The history includes age, pain, injury, blood loss, diseases, treatment, intake, and output, etc. Remember, the preoperative state is history to the intraoperative period, while both the pre- and intraoperative periods are history to the postoperative period. When you manage fluid therapy intraoperatively, you want to know what happened preoperatively, while postoperative fluid management is determined by what happened intraoperatively.

During the *clinical examination* the following should be noted:
- Anatomy: Injury, active bleeding, deformities, signs of limb ischaemia, tumours, abdominal distension, peritonism, etc.
- Physiology: Consciousness, ventilation, movement, speech, mucous membranes (anaemia, cyanosis, moist, dry), skin and subcutaneous tissue (hair, pigmentation, colour, turgor, oedema), fontanels in babies, capillary filling, blood pressure, pulse (character, rate, and rhythm), vomiting (clear, bile, blood), diarrhoea, drainage of fluid from the body (urinary and nasogastric catheter, fistulae), etc.
- Pharmacology: Are there symptoms or signs of drug therapy, e.g. digoxin (heart rate and rhythm), oncotherapy (alopecia, anaemia), corticosteroids (Cushingoid habitus), recreational drugs (miosis, mydriasis, puncture sites, consciousness, hydration, cardiovascular activation), etc?

Special investigations may include the following:
- Anatomy: Radiological investigations.
- Physiology: Blood investigations (blood count, osmolality, electrolytes, acid-base state, glucose, proteins, urea, creatinine, lactate, ketones, endocrine functions, coagulation profile), urinalysis (proteins, pigments, electrolytes, osmolality), ECG, etc. Although electrolyte and acid-base state are usually mentioned separately, they form part of the same entity (H^+, HCO_3^-, and OH^- are electrolytes). "Electrolyte" abnormalities are also, perhaps without exception, accompanied by some degree of "acid-base" abnormality, and *vice versa*.
- Pharmacology: Toxicology, digoxin levels, blood glucose, electrolytes, endocrine function, etc.

It may be necessary to utilise **invasive cardiovascular monitoring to assess volume status**:

a) **Central venous pressure (CVP)**

This measures the pressures in the right side of the heart (normal about 0 mm Hg to 5 mm Hg) and although it provides useful information, it is not a direct measurement of fluid status. For example, a patient with poor ventricular function can have a fluid deficit in the presence of a normal or even high central venous pressure. A normal patient, on the other hand can be fluid overloaded as seen by interstitial oedema and diuresis and have a completely normal CVP. Therefore, each case must be individualised and we use the *trend of the CVP in relation to other variables*, e.g. blood pressure, heart rate, and the end-tidal CO_2.

b) **Pulmonary artery wedge pressure**

To assess the left side of the heart a pulmonary artery catheter has to be inserted to indirectly measure the pressures on the left side of the heart.

c) **Intra-arterial blood pressure measurement**

Stroke volume affects pulse pressure (PP). PP is the difference between systolic (SBP) and diastolic blood pressure (DBP). Besides giving a beat-to-beat measurement of blood pressure, the swing of the blood pressure under the influence of ventilation can give an idea of the fluid status of the patient.

The *preload-sensitivity of stroke volume* is reflected by the effect of ventilation on it. The physiology behind these observations is as follows: Ventilation causes changes in the intrathoracic pressure; during positive pressure inspiration the increased intrathoracic pressure is transferred to the right heart; the lungs compress the heart. Therefore, the difference between the pressure in the peripheral veins and the heart decreases, which results in a decreased venous return (preload, volume in heart before systole) and consequently, stroke volume. The opposite happens during expiration. These changes are responsible for the variations in stroke volume, and consequently blood pressure, during ventilation. This variation during positive pressure ventilation is expressed as the ***pulse pressure variation (PPV)***. This is the difference between the PP during expiration and inspiration, divided by the mean of the PP during the phases of ventilation, expressed as a percentage. The PPV has the same pathophysiology of *pulsus paradoxus*, which you can observe when measuring blood pressure with an ordinary sphygmomanometer.

Ask the anaesthetist to demonstrate this phenomenon to you in theatre. On the arterial pressure tracing, observe the undulating effect of ventilation on the blood pressure. Identify the highest SBP and DBP and the lowest SBP and DBP. Subtract the highest DBP form the highest SBP and the lowest DBP from the lowest SBP. These render the respective highest and lowest pulse pressures. Divide the difference between the PPs by the mean between them and multiply by 100:

$$PPV = \frac{100(PP \text{ during expiration} - PP \text{ during inspiration})}{0.5(PP \text{ during expiration} + PP \text{ during inspiration})}$$

In adults, a PPV > about 12 % may be an indication of hypovolaemia. These patients usually respond (increased blood pressure, decreased PPV) to an increase in preload (volume loading) and are *volume responders*. Those with a PPV < about 8 % are non-responders; hypotension in these patients is probably due to cardiac (inotropic) failure. There is a grey area of between 8% and 12 %. Remember, since PPV reflects the heart-lung interaction, it is recommended that the patient is ventilated with a tidal volume of > 8 ml kg^{-1}, i.e. ***9 ml kg^{-1} ideal body mass*** during the measurement. Furthermore, a PEEP level of ≤ 5 cm H_2O (not 8 cm H_2O) is acceptable during the measurement.

Example:
Highest SPB = 100 mm Hg
Highest DPB = 60 mm Hg
Lowest SBP = 90 mm Hg
Lowest DBP = 55 mm Hg
Highest PP = 100 – 60 = 40 mm Hg
Lowest PP = 90 – 55 = 35 mm Hg
Difference between the PPs = 40 – 35 = 5 mm Hg
Mean PP = (40 + 35)/2 = 37.5 mm Hg
Therefore, the PPV = (5/37.5) x 100 = 13.3 %
This indicates that the patient will probably respond to an increased blood volume.

Although PPV is commonly calculated from invasive blood pressure measurements, the phenomenon is also observed on the plethysmogram of the pulse oximeter.

The *awake shock index (ASI)* is an entity which signifies a low cardiac output – due to hypovolaemia or cardiac failure. The ASI = pulse rate/systolic blood pressure, e.g. (60 beats per minute/120 mm Hg) = 0.5. The normal ASI varies from 0.4 to 0.7. A high or an increasing ASI is a sign of compromised cardiac output – hypovolaemia or cardiac failure (Table 4 and Figure 1). The ASI comes in very useful since both the heart rate and blood pressure may still be within normal limits, but the ASI is on the increase. An ASI of > 0.8 to 1.0 indicates a loss of about 10% of the blood volume loss, 1.0 to 1.5 of 20% to 33%, > 1.5 to 2.0 of 33% to 50%, and > 2.0 of > 50%. Please note that it refers to blood volume loss, which may be *due to dehydration or to haemorrhage*.

Table 4 Heart rate, systolic blood pressure and ASI

Heart rate	SBP	ASI
50	120	0.42
55	117	0.47
60	115	0.52
65	113	0.58
70	110	0.64
75	108	0.69
80	105	0.76
85	102	0.83
90	100	0.90
95	98	0.97
100	95	1.05
105	90	1.17
115	85	1.35
120	80	1.50

Note that the ASI has increased to > 0.7 even when both heart rate and blood pressure were still within normal limits
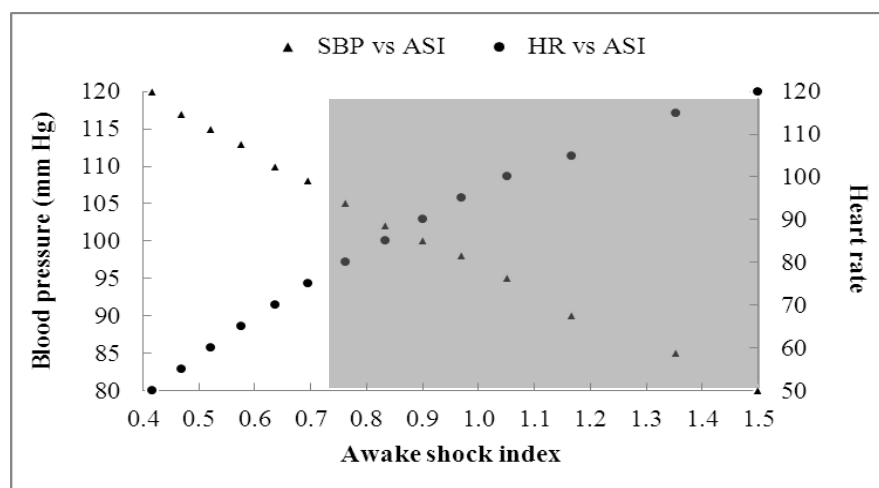
Figure 1 Heart rate, systolic blood pressure, and ASI

Hypovolaemia

Hypovolaemia is the most common cause of intra-operative hypotension. Hypovolaemia is *absolute* due to real losses from the body, or *relative* due to vasodilatation or sequestration (capillary leak). Common causes of *absolute hypovolaemia* include *haemorrhage and dehydration* (burns, prolonged fasting, gastrointestinal losses, diuresis, sweating, etc.). *Relative hypovolaemia* is probably the most common cause of intraoperative hypotension. All anaesthetic hypnotics, analgesics (except ketamine), and neuraxial blockade cause vasodilatation, which is complicated by relative hypovolaemia and hypotension. In this chapter, we shall discuss absolute hypovolaemia or volume loss, and will henceforth be referred to as "hypovolaemia".

The clinical signs of hypovolaemia include dry mucous membranes, cyanosis, pallor, dry skin (intracellular dehydration) or cold clammy skin (extracellular dehydration), decreased skin turgor, delayed capillary refill, tachycardia, hypotension (increased ASI), and oliguria. *Intracellular dehydration* follows decreased water intake (prolonged fasting, unconsciousness), water diuresis (diabetes insipidus), and increased insensible sweating in dry warm conditions (*passive evaporation* of mainly water through the skin). *Extracellular dehydration* is caused by the simultaneous loss of water and electrolytes, e.g. gastrointestinal losses, diuresis, sensible sweating (sympathetically mediated *secretion* of water and electrolytes). See Table 4 and Figure 1)

The influence of hypovolaemia on the *blood count and blood biochemistry* depends on the causes of hypovolaemia, namely haemorrhage or dehydration. The pH and electrolytes profile depends on pH

and electrolyte composition of the fluid has been lost and on the degree of physiological compensation (increased aldosterone and vasopressin secretion) (see Chapter 20). *Intracellular dehydration* causes haemoconcentration (increased haematocrit, albumin, sodium, chloride, osmolality (normally 270 mOsm L^{-1} to 300 mOsm $L^{-1)}$, and the numerical molar urea/creatinine ratio > 1/20). *Extracellular dehydration* is caused by the simultaneous loss of water and electrolytes. These patients are also hypovolaemic, but the electrolyte concentrations are often low. After *acute blood loss*, the blood tests may initially be normal but is followed by haemodilution, and a metabolic (lactic) acidosis. *The treatment of hypovolaemia* depends on the cause, rate, type of fluid loss, and *monitoring* (clinical signs and special investigations).

Hypovolaemia must as far as possible be corrected pre-operatively since the induction of anaesthesia and positive pressure ventilation in a hypovolaemic patient can lead to circulatory collapse.

Resuscitation of the dehydrated patient
- In general, the volume, concentration (hyper-, iso-, or hypotonic), and composition (electrolytes, glucose, colloid substances, pH) of the fluid lost, determine the volume, concentration, and composition of the resuscitation fluid administered.
- *Intracellularly dehydrated* patients must receive water. Patients presenting with e*xtracellular dehydration* are treated with an isotonic electrolyte solution depending on the cause.
- Euvolaemia must be achieved as soon as possible but at a rate, which the patient can tolerate.
- Resuscitation should take place while continually evaluating the parameters of volume status of the patient, i.e. blood pressure, heart rate, urine output, and blood tests.
- Fluid boluses of 3 ml kg^{-1} to 5 ml kg^{-1} (200 ml to 400 ml in the average adult) of crystalloid or colloid should be administered according to the clinical and laboratory variables mentioned above.
- Resuscitation should continue with intermittent boluses until the above variables have reached acceptable levels.
- Should a CVP be used, we make use of the "2-5" rule: after a fluid bolus (as described above), an increase of the CVP of < 2 cm H_2O requires further boluses, while an increase of more than 5 cm H_2O indicates that the patient is fully *volume* resuscitated (not necessarily composition and concentration resuscitated) and further bolusing will only cause fluid overload. An increase of between 2 cm H_2O and 5 cm H_2O should be observed for 10 minutes to 20 minutes and physiological variables checked before deciding whether to continue with further fluid boluses.

Fluid overload
In surgical patients fluid overload is usually iatrogenic, although congestive cardiac failure, liver cirrhosis with ascites and renal failure can present with the same picture, i.e. soft tissue oedema, pulmonary oedema, and hypertension. Blood pressure may initially increase, but will decrease when the heart fails (over distension of the heart); such a patient will usually have a tachycardia. Again, overload may be *intracellular or extracellular*. *Extracellular overhydration* may be iatrogenic (over-transfusion of electrolyte solutions) or due to water retention (cardiac, renal, liver, or pulmonary failure). *Intracellular overhydration* is caused by the administration of electrolyte free solutions, e.g. dextrose solutions, irrigation solutions during trans-urethral resection the prostate, and uteroscopic procedures. These patients suffer from severe haemodilution (low haematocrit and electrolytes), often neurological signs of hyponatraemia (convulsions, unconsciousness). *Treatment of fluid overload* includes fluid restriction, diuretics and positive pressure ventilation if pulmonary oedema is severe.

Intraoperative fluid management
Intraoperative fluid requirements are the sum of the following: Maintenance fluid, the fasting period, and acute losses. It must be stated at the outset that anaesthetists are prone to fluid- and salt-overload patients. These errors in fluid management probably stem from the ill-defined (or fictitious) "third space" losses and a tendency to treat relative hypovolaemia with volume expanders. The traditional approach is reflected in the recommendations below, but is not necessarily, and probably, not physiologically correct and may even be harmful.

To prevent fluid overload, fluid administration must always be individualized according to the particular procedure, the patient co-morbidity (the elderly, cardiac failure, renal failure, respiratory failure) and treatment, and information obtained from the physiological monitoring variables. The so-called *fluid restriction approach* is currently propagated, but needs careful monitoring to prevent fluid deficits. Fluid should be administered using a volumetric infusion pump or flow regulator to prevent inadvertent administration of large volumes of fluid.

The following fluid must be administered:
- The fasting (nil per os, NPO) period fluid
- Maintenance fluid
- Intraoperative losses

Maintenance fluid
Kidney function is completely developed at the age of 6 months. Patients younger than 6 months have a decreased creatinine clearance, impaired sodium retention (making them obligate *sodium losers*), poor dilutional and concentrating abilities, and impaired glucose excretion and bicarbonate reabsorption. On the first day, a neonate excretes a mean of 8.5 ml kg^{-1} day^{-1}, and a mean of 76 ml kg^{-1} day^{-1} on day 7, while young men excrete a mean of 20 ml kg^{-1} day^{-1}. *Therefore, infants need more fluid than children and adults.* Meticulous detail to fluid administration in the perioperative period is imperative. Adequate exogenous sodium, glucose and water must be provided without volume overload.

In both adults and paediatric patients, we use the "4-2-1" rule to calculate the volume of fluid required by the patient per hour (Table 4).[xxii] The purposes of maintenance fluid are:
- Post-operative fluid maintenance by replacing losses (water and electrolytes) from respiration, skin, urinary tract, and bowel.
- Provision of energy, usually in the form of glucose. In uncomplicated cases, the energy requirements in an adult are about 400 kJ kg^{-1} day^{-1}, which is numerically equal to the water requirements in ml kg^{-1} day^{-1}.

Maintenance fluid usually consists of an isotonic fluid, e.g. Ringer lactate (RL) and Balsol[R]. ***However, it is probably more correct and physiological to administer a glucose-containing maintenance fluid – if you monitor the blood glucose and administer insulin if necessary. Intraoperative monitoring of blood glucose forms part of any major surgery, anyway.*** Examples of these preparations are given in Table 6. Half Darrow's solution contains too much dextrose and potassium to be used for intra operative maintenance fluid in babies.

Replacement of the deficit due to the nil per os period
Due to on-going urinary and insensible losses during the fasting period, patients develop preoperative fluid deficits. This is the maintenance requirements per hour multiplied by the number of hours the patient has been NPO, e.g. if a patient of 71 kg has been NPO since 22:00 the previous night and surgery commences at 8:00, the deficit is 111 ml $h^{-1} \times 10$ hours = 1110 ml. We replace 50% during the first hour of surgery and then 25% during the second and third hours respectively. The NPO fluid should probably consist of a maintenance type of fluid (see Table 6). Remember, Ringer lactate and similar solutions are resuscitation fluids – not maintenance fluids. Other pre-operative losses that may need replacement are losses due to vomiting or diarrhoea and is replaced with fluid with a composition similar to the fluid lost.

[xxii]The first practical method to prescribe fluid was presented by Holliday and Segar in 1957. They described the 4-2-1 rule. This maintenance amount was based on caloric expenditure; caloric needs translated into a water requirement of 1 ml for each kcal expended. However, this formula may overestimate needs in adults and in the paediatric patients intraoperatively since intraoperative basal metabolic rate and caloric expenditure is decreased.

Table 4 Maintenance fluid

Mass (kg)	ml per hour*	Example
≤ 10	4 ml kg^{-1} h^{-1}	7 kg: 7 kg × 4 ml kg^{-1} h^{-1} = 28 ml h^{-1}
> 10 to 20	40 ml h^{-1} + 2 ml kg^{-1} h^{-1}×(mass-10) kg	17 kg: 40 ml h^{-1}+2 ml kg^{-1} h^{-1}×(17-10)kg = 54 ml h^{-1}
> 20	60 ml h^{-1} + 1 ml kg^{-1} h^{-1}× (mass - 20) kg	71 kg: 60 ml h^{-1} + 1 ml kg^{-1} h^{-1}× (71 –20) kg = 111 ml h^{-1}
OR		
	ml per day in patients > 5 kg	
≤ 10	100 ml kg^{-1} day^{-1}	7 kg: 7 kg × 100 ml kg^{-1} day^{-1} = 700 ml day^{-1}
> 10 to 20	1000 ml day^{-1} + 50 ml kg^{-1} day^{-1}× (mass -10) kg	17 kg: 1000 ml day^{-1} + 50 ml kg^{-1} day^{-1} × (17-10) kg = 1350 ml day^{-1}
> 20	*For patients ≤ 50 years:* 1500 ml day^{-1} + 20 ml kg^{-1} day^{-1}× (mass - 20) kg	71 kg: 1500 ml day^{-1} + 20 ml kg^{-1} h^{-1}× (71 –20) kg = 2520 ml h^{-1}
	For patients > 50 years 1500 ml day^{-1} + *15* ml kg^{-1} day^{-1}× (mass - 20) kg	71 kg: 1500 ml day^{-1} + 15 ml kg^{-1} h^{-1}× (71 –20) kg = 2265 ml h^{-1}

*Easier: (First 10 kg give 4 ml kg^{-1} h^{-1}) + (Second 10 kg give 2 ml kg^{-1} h^{-1}) + (> 20 kg give 1 ml kg^{-1} h^{-1})

Acute pre- and intraoperative losses

Blood loss is replaced with a crystalloid such as Ringer lactate in a ratio of 3 RL:1 blood loss or a 1 colloid:1 blood loss – until a minimum haematocrit has been reached.

The "third space" losses, first described by Shires in the 1960s, are thought to be the movement from the interstitial fluid to the intracellular space during surgery or trauma. There is a great deal of uncertainty regarding the existence of the third space. It is probably true that tissue trauma, surgical or otherwise, cause loss of intravascular fluid due to tissue oedema. However, *liberal* replacement of *procedure-related non-haemorrhage fluid losses* may cause volume and solute (salt) overload and a more *restricted approach* should be considered. If a restricted approach is followed, __*the "4-2-1" rule is replaced by a "3-1.5-0.75" rule*__. *Procedure-related non-haemorrhage fluid losses are replaced in* a *monitored way*. It is replaced with balanced salt solutions such as RL (Table 5).

Table 5 Additional procedure-related fluid requirements

Tissue trauma	Examples	Fluid (ml kg^{-1} hr^{-1})
Minimal	Ear or dental surgery	0 to 1
Moderate	Hysterectomy, prostatectomy, laparoscopic surgery	1 to 3
Large	Major abdominal surgery	3 to 5

Intraoperative fluid therapy in paediatric patients

The same principles described above are valid in children and babies. However, meticulous attention to fluid management is essential since the margin of error is small – both under- and over-transfusion.

It is strongly advised that use be made of programmable infusion pumps. These pumps allow you to key in the amount of fluid to be transfused as well as the transfusion rate (time over which the volume should be infused). Only if an infusion pump is not available and for minor procedures, 60-drops per ml infusion sets with graded volume chamber (Buratrol^R) may be used. *When using an infusion pump, you must be sure that the intravenous cannula is correctly placed and allows free flow, since the infusion may not stop when infusing fluid into the delicate subcutaneous tissue.*

The type of fluid required for maintenance is RL with dextrose added to make a 1.0% to 1.25% dextrose solution. How do you prepare these solutions?
Remember, % means g per 100 ml of solution.
Therefore, a solution containing 1.25% of dextrose contains 1.25 g dextrose in 100 ml of solution, while 200 ml (volume of infusions used in small patients) contains 2.5 g.

Where do you get the 2.5 g of dextrose? From the 20 ml dextrose 50% injection.

How much of this 50% dextrose is added to the 200 ml of RL?

The 50% dextrose injection contains 50 g of dextrose in 100 ml.

Therefore, 2.5 g is present in (2.5 g per 50 g) × 100 ml = 5 ml of the 50% dextrose injection.

So, you withdraw **_STERILELY_** 5 ml from the 50% dextrose ampoule and inject it **_STERILELY_** into the 200 ml of RL. Remember, do not use 5% dextrose to make this infusion since the volume needed will be too large (50 ml instead of 5 ml) and dilute the RL. **_ALWAYS LABEL THE INFUSION; WRITE WHAT AND HOW MUCH OF WHAT HAS BEEN ADDED._**

TYPES OF SYNTHETIC INTRAVENOUS FLUID

Crystalloids (Table 6)

These fluids consist of water in which electrolytes and/or glucose are dissolved and are hyper- (osmolarity > 300 mM), iso- (osmolarity ≈ 300 mM), or hypotonic (osmolarity < 300 mM) relative to plasma.

Resuscitation crystalloids

Resuscitation fluid is usually isotonic with an electrolyte content similar to that of plasma, e.g. Ringer lactate solution (Hartman solution), Plasmalyte B, and Balsol. Sometimes, patients are resuscitated with hypotonic fluid (NaCl 0.45 %, NaCl 0.45 % in glucose 5 %, or glucose 5 %) depending on the molarity and composition (electrolytes and pH) of the fluid lost (diarrhoea, vomiting, sweating). NaCl 0.9 % is an isotonic fluid but is only used to resuscitate patients with a metabolic alkalosis, e.g. pylorus stenosis, as resuscitation with NaCl is known to cause a metabolic acidosis.

Advantages of crystalloid resuscitation fluid include the following: easily obtainable, cheap, just as effective a volume expander as colloid if given in sufficient amounts, and patients may also be dehydrated intracellularly and therefore benefit from fluids which move intracellularly.

Disadvantages of crystalloid resuscitation fluid:

- Short intravascular $t_{1/2}$ (within 2 hours of administration < 20% remains intravascularly)
- Increased risk of diffuse interstitial oedema
- It may make patients hypercoagulable.

Maintenance fluids

Maintenance fluids have low sodium concentrations**,** since insensible losses do not contain much sodium. They are physically (calculated and measured) hypertonic due to the glucose content, e.g. Maintelyte in 5 % glucose, Maintelyte in 10 % glucose, Electrolyte No 2, Postsurgisol, and Neonatalyte. Remember, a glucose 5% solution contains 50 g of glucose per litre of solution. The molecular mass of glucose is about 180 g. So the solution contains about (50 g/180 g) = 0.278 mol = 278 mmol of glucose. This gives a solution with a concentration of 278 mmol L^{-1} = 278 mM = isotonic. A solution containing 10% has a osmolarity of 556 mM. Therefore, once the glucose has been removed from the plasma, a hypotonic solution remains.

Rehydration fluids

Isotonic fluids are usually used for *extracellular dehydration*. The composition of this fluid aims to replace the fluid deficit due to loss or sequestration of poly-ionic body fluids. Large gastrointestinal losses may require extra Na^+, K^+, bicarbonate or chloride. This will be determined by serum electrolyte content:

- Hypovolaemia due to **gastro-intestinal fluid loss** should be replaced with solutions that contain sufficient sodium and potassium. If the loss occurs due to an obstruction **above the duodenum** (high K^+, Cl^-, and H^+ but low Na^+ concentrations) the patient is initially hypokalaemic and alkalotic. Upper GIT losses are usually replaced volume for volume with NaCl 0.9 %; an extra 15 mmol KCl must be added per litre NaCl 0.9 %. If gastro-intestinal losses are so large that circulatory shock develops, resuscitation with RL, Plasmalyte B, or Balsol may be necessary.
- If the loss occurs due to an obstruction **below the pylorus** (high Na^+ and HCO_3^- concentrations)

the patient is hyponatraemic and acidotic. These losses are usually replaced with RL, Plasmalyte B, or Balsol.

- Losses from below the pylorus (fistulae, diarrhoea) contains pancreas fluid and bile, which are rich in Na^+ and HCO_3^-. These patients become hyponatraemic and acidotic. Lower gastro-intestinal losses, e.g. diarrhoea are replaced with Half Darrows in glucose 5%.

Table 6 Composition of some crystalloid solutions

Fluid	Na^+	K^+	Mg^{2+}	Ca^{2+}	Cl^-	P	L	BC	G	pH	O
Resuscitation											
NaCl 0.9%	154				154					5.5	308
Ringer Lactate	131	5		1.8	112		29			6.5	279
Plasmalyte B	131	5	3		112			28		7.4	273
Balsol	131	5	3		112			28		7.4	273
Maintenance											
Maintelyte 10%	35	25	2.5		65				100	4.0	683
Maintelyte 5%	35	25	2.5		65				50	4.0	405
Neonatalyte	20	15	0.5	2.5	21	3.75	20		100	4.2	670
Electrolyte 2	57	25	6		50	12.5	25		100	5.0	723
Rehydration											
NaCl 0.45% in G 5%	77				77				50		432
Half Darrows in G 5%	61	17			52		27		50	5.0	434
Specific replacement											
NaCl 0.45% in G 5%	77				77				50		432
Glucose 5 %									50		278
$NaHCO_3$ 8.4 %	1000							1000		8.2	2000
NaCl 5 %	833				833						1666

The unit for the electrolytes is mM, but g L^{-1} for glucose.
P = HPO_4^{2-} ; L = lactate ; BC = bicarbonate; G = glucose g l^{-1}; O = osmolarity

Colloids

Colloids consist of large molecules dispersed in the dispersion medium (usually NaCl 0.9 %). These macromolecules (sugars, starches, or proteins) are much larger than crystalloid molecules or ions. They are hydrated and kept in suspension by the dispersion medium. These molecules are too large to dissolve in the dispersion medium, but too small to settle out under the influence of gravity. These fluids are iso-oncotic or hyperoncotic, and natural or synthetic. The concentration of the iso-oncotic colloids is about the same as the total protein concentration in normal plasma, namely about 60 g/l with an oncotic pressure of about 20 mm Hg (the normal plasma oncotic pressure is 28 mm Hg).

The synthetic colloids (Table 7)

These colloids are composed of protein (gelatine compounds), sugar (dextrans), or starch. They can bridge the time from fluid loss to transfusion with blood products. *The jury is not out regarding the real value (survival) of the synthetic colloids.*

Table 7 Synthetic colloids commonly used

Group	Product	%	Mass (kDa)	Effect (h)	Elimination	Maximum daily dose (ml kg^{-1})
Starch	Voluven, Venofundin	6	130	6	α-Amylase → fragments → kidney	< 70
Gelatine	Haemaccel	3.5	30	4	Kidney	< 15
Gelatine	Gelofusin	4	30	4	Kidney	< 15

The starches[xxiii]

These colloids are substituted starch molecules from maize (Voluven) or potato (Venofundin).

- Voluven 6% and Venofundin are the colloids of choice at present as they have the least side effects of all the colloids. The maximum daily dose of Voluven is about 70 ml kg^{-1} day^{-1}. Voluven and Venofundin are marketed as solutions with saline (0.9% NaCl) as solvent. Starches are also available as solutions with a balanced electrolyte solution as solute (Na^+, Cl^-, K^+, Mg^{2+}, and acetate), e.g. Voluven 6% Balanced.
- α-amylase degrades starches to samller fragments, which are excreted by the kidneys.
- Renal dysfunction can occur with the older starches such as Haes-steril
- Accumulation in the tissues can cause pruritus (the older starches such as Haes-steril)
- The infusion of hydroxyethyl starch produces elevated serum α-amylase concentrations. This effect is the result of the formation of an amylase complex of hydroxyethyl starch with delayed renal and extrarenal elimination. It is not evidence of a pancreatic disorder.

Gelatines

- Haemaccel and Gelofusin are gelatine colloids marketed as a 3.5 % and 4 % respectively. They are iso-oncotic solutions in an isotonic electrolyte solution.
- This substance is hydrolysed from beef collagen. The $t_{1/2}$ is about 5 hours and may be prolonged in renal failure.
- Sudden hypotension can occur due to an anaphylactic reaction.

Dextrans

- Dextrans are polymers produced from sucrose by fermentation by the bacterium Leuconostroc mesenteroides B512. Dextran-70 has a molecular mass of 70 kDa and is available in a concentration of 6% in a dextrose-saline solution. It is used for plasma volume expansion. Dextran-40 has a lower molecular mass (40 kDa) and is therefore cleared rapidly by the kidneys. The dextrans can cause renal dysfunction.
- Dextrans are antithrombotic. Platelets are coated by dextrans. This decreases their stickiness and clumping. The dextrans have a direct inhibiting effect on blood clotting. Dextrans primarily have an effect on factor VIII and the incorporation of fibrin clots. Dextran improves blood rheology and may be used to improve blood flow in reconstructive and vascular surgery.
- The dextrans have an effect on cross matching and this may lead to errors in the typing of blood.
- The dose should be kept at 1,5 g kg^{-1} day^{-1}.

Synthetic oxygen carriers

- The perfluoro-chemical emulsions are organic solutions that are able to bind oxygen. Higher inspiratory oxygen is essential to increase the oxygen content. Fluosol DA is an example of such a solution and has already been used in Jehovah's witnesses.
- The recombinant beef haemoglobin solution is on the South African market (Haemopure). It carries oxygen and can be used to decrease the need for blood transfusion. It does not require cross matching, has no risk of infection transmission and has a shelf life of 2 years.

Disadvantages and side effects of all the synthetic colloids:

- They are expensive
- The dispersion medium of the starches is either NaCl 0.9 % or a balanced buffered solution. The 0.9% NaCl solution causes a hyperchloraemic metabolic acidosis when large volumes are transfused. This normal anion gap acidosis must be differentiated from other causes of a normal anion gap acidosis, e.g. renal tubular acidosis, as well as from a lactic acidosis or other organic acid acidoses, which causes an increase in the anion gap.
- All the synthetic colloids may cause anaphylaxis.
- All the synthetic colloids cause dilution of red blood cells, platelets, and clotting factors. Therefore, large volumes cause a hypocoagulability due to dilutional thrombocytopenia, decreased platelet function, and abnormal functioning of factor VIII Von Willebrand.

[xxiii] Due to research and publication corruption, uncertainty exists about the real value of starches.

BLOOD AND BLOOD-DERIVED COLLOIDS

The aetiology of the blood component deficiency determines the management: pharmacologically or blood components; slowly or rapidly (resuscitation). What are the causes of blood component deficiency? They include decreased production, increased consumption or destruction, increased losses, or dilution. The losses may be externally (e.g. blood loss) or internally (internal bleeding), while haemodilution may also be externally by the transfusion of synthetic plasma expanders, or internally by movement of interstitial fluid to the intravascular space. Likewise, haemoconcentration may be externally (dehydration due to diarrhoea, diuresis, sweating, etc.) or internally due to oedema formation.

Blood products used during resuscitation therefore include packed red cells, albumin, fresh frozen plasma (FFP), cryoprecipitate (fibrinogen, factor VIII/Von Willebrand complex, and factor XIII) and blood platelets. These fluids are only transfused when a deficit of the particular blood component needs replacement.

Blood products

Traditionally, blood products formed part of perioperative fluid therapy but the risk of transmittable disease restricts its use. Therefore, **guidelines** have been laid down to minimise the transfusion of blood products:

- Transfuse the *smallest volumes* possible.
- Blood components form *individual donors* are preferable over pooled components.
- *Autologous blood transfusions* should be considered for elective surgery. The patient donates 4 units to 6 units over a period of about 3 weeks before surgery. Oral iron supplements are given during this period. (One unit = about 400 ml)
- Intra-operative *isovolaemic haemodilution*. One unit to two units are collected into blood donation bags (containing Adsol) intraoperatively while it is being replaced with the same amount of synthetic colloid or 3 times the amount of resuscitation crystalloid. When the patient needs blood, these units are transfused first. This blood must be used within eight hours if stored at room temperature and within 24 hours if kept at 4ºC.
- *Cell salvage apparatus* washes blood that is sucked from the surgical field, and re-suspended in saline. This blood contains no platelets or clotting factors and if large volumes are given, clotting abnormalities can develop necessitating administration of FFP and/or platelets.

When should blood products be transfused?
Indications for red blood cell transfusion

In this regard the concept of **oxygen flux (DO_2) applies**. Mammals are aerobic organisms and therefore require a constant supply of oxygen. The amount of oxygen that is transported to tissues is known as the DO_2.

$$DO_2 = Qt \times CaO_2 = Qt[(Hb \times 1.34 \times SaO_2) + (0.031 \times PaO_2)] = 1000 \text{ ml min}^{-1}$$ (or oxygen flux index of 600 ml min^{-1} m^{-2})

Qt = cardiac output (L min^{-1}); CaO_2 = oxygen content in arterial blood (ml L^{-1}); Hb = Hb concentration (g L^{-1}); 1.34 = the Hb oxygen binding capacity in ml g^{-1}; SaO_2 = Oxygen saturation of Hb in arterial blood (normally about 0.95 or 95 %); 0.031 = solubility of oxygen in blood (ml mmHg^{-1} L^{-1}); PaO_2 = arterial oxygen tension (mm Hg)

DO_2 decreases with blood loss. Although haemoglobin is numerically the greatest factor in the DO_2, it is not always possible or necessary to replace it rapidly, or to replace it at all. Fluid therapy is usually initiated by the administration of an isotonic crystalloid plasma volume expander e.g. RL (not with NaCl 0.9%); this increases Qt. The administration of O_2 increases SaO_2 and PaO_2. These measures increase DO_2, which may eliminate the need for blood transfusion.

Blood loss is treated according to the rate and volume of blood loss. *Acute loss* of a significant

volume, i.e. more than about 10% of the blood volume causes clinically detectable hypovolaemia (increased ASI), while the haematocrit is initially normal but diluted during physiological compensation or cell-less resuscitation. Therefore, during substantial acute blood loss, the emphasis of management is on volume replacement with resuscitation fluid, followed by blood product transfusion as indicated (*monitoring* of the blood component levels, i.e. clinically, haematocrit, platelet count, and clotting profile), and/or pharmacologically with antifibrinolytics (tranexamic acid, ε-aminocaproic acid).

Chronic blood loss presents with chronic anaemia and cardiovascular compensation or decompensation, i.e. cardiac failure or angina pectoris. With chronic anaemia, the emphasis in treatment is on the cause and the time available to correct the anaemia, e.g. the correction of anaemia is more urgent in a patient with ischaemic heart diseases awaiting major non-cardiac surgery. Otherwise, chronic anaemia is treated by addressing the cause (surgical or non-surgical), and often includes the administration of iron, vitamins, erythropoietin, etc. *The anaesthetist must take particular cognisance of the cause of anaemia*.

At a certain point, an increase in volume and therefore Qt as well as the administration of O_2 is no longer enough to maintain O_2 *consumption (VO_2)*. This point is known as the *critical DO_2 (DO_2crit)*. The critical DO_2 in healthy resting persons is about 8.5 ml kg^{-1} min^{-1}, *but increases when VO_2 rises*, e.g. perioperatively. At this point red blood cells become essential to increase oxygen carrying capacity and therefore, CaO_2, to maintain aerobic metabolism (low lactate) (Figure 2). In young fit adult patients, this point is thought to be a haemoglobin concentration of 50 g L^{-1} to 60 g L^{-1} (haematocrit of 15% to 18%). This point, i.e. the lowest possible haemoglobin concentration that will ensure adequate oxygen supply to the organs is called the *transfusion trigger* (Table 8). Physiological disturbances, e.g. increased heart rate, decreased blood pressure, myocardial ischaemia, or low saturations may require volume expanders before reaching the critical haemoglobin level or *transfusion trigger in a particular patient* (Table 8).

Remember that, in general, anaemic hypoxia (low viscosity) is tolerated better than stagnation hypoxia (low cardiac output). However, ischaemic organs with limited perfusion (ischaemic heart and cerebrovascular disease) are dependent on higher concentrations of haemoglobin to compensate for the lower flow. The same applies to patients with a high metabolic rate (children, babies). These patients need higher concentrations of haemoglobin. In these cases, the transfusion trigger is 70 g L^{-1} to 80 g L^{-1} (Table 8).
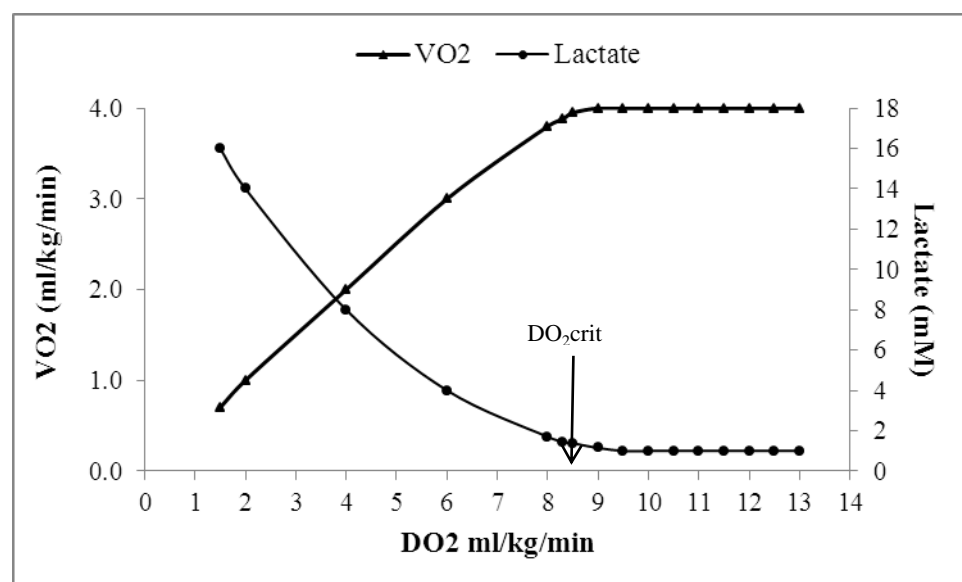

Figure 2 Relationship between oxygen flux (DO_2), oxygen consumption (VO_2) and plasma lactate. Note the increase in lactate (anaerobic metabolism) when DO_2 decreases below the DO_2crit of about 8.5 ml kg^{-1} min^{-1}.

Table 8 Intra-operative blood transfusion triggers[24]

Situation	Patient		Haemodynamic*		MCI#		CV Oximetry##	Trigger (g per dL)
Theatre	All	OR	Relative ↑HR or ↓MBP	OR	ECG	OR	Yes	6
	> 80 years							7
	CVD							8
	↑VO₂							8
	Infants		-		-		-	9
Ward	All		Relative ↑HR or ↓MBP		Clinical		Not applicable	6
	> 80 years							7
	CVD							8
	↑VO₂							8
	Infants		-		-		-	9

MCI, myocardial ischaemia; **CV Oximetry:** $PcvO_2$ and $ScvO_2$ = PO_2 and SO_2 in central venous blood, respectively; **Trigger,** Haemoglobin transfusion trigger (g dL^{-1}); **CVD,** cardiovascular disease, including coronary artery and cerebrovascular disease; VO_2, oxygen consumption: high temperature, high metabolism; MBP, Mean BP = (SBP + 2DBP)/3; HR, heart rate; ECG, electrocardiogram.
*Relative tachycardia or hypotension: Heart rate: > 120 to 130 % of baseline or > 110 to 130 beats min^{-1}
Relative hypotension: MBP < 70% to 80% of baseline or < 60 mm Hg (< 55 mm Hg in young healthy patients, < 70mm Hg to 80 mm Hg in patients with CVD and in hypertensive patients, and higher in severely hypertensive patients.
OR, **# Myocardial ischaemia:** New ST-segment depression> 0.1 mV or elevation > 0.2 mV
OR, **Clinical signs** confirmed with ECG and/or troponin levels in a timely fashion
OR, **## Central venous oximetry (one or more):** PvO_2 < 32 mm Hg, $ScvO_2$ < 50%, O_2ER > 50%, ↓VO_2 > 10% [O_2ER = oxygen extraction ratio (normally about 25 %) = $(SaO_2 - SvO_2)/SaO_2$]

What is the dose of blood?
If is blood is replaced with fluid while the patient is bleeding, the remaining blood (red cells, platelets, albumin, and clotting factors) is constantly diluted by the cell-less resuscitation fluid. Therefore, while the patient is bleeding, the blood lost will be more and more diluted (lower haematocrit). If the initial haematocrit (Hct 1) and the allowable end-haematocrit after dilution (Hct 2) are known, the blood loss (BL) is determined by the change in haematocrit (ΔHct) and the patient's ideal blood volume (IBV):

$$BL = \frac{(IBV)(Hct\ 1 - Hct\ 2)}{(Hct\ 1 + Hct\ 2)/2} = (IBV)(\Delta Hct)/Mean\ Hct$$

The haematocrit of packed red blood cells is about 70%. The volume of packed red blood cells (VPC) is calculated as follows:
$70 \times VPC = BL \times mean\ Hct$
Therefore, $VPC = (BL \times mean\ Hct)/70$
Of cause, the target haematocrit will only be reached once the excess cell-less fluid has been excreted and no other losses have occurred.

An alternative easier formula, which gives similar volumes is as follows:
BVT = ΔHct × body mass × 2.5 ml kg^{-1} $\%^{-1}$, or
the volume of *packed cells needed* = ΔHct × body mass × 1.5 ml kg^{-1} $\%^{-1}$
<u>***NB: THIS FORMULA IS VALID ONLY IF THE HIGHER HCT IS ≤ 40%***</u>

Example:
A baby of 8 kg is undergoing surgery. The preoperative haematocrit was 40%. It has decreased to 22%. How much blood has been lost? How much packed cells must be transfused to increase the haematocrit to 30%?
Ideal blood volume = 8 kg × 85 ml kg^{-1} = 680 ml
ΔHct = 40% - 22% = 18%
Mean Hct = (40% + 22%)/2 = 31%
Blood loss = (IBV)(ΔHct)/Mean Hct = 680 ml × (18%)/31% = 471 ml of diluted blood
Therefore, the VPC to be transfused = (471 ml × 31%)/70% = 209 ml of packed cells

Or,

Packed cells needed = ΔHct × body mass × 1.5 ml kg⁻¹ %⁻¹ = 18% × 8 kg × 1.5 ml kg⁻¹ %⁻¹ = 216 ml of packed cells
The difference between these methods is clinically acceptable.

Example:
A 85 kg man of 75 kg has a haematocrit of 35%. What is his allowable blood loss if you regard a haematocrit of 24% as acceptable in this patient?
Acceptable blood loss = 75 kg × 65 ml kg⁻¹(35% - 24%)/[(35% + 24%)/2] = 4875 ml × (11%)/29.5% = 1817 ml
Or
Blood loss (remember, one bleeds whole blood) = ΔHct × body mass × 2.5 ml kg⁻¹ %⁻¹
$$= 11\% \times 75 \text{ kg} \times 2.5 \text{ ml kg}^{-1} \%^{-1} = 2063 \text{ ml}$$

Indications for fresh frozen plasma (FFP)

The indication for FFP is only when coagulation factors or other plasma factors are needed. This occurs most often in theatre when a patient has bled more than their total blood volume, which has been replaced with plasma free fluids and packed red cells only. The patient will start to ooze from sites of tissue trauma. The international normalized ratio (INR) will increase (normal 0.9 to 1.2). A dose of 10 ml kg⁻¹ to 15 ml kg⁻¹ is given and is estimated to increase the level of clotting factors by 30 %, which is the amount required for normal clotting.

Should FFP be cross matched?[25]
Plasma with *low titres of anti-A and anti-B antibodies* are usually supplied by blood transfusion services. Plasma from Group O blood contains higher titres of ant-A and anti-B antibodies than plasma from group A or B donors, but activities vary between donors. Blood services test blood for 'high-titre' antibodies. Unreactive donations are labelled to indicate a relatively low risk of causing ABO-related haemolysis. FFP with a different ABO group as the recipient should only be transfused if it contains low titres of anti-A and anti-B antibodies. It is preferable to use group A FFP for group A, group B plasma for group B patients, group AB plasma for group AB patients, and group O plasma for group O patients. Since no *in vitro* test can always predict *in vivo* haemolysis, especially when large volumes of FFP are transfused, clinicians and blood bank technologists must be aware that haemolysis can still occur with ABO-incompatible FFP. This includes FFP from a group A donor transfused to group B patient, and vice versa – even if the FFP is 'high-titre negative'. In an emergency when a patient's blood group is not known, group AB FFP can be used. Plasma transfused to infants should be free of clinically significant irregular blood group antibodies (plasma from group AB donors).

The following recommendations regarding FFP compatibility have been put forward:
The first choice of FFP is that of the same ABO group as the patient. If this is not available, FFP of a different ABO group is acceptable as long as it does not possess anti-A or anti-B activity above a certain limit ("high titres"). FFP of group O should only be given to O recipients. Group O FFP should not be used in infants who are not group O since the relatively large volumes required can cause passive immune haemolysis.

Indications for platelet transfusion

Platelets are only transfused when there is a clinical suspicion of a bleeding abnormality, e.g. oozing from sites of tissue trauma in the face of massive blood loss (one blood volume within 24 hours) or when the platelet count is $< 50 \times 10^9$ L⁻¹ (normal 150×10^9 L⁻¹ to 450×10^9 L⁻¹). Below a count of 100×10^9 L⁻¹ the bleeding time increases but below 50×10^9 L⁻¹ severe bleeding may occur in the presence of trauma.

If thrombocytopaenic patients present for surgery, platelets should be ordered and be transfused just before surgery. In thrombocytopaenic patients presenting for splenectomy, platelets are transfused once the splenic artery has been tied off. Platelet transfusion triggers are summarized in Table 9 and the dose of platelet transfusion in Table 10.

Platelets are, like packed cells and plasma, transfused through a filter – but a *special platelet filter*. This filter has a 170 μm pore size, but has a much smaller filter area with a much smaller platelet retention in the filter. This filter must be supplied by the blood transfusion service. If a platelet filter is not available, it is recommended that the product is transfused through an ordinary 170 μm pore size blood filter.

Table 9 Platelet transfusion triggers

Scenario	Trigger ($10^9 L^{-1}$)
No bleeding or other haemostatic abnormalities	10
Patients without other haemostatic abnormalities presenting for: Central venous catheter placement Internal organ biopsies (transcutaneous, endoscopic, open) Laparotomy	50
Neurosurgery, eye surgery	100
On-going bleeding and blood transfusion	50
Diffuse intravascular coagulopathy	50

Table 10 Platelet transfusion dosage guidelines

Product	Volume (ml)	Content (10^9)	Dosage (ml kg^{-1})	Increment ($10^9 L^{-1}$)
Random unit	50	60 to 80	5*	30 - 50
Aphaeresis unit (pooled unit)	200 to 300	> 300	3.4**	50 - 60

* In adults and children 1 unit/10 kg and in infants < 10 kg 5 ml kg^{-1} will increase the platelet count by about $5 \times 10^9 L^{-1}$ to $10 \times 10^9 L^{-1}$.

** 1 unit for the average adult or about 3.4 ml kg^{-1} in a child, **_but_** about 10 ml kg^{-1} in infants

Changes in stored blood

- *Decreased pH* secondary to continued red cell metabolism with the production of lactate and CO_2. The PCO_2 of stored blood may be as high as 80 mm Hg, which is partly responsible for the increase in $PaCO_2$ during rapid blood transfusion.
- Increased *potassium* due to increased friability of red cells lysis and release of intracellular potassium.
- Decreased *2,3 DPG*, which shifts the O_2-Hb dissociation curve to the left and therefore decreases efficacy of oxygen release to the tissues.
- *Platelets* are viable in stored blood for only one day. (Platelets are stored at room temperature and packed cells at 4ºC.)
- Decrease in labile *clotting factors* V and VIII.

Complications of blood product transfusion

These are *immune-mediated or non-immune-mediated.*

Immune-mediated haemolytic reactions

This occurs when specific antibodies from the recipient react with antigens on the donor's red blood cell membranes. This means that the blood is *incompatible*. Complement activation occurs and this contributes to the haemolysis.

- *Acute haemolytic reactions* are due to ABO incompatibility and are usually the result of human error. Therefore, it is important to check the blood before administering it. In the awake patient the first manifestations are usually shivering, fever, nausea, chest or flank pain, skin blush, hypotension, and tachycardia. During a general anaesthetic, the signs of haemolysis are masked, except perhaps for an unexplained hypotension and tachycardia. Late manifestations are haemoglobinuria, renal failure, bleeding tendencies and jaundice. It must be emphasized that urticaria and erythema are usually signs of an allergic reaction and not of a haemolytic reaction. Management includes stopping the transfusion, cardiovascular support, maintenance of urine output, and treatment of the diffuse intravascular coagulation (DIC) should it develop. It should be verifying that the patient has received the correct unit. If correct, the blood should be sent to the blood bank for testing,
- *Delayed haemolytic reactions* are usually due to incompatibility in the Rh or other red blood cell antigen. The recipient does not have sufficient antibodies to cause an immediate reaction. It is a clinical diagnosis, diagnosed about two weeks after a transfusion when the patient becomes anaemic (haematocrit decreases) and jaundiced. This is usually a mild and transient reaction.

Immune-mediated non-haemolytic reactions

- *Allergic reactions* occur despite correctly typed and cross-matched blood. The cause is probably incompatible proteins in the plasma, leukocytes, or platelets. These reactions can occur in up to 3% of blood transfusions and the treatment is to stop the infusion and to administer antihistamines.
- *Pyrexial reactions* are the most common non-haemolytic response and may occur in 0.5% to 1% of cases. It is probably the result of an interaction between a recipient's antibodies and the antigens present on the leukocytes and platelets of the donor. As pyrexia is also an early sign of haemolytic reactions, the diagnosis will depend on the presence of haemolysis.
- *Graft versus host disease* occurs when the transfused white blood cells mount an immune response against the recipient's normal tissues. The patients present with fever, rash, pancytopaenia, liver damage, and sepsis. It has a very high mortality rate.
- *Post transfusion purpura* develops when antibodies destroy the patient's own platelets causing an acute thrombocytopenia.

Non-immune-mediated complications

These complications include metabolic derangements, transmission of infective diseases, the transfusion of micro-aggregates, bleeding tendencies, immune depression, hypothermia, bacterial contamination, and circulatory overload. Non-immune complications are usually dose-dependent. A *massive blood transfusion* is defined as the transfusion of one whole blood volume within 24 hours and is more likely to cause complications.

Metabolic derangements

- *pH changes*

  Continued metabolism by the red blood cells with continued production of lactate and CO_2 results in a low pH in stored blood. The PCO_2 in banked blood is about 200 mm Hg after 20 days and the pH about 6.9. Despite these changes, an acidosis following even a massive transfusion is a rare occurrence. A metabolic alkalosis following large volumes of blood is more common. This is due to the metabolism of citrate (the anticoagulant in stored blood) to bicarbonate in the Krebs cycle.

- *Citrate toxicity*

  Blood is donated into bags containing, amongst others, sodium citrate. The citrate binds calcium. Since calcium is a clotting factor, the citrate prevents blood clotting. Therefore, citrate can cause a hypocalcaemia. Despite this, hypocalcaemia is a rare phenomenon except with rapid transfusion rates (> about 2 ml kg^{-1} min^{-1}). Citrate is cleared in the Krebs cycle in the liver to form HCO_3^-. Therefore, any condition that impairs liver function (intrinsic liver disease, hypoperfusion, hypothermia) will limit the clearance of citrate and increase the risk of hypocalcaemia.

  In the anaesthetized patient, citrate toxicity is characterized by acute hypocalcaemia, namely hypotension (due to cardiac failure and vasodilatation) and a prolonged QT interval (not a consistent finding). Hypocalcaemia is treated with calcium chloride 1.5 mg kg^{-1} min^{-1} intravenously. In the setting of a rapid blood transfusion, the effects of hypocalcaemia are overshadowed by those of hyperkalaemia.

  Remember:
  1. The most common cause of hypotension in the resuscitation scenario is hypovolaemia – not hypocalcaemia.
  2. There is a poor relationship between total and ionised plasma calcium.
  3. Hypocalcaemia is not readily corrected with the administration of the recommended dose of $CaCl_2$ of about 15 mg kg^{-1} *obese dose-determining mass* (ODDM).[xxiv]
  4. β stimulant catecholamines mobilize intracellular calcium and also correct a low calcium levels. (β stimulants also promote the movement of potassium into cells, causing a decrease in plasma potassium.)
  5. Low calcium concentrations quickly normalize as general tissue perfusion improves

---

[xxiv] ODDM (kg) = Ideal body mass + 0.4(total body mass – ideal body mass)

- *Hyperkalaemia*
  The potassium content of stored blood can increase to 12 mM to 32 mM depending on how long it is stored. Rapid administration of large volumes (> about 2 ml kg^{-1} min^{-1}) of bank blood causes an acute hyperkalaemia. Acute hyperkalaemia presents with the ECG signs of hyperkalaemia (dysrhythmias, including ventricular fibrillation) and is treated with its physiological antagonist calcium.

- *Decreased 2,3 DPG*
  Bank blood has low red blood cell 2,3 DPG. This causes a leftward shift of the oxygen-haemoglobin dissociation curve.

- *Hypomagnesaemia*
  Magnesium is also a bivalent ion and bound by citrate.

Transmission of infective disease
Blood products may be contaminated with organisms, depending on the quality of the blood transfusion service and prevalence of infection in the donor pool of the particular area. These organisms include cytomegalovirus (occurs in the leukocytes), HIV, Epstein-Barr, hepatitis B and C, malaria, Brucella, syphilis, etc. The risk to be transfused with HIV-contaminated blood is estimated at 1 in 800 000 transfused units of blood, but the chance of infection with HIV from a contaminated blood product is 95%.

Bacterial contamination occurs when aseptic techniques are not followed during transfusion. Bacterial sepsis may be transmitted by blood platelet products, since they are stored at room temperature. All blood-derived products, except albumin which is pasteurised, can be contaminated and be responsible for the transmission of organisms. *Remember, bacterial contamination is the most important cause of infection-related mortality; of these, platelet transfusion is the leading cause (1 in 2000 cases).*

Micro-aggregates
Blood cell products (red, white, platelets) and plasma must be administered through a blood filter. The *standard blood filter* contains a mesh with a pore size of 170 μm. A standard blood filter should be replaced after the transfusion of about three units of blood cells. Micro-aggregates consist of aggregates occurring in blood products. They cause pulmonary vascular obstruction and release of vasoactive substances. This causes transfusion related acute lung injury (TRALI). *FFP is considered the most important cause of TRALI.* The benefit of *microfilters* (pore size of < 40 μm) to scavenge the particles smaller than 10-40 μm has not been proven. It does however not decrease the incidence of bacterial platelet contamination, haemolytic reactions or TRALI.

Bleeding tendencies usually occur due to dilutional thrombocytopenia i.e. massive blood loss with resuscitation using fluids and packed cells only and no replacement of clotting factors or platelets. However, a decrease in fibrinogen, and the labile factors V and VIII in stored blood can contribute. A consumption coagulopathy can also cause bleeding. The use of the freshest blood possible limits clotting problems and platelet administration is rarely necessary. A bleeding diathesis in the patient needing large volumes of blood products is probably rather caused by the development of a coagulopathy complicating the underlying pathology, e.g. massive trauma, sepsis, ischaemia, inflammation, etc. A transfusion-related coagulopathy should therefore not be treated blindly but according to coagulation tests to identify the appropriate therapy. (This is however often time-consuming and of retrospective value only.)

Transfusion related immunomodulation (TRIM) is immune depression occurring after blood transfusion. It is caused by depression of "natural killer cell" activity bringing about an increase in T-suppressed cells. This may contribute to the spread of tumour cells and infection. Removal of leukocytes (*leukoreduction*) decreases transfusion of cytomegalovirus and immunomodulation. Leukoreduction is routinely done in most developed countries.

Hypothermia may develop when banked blood is not adequately heated prior to administration. This in turn can cause a left shift of the oxy-haemoglobin dissociation curve, citrate toxicity, and a tendency to dysrhythmias.

Circulatory overload may occur if the volume of blood product necessary to treat the deficit exceeds the ability of the cardiovascular system to cope with the extra volume.

ELECTROLYTE DISTURBANCES

Electrolyte abnormalities must always be seen as a sign of underlying deranged homeostasis; they never occur in isolation. It is often accompanied by acid-base and volume disturbances. Electrolytes form the basis of membrane function and will therefore affect all organs dependent on normal trans-membrane potentials. Moreover, electrolytes are responsible for crystalloid osmotic pressure. Conversely, volume disturbances almost always affect electrolyte concentrations and therefore crystalloid osmotic pressure. Abnormal electrolyte levels are often associated with prolonged hospitalization and should therefore be corrected prior to elective surgery.

Sodium
The normal sodium is 135 mM to 145 mM.

Hyponatraemia (Na^+ < 135 mM)
The plasma is usually hypotonic but the patient may be hyper-, normo-, or hypovolaemic. Acute hyponatraemia causes brain oedema, which may be complicated by lethargy, confusion, seizures, and coma. During chronic hyponatraemia the brain cells compensate by decreasing their osmotically active substances thereby minimising fluid shifts.
- *Hypervolaemic hyponatraemia* is caused by renal losses and fluid retention in renal failure or dilutional due to heart failure, and cirrhosis. These causes are usually accompanied by secondary hyperaldosteronism and oedema. Hypervolaemic hyponatraemia is treated with fluid restriction and diuretics.
- *Normovolaemic hyponatraemia* occurs in syndrome of inappropriate ADH secretion (SIADH), hypothyroidism, and mineralocorticoid insufficiency (Addison disease). Normovolaemic hyponatraemia due to SIADH is managed with ADH antagonists or fluid restriction. Patients with hypothyroidism and Addison are treated with hormone replacement, namely thyroid and gluco- and mineralocorticoid hormones respectively.
- *Hypovolaemic hyponatraemia* is caused by renal losses (thiazide and loop diuretics and cerebral salt wasting syndrome in brain injuries), and extrarenal losses (diarrhoea, vomiting, fistulae, burns). Hypovolaemic hyponatraemia is treated with sodium-containing fluid, e.g. 0.9 % NaCl and Voluven.
- *Anaesthetic considerations in hyponatraemia*
  Hyponatraemia is often accompanied by significant underlying disease, which should be treated preoperatively. An abnormal volume, electrolyte, and acid-base status impact negatively on outcome. If the serum Na < 130 mM elective surgery should be postponed as there is an increased risk of cerebral oedema with delayed awakening, seizures etc. A serum Na^+ < 120 mM is often complicated by neurological (convulsions) derangements. Hyponatraemia must always be corrected slowly (over about 24 hours) as rapid correction may lead to pontine demyelinization.

Hypernatraemia (Na^+ > 145 mM)
The serum is usually hypertonic but the patient may be hyper-, normo-, or hypovolaemic. An inadequate fluid intake is a prerequisite for the development of a hypernatraemia. It rarely occurs in patients with an intact thirst mechanism, access to water and an ability to drink. Hypertonicity causes dehydration of brain cells causing confusion, hyperreflexia, coma, and tearing of blood vessels with intracranial bleeding.
- *Hypervolaemic hypernatraemia* is cause by a sodium load when infusing hypertonic Na^+-containing solutions, e.g. $NaHCO_3$ 4.2 % or 8.4 %, or NaCl 5 %. Hypervolaemic hypernatraemia is

treated with loop diuretics (to excrete Na^+ excess) and infusion of glucose 5 % to dilute the hyperosmolality and to maintain normovolaemia.

- *Normovolaemic hypernatraemia* is caused by diabetes insipidus. Treatment consists of vasopressin, desmopressin, oral water, or intravenous glucose 5 % to maintain normovolaemia.
- *Hypovolaemic hypernatraemia* is caused by renal losses due to osmotic diuretics (mannitol), or extrarenal losses caused by diarrhoea, vomiting, or sweating. Treatment consists of replacement with fluid with an electrolyte composition similar to the fluid lost. Usually normovolaemia is reinstituted with NaCl 0.9 % and water is replaced over about 3 days using oral water or intravenous glucose 5 %. Hypertonic dehydration following diarrhoea is replaced with fluid like ½ Darrow's in dextrose 5 %.

Anaesthetic considerations in hypernatraemia

Hypernatraemia must be corrected slowly to allow equilibration of water over membranes. If hypernatraemia is corrected rapidly, brain oedema may develop. A serum $Na^+ > 150$ mM and the concomitant volume deficit or excess must be corrected prior to elective surgery.

Potassium

The normal serum sodium is 3.5 mM to 5 mM. Abnormal potassium levels are almost always accompanied by an abnormal primary or secondary acid-base abnormality.

Hypokalaemia ($K^+ < 3.5mM$) (See also Chapter 12)

Hypokalaemia is caused by:

- *Redistribution* from extra- to intracellular due to, e.g. alkalosis, insulin therapy, and β agonists
- *Decreased intake*, e.g. anorexia, alcoholics, and terminal illness
- *Increased losses*, e.g. renal (DKA, loop and thiazide diuretics, mineralo- and glucocorticosteroids), secondary hyperaldosteronism (do you remember the causes?) vomiting, and diarrhoea
- *Symptoms and signs of hypokalaemia*

  Hypokalaemia is often accompanied by an alkalosis. The major concern with hypokalaemia is cardiovascular malfunction, including ECG abnormalities (large P waves, prolonged PR interval, ST segment depression, T wave flattening, large U waves, and dysrhythmias), decreased contractility and hypotension. Hypokalaemia is also complicated by muscle weakness, muscle cramps, rhabdomyolysis, and renal failure.
- *Treatment of hypokalaemia*

  Treatment of hypokalaemia is started by correcting the causes, e.g. vomiting and diarrhoea, and alkalosis. Hypokalaemia following diuretic therapy is usually corrected with oral replacement or the addition of potassium sparing diuretics. If intravenous replacement is necessary, the dose is 0.25 mmol kg^{-1} to 0.5 mmol kg^{-1} lean mass over 30 min to an hour (in an adult 20 mmol to 40 mmol). KCl solutions are very irritating for the veins. Therefore, K^+ solutions of > 40 mmol L^{-1} must be administered through a central venous catheter or in a maintenance or resuscitation line that dilutes the potassium solution. Hypokalaemia is often accompanied by a hypomagnesaemia, which should also be replaced (usually 1 g $MgSO_4$ for every 20 mmol of K^+). If potassium is administered at this rate, it must be done under ECG guidance (increasing T wave amplitude). Hypokalaemia is often caused or accompanied by hypomagnesaemia. Magnesium is also required for the trans-membrane transport of potassium (NaK-ATPase co-factor). Therefore, magnesium is usually co-supplemented with potassium. For each 20 mmol of K^+, 1 g of $MgSO_2$ is added.
- *Anaesthetic considerations in hypokalaemia*

  Remember that hypokalaemia is almost always a sign of significant co-morbidity. Chronic hypokalaemia is less of a risk than acute hypokalaemia. Elective surgery must be postponed if the serum K^+ is < 3 mM. In patients with ischaemic heart disease or treated with digoxin the serum K^+ must be > 4 mM.

Hyperkalaemia ($K^+ > 5mM$)

Hyperkalaemia is caused by:

- *Redistribution* from intra- to extracellular eg. Acidosis, insulin deficiency, β blockers, severe tissue damage (tumorlysis, haemolysis, rhabdomyolysis and burns)
- *Pseudohyperkalaemia* due to haemolysis of the sample or an old sample
- *Increased intake* e.g. Potassium replacement, blood transfusion
- *Decreased excretion* e.g. renal failure, potassium sparing diuretics
- *Symptoms and signs of hyperkalaemia*
  Patients may present with muscle weakness, paralysis, and ileus. ECG changes include flattened P wave, prolonged PR interval, widened QRS, flattened R wave, depressed ST segments, and peaked T wave.
- Treatment of hyperkalaemia
  - Serum potassium > *6 mM* must always be treated.
  - *Stop* all sources of potassium e.g. Ringers-lactate.
  - *Promote excretion* if the potassium is < 6.5mM. Use a loop diuretic (*furosemide* about 0.3 mg kg^{-1}) or sodium polystyrene sulphonate (*Kayexelate*) about 0.5 g kg^{-1} per os or rectum (1 g binds about 1 mmol K^+ and releases 1.5 mmol of Na^+)
  - If the K^+ is > 6.5mM the cardiac effects of K^+ *must be antagonized with $CaCl_2$* (about 10 mg/kg IVI over 10 min).
  - *Movement of K^+ into cells* can be promoted by *insulin plus dextrose* (about 0.1 U kg^{-1} and 0.5 g kg^{-1} respectively IVI over 20 min), treatment of *metabolic acidosis with $NaHCO_3$* (about 0.5 mmol kg^{-1} = 0.5 ml/kg of a 8.4 % solution), *β agonists* (*adrenaline* about 20 ng kg^{-1} min^{-1} = about 1.5 μg min^{-1} in a 70 kg patient), and hyperventilation.
  - Refractory hyperkalaemia is treated with *dialysis*.
- *Anaesthesia considerations in hyperkalaemia*
  Always determine the cause of the high potassium. NO elective surgery is undertaken if the serum K^+ is > 5.5 mM.

Calcium

The calcium ion is essential for many biological functions, including electrophysiological [cardiac impulse generation and conduction, muscle contraction (skeletal, smooth, myocardial), neuronal conduction, synaptic transmission], blood coagulation, and homeostasis [hormone secretion and effect, enzyme activity (second messenger)]. The normal total serum calcium is 2.2 mM to 2.6 mM and ionized 1.0 mM to 1.25 mM.

Hypercalcaemia

The patient may present with fatigue, psychiatric symptoms (anxiety, dementia, depression, irritability, psychosis), neurological symptoms (hyporeflexia, lethargy, headache, confusion, coma), muscle weakness, **severe dehydration** (anorexia, nausea, vomiting, polyuria), and cardiovascular compromise (hypertension, arrhythmias, ECG changes (reduced QT interval), digitalis sensitivity, cardiac arrest), and thrombosis.

Urgent treatment of the hypercalcaemia is necessary, especially in symptomatic patients. A *total serum $Ca^{2+} \geq 3.2$ mM* is dangerous and must be corrected before anaesthesia.

- *Management of hypercalcaemia:*
  - Monitoring of the cardiovascular and serum electrolyte status (Acid-base, Na^+, K^+, Mg^{2+})
  - **Rehydration** and forced diuresis with NaCl 0.9 % (5 L day^{-1} to 10 L day^{-1}) and furosemide about 100 mg every 2 hours. Rehydration alone may decrease calcium with about 1.0 mM.
  - Intravenous *bisphosphonates* (etidronate)
  - *Glucocorticoids* in patients with lymphoproliferative diseases and patients with high calcitriol levels (granulomatous diseases, sarcoidosis, vitamin D toxicity)
  - *Intravenous phosphate* is potentially toxic and should be reserved for life-threatening hypercalcaemia if etidronate is ineffective and plicamycin is contraindicated.

Hypocalcaemia

Patients present with psychiatric (anxiety, dementia, depression, irritability, psychosis, confusion), haemodynamic (hypotension, impaired contractility, digitalis insensitivity, bradycardia, arrhythmias, ECG changes (QT and ST prolongation, T inversion), cardiac arrest), respiratory (laryngospasm, bronchospasm), neurological (hyperreflexia, convulsions), and neuromuscular (paraesthesiae, Chvostek's and Trousseau's signs, muscle cramps, tetany, muscle weakness) symptoms and signs. The symptoms cause by hypercalcaemia is often referred to as "moans, groans, and stones".

Mild degrees of hypocalcaemia with an *ionized Ca^{2+} of < 0.8 mM* (total serum Ca^{2+}< about 1.6 mM) are usually asymptomatic and seldom require treatment. Lower serum Ca^{2+} may cause symptoms and needs replacement. Serum *ionized Ca^{2+} < 0.5 mM* (total serum Ca^{2+} < about 1.0 mM) is frequently associated with life-threatening complications and needs urgent intravenous Ca^{2+}. Hypocalcaemia should be corrected before elective surgery.

In the anaesthetic scenario the most common cause of life-threatening hypocalcaemia is seen during transfusion of large volumes of blood or FFP. These fluids contain citrate, which binds Ca^{2+}. Bank blood also contains high concentrations of K^+, which aggravates the effects of hypocalcaemia. Acute life-threatening postoperative hypocalcaemia is also sometimes observed after thyroidectomy.

- *Management of hypocalcaemia:*
  - *Correct any respiratory or metabolic alkalosis* and concurrent electrolyte disturbances.
  - *$CaCl_2$ injection* contains 10 % $CaCl_2$ = 1000 mg/10 ml = 272 mg Ca^{2+} per 10ml
    Calcium gluconate injection contains 10 % calcium gluconate =1000 mg/10 ml = 93 mg Ca^{2+} per 10ml. Therefore, the mg kg^{-1} dose of the gluconate is about 3 times that of the chloride. (Remember, the atomic mass of Ca is 40, the molecular mass of $CaCl_2$ 111, and the molecular mass of calcium gluconate 430.)
  - $CaCl_2$ about 6 mg/kg over 10 min followed by a maintenance infusion of 0.6 mg/kg/h, which will normalize the serum calcium after about 9 hours. Thereafter, the rate is decreased to 0.2 mg kg^{-1} h^{-1}. Acute hypocalcaemia, is treated by boluses of $CaCl_2$ at doses of about 15 mg kg^{-1}. This is done under ECG monitoring.

Magnesium

The normal serum magnesium is 0.7 mM to 1.2Mm.

- *Hypermagnesaemia* can occur in patients with imminent eclampsia, who have received magnesium sulphate. This can potentiate the action of the depolarising and non-depolarising muscle relaxants.
- *Hypomagnesaemia* is seen in alcoholics who have a decreased intake and can result in dysrhythmias; most commonly torsades de pointes (polymorphic ventricular tachycardia)
- *Uses for magnesium sulphate in theatre include* :
  - bronchodilatation
  - acute lowering of blood pressure
  - potentiation of regional blocks
  - as an analgesic (NMDA antagonist)
  - prevention of catecholamine release during resection of a phaeochromocytoma

An important ion, which is very often involved in fluid therapy and electrolyte disturbances, is hydrogen (H^+). Acid-base homeostasis and abnormalities are dealt with in the lecture: Anaesthesia and acid-base abnormalities (Chapter 20).

CHAPTER 19+

ANAESTHESIA AND BLOOD

(See also Chapters 2, 14, and 18. For a discussion of the diseases and pharmacology of the drugs mentioned in this chapter, please see your physiology, pharmacology, internal medicine, and surgery notes.)

It is not expected from the students to memorise the content of tables that summarise the pharmacology of drugs; but you must know the principles behind it, and where to find the information. It is only given for the sake of completeness.

Key points

- *Blood components*
- *Preoperative evaluation* of the patient with diseases affecting blood cells and haemostasis
    - *The cause*: anatomical, physiological, pharmacological.
    - *The effects* of abnormal blood components on vital organs: Anatomical (the airway), physiological (anaemia, immunoparesis, abnormal clotting), pharmacological
    - *The procedure*
- *The anaesthetic plan*: the procedure, the cause, clotting profile availability of blood components must be considered.
- *The anaemic patient*
    - Anaemia is not a disease but an indicator of underlying pathology.
    - The decision to administer blood perioperatively
- The polycythaemic patient
    - Appropriate polycythaemia (hypoxaemic polycythaemia)
    - Inappropriate polycythaemia (non-polycythaemic polycythaemia)
    - Approach to the patient presents with polycythaemia
- *Perioperative management* of the patient with abnormal haemostasis
- *Clinical presentation* of abnormal haemostasis
- *Causes* of abnormal haemostasis
- *Abnormal haemostasis and control of haemostasis*
- *Antihaemostatic therapy*
    - Perioperatively management of antihaemostasis
    - Risk for arterial (systemic) embolism in patients with atrial fibrillation
    - Surgery and the patient on anticoagulants
    - The patient receiving warfarin
    - Bridging warfarin and starting with heparin
    - Therapeutic and prophylactic (low dose) UFH and LMMH for bridging
    - Restarting anticoagulation
- *Regional anaesthesia* in the patient receiving antihaemostatic agents
- *Intraoperative heparinisation*
    - The dose of heparin
    - Reversal of heparin: the dose of protamine
- *The bleeding trauma patient*

It is not expected from the students to memorise the content of tables that summarise the pharmacology of drugs; but you must know the principles behind it and where to find the information.

In this chapter, emphasis is placed on the aspects of blood that the anaesthetist encounters *pre-, intra-, and postoperatively*. These include the *cellular components* of blood, namely erythrocytes, platelets, and leukocytes, as well as the *plasma components*. Regarding the plasma components, aspects of *haemostasis and antihaemostasis* are highlighted.

Diseases affecting blood components occur commonly and you will come across them often – in general practice as well as in specialized practice. *All the drugs mentioned are on the South African market*; they are not only prescribed to patients living in large cities, but *also to patients from rural areas*. Although patients on drugs affecting coagulation are usually referred to secondary and tertiary hospitals for surgery, you may become involved in their perioperative management at peripheral hospitals.

Blood components

Blood consists of red blood cells (RBC), white blood cells (WBC), platelets, and plasma. The plasma component consists of water, electrolytes, glucose, albumin, globulins, lipids, non-protein nitrogen (NPN)[xxv], including *urea*, urate, creatinine, *heparin*, enzymes, hormones, and cytokines. The *globulin fraction* includes carrier proteins (for minerals, vitamins, hormones, and drugs such as anaesthetic agents and warfarin), antibodies, *all the clotting factors* (except *calcium*), and substrates for enzymes, e.g. angiotensinogen is a substrate for renin.

[xxv] NPN usually refers to urea and creatinine.

Albumin and all the globulins (except antibodies, which are produced by plasma cells) are produced by the liver. Diseases that affect the plasma protein production and destruction affect plasma protein concentration, e.g. *liver* and *plasma cell pathology* (myeloma). *Kidney* disease affects plasma components in several ways, including homeostasis of water, electrolytes, acid-base, plasma protein (proteinuria), *urea*, etc. All cellular components of blood take their origin from stem cells in red bone marrow.

Several plasma components affecting haemostasis are secreted from *the endothelium*, including *nitrogen monoxide* (nitric oxide) and *prostaglandins*, e.g. prostacyclin.

Clinical presentation of abnormal haemostasis
- The clinical picture of *abnormal bleeding* depends on the haemostatic defect, i.e. abnormal platelets or abnormal factors (Table 1)
- *Thrombosis*
- *Thromboembolism*
- *Hypoxia*: Abnormal haemostasis will, depending on the degree and distribution of the abnormality cause hypoxia. The hypoxia may be *systemic* (anaemia, hypovolaemia, pulmonary embolism, cardiac failure) or *regional*, e.g. stroke (thrombosis, embolism, haemorrhage), myocardial infarction, mesenteric thrombosis, peripheral arterial occlusion (thrombosis, embolism), and deep venous thrombosis (DVT).
- All these conditions are *potentially fatal*.

Table 1 Bleeding tendencies in platelet and clotting factor disorders

Abnormality	Platelet disorder	Factor disorder
Start of haematoma formation	Within minutes	Delayed for hours to days
Site of spontaneous bleeding	Superficial: Skin, mucosae (nose, gingiva, gastrointestinal, urogenital tract)	Deep: Muscles, joints, skin, retroperitoneal
Clinical sign	Petechiae, ecchymosis	Haematoma, haemarthrosis, ecchymosis, purpura

All the following abnormalities may affect haemostasis in the perioperative period and occur commonly and determines the risk of thrombosis and embolism:
- *Old age*
- *Cardiovascular disease*: These include congenital cyanotic heart disease (*hyperviscosity*, thrombocytopaenia), mechanical heart valves, atrial fibrillation, ischaemic heart disease, cardiac failure, and hypertension. Venous *stasis* and arterial and venous disease affecting the *endothelium* (atherosclerosis, vasculitis) cause hypercoagulability.
- *Lung disease*: chronic obstructive airways disease (polycythaemia), pulmonary embolism
- *Gastrointestinal tract* including the liver, bile excretion (jaundice), nutrition: non-vitamin K-dependent and vitamin K-dependent clotting factors
- *Kidney function*: acidosis, uraemia. Although no clear correlation exists between bleeding time and urea concentration, uraemia causes a reversible thrombocytopathy.
- *Endocrine disease and treatment*: obesity, pregnancy, oestrogen, anabolic steroids, and *diabetes mellitus*
- *Malignancies*: activate coagulation and invade blood vessels (bleeding)
- *Immune system*: immunoparesis, lymphadenopathy, splenomegaly, hepatomegaly
- *Plasma proteins*: abnormal procoagulants, e.g. antiphospholipids of systemic lupus erythematosus, myeloma inactivates procoagulants and platelets and cause renal failure.
- *NPN*: uraemia
- *Blood count*:
  - *Anaemia and polycythaemia*. Remember, that *anaemia per se can decrease blood clotting* since the red blood cell membrane promotes activation of *factors IX and X*, platelet *thromboxane production*, and *rouleaux formation.* The red blood cells in the centre of the flowing blood

column in the blood vessels and pushes platelets to the periphery and thereby *promote platelet-endothelium interaction*.

- o *Thrombocytopaenia*: decreased production, sequestration in the spleen, increased destruction due to sepsis, disseminated intravascular coagulation, vasculitis, cardiovascular prostheses, and immune destruction (ITP), and HIV.
- o *Thrombocytopathy*: The platelet count may be normal but platelets do not function normally due to decreased adhesion (Von Willebrand), aggregation (gpIIb/IIIa defects: Glanzman, drugs), or secretion (NSAIDS, uraemia)
- o *Leucocytosis, leucopoenia, leukaemia, and lymphoma. Myeloproliferative malignancies* often displace the other components and/or cause decreased production, dysfunction, or destruction of the other components. These include haemolysis, thrombocytopathy, and thrombocytopaenia. *Like other malignancies*, these diseases *activate coagulation* and may give rise to a *consumptive coagulopathy*.
- *Abnormal haemostasis and control of haemostasis*: thrombosis (e.g. deep venous thrombosis due to abnormal clotting factors such as Factor V Leiden, antithrombin III deficiency), bleeding (haemophilia, Von Willebrand disease), embolism (pulmonary or systemic), sepsis and inflammation (activation and consumption of platelets and coagulation factors), massive tissue trauma (hyperfibrinolysis of trauma), and surgery (hypercoagulability)
- *Antihaemostatic therapy* (See also Table 7):
  - o Vitamin K antagonists: Warfarin
  - o Heparin: Unfractionated heparin (UFH), low-molecular mass heparin (LMMH) such as enoxaparin and deltaparin), and the factor Xa-inhibiting heparin fraction fondaparinux.
  - o Activated protein C (drotrecogin alpha)
  - o Thrombin inhibitors: Desirudin, lepirudin, and ximelagatran
  - o The oral oxazolidinone derivative rivaroxiban, which inhibits factor Xa
  - o Antiplatelet agents: Aspirin, the irreversible non-competitive ADP antagonists clopidogrel and ticlopidine, the glycoprotein IIb/IIIa antagonists absiximab, eptifibatide and tirofiban, non-steroidal anti-inflammatory drugs (NSAIDS)
  - o Thrombolytics: Streptokinase, alteplase (tissue plasminogen activator), and tenecteplase
  - o Herbal therapy, including garlic, ginko, and ginseng (Table 2)
- *Conditions that prevent optimal cell membrane and enzyme activity*: hypothermia, hyperthermia, acidosis, dilution of coagulation factors and platelets (massive transfusion), and hypocalcaemia (citrate toxicity)

Table 2 Herbal medication and haemostasis[26]

Herb	Effects	Concerns	Time to normal haemostasis
Garlic	Inhibits platelet aggregation (?irreversible) Increases fibrinolysis Equivocal antihypertensive	Increased bleeding, especially with other platelet inhibitors	7 days
Ginko	Inhibits platelet activation	Increased bleeding, especially with other platelet inhibitors	36 hours
Ginseng	Lowers blood glucose Increases prothrombin time and PTT in animals	Hypoglycaemia Increased bleeding May decrease anticoagulant effect of warfarin	24 hours

Preoperative evaluation of the patient with diseases affecting blood cells and haemostasis
Conditions affecting blood components have *multisystem effects. The following are considered*:
- *The cause (all the conditions mentioned above)*: *anatomical* (tumours, bleeding, clotting), *physiological* (function, production and destruction of blood components), or *pharmacological* (drugs affecting blood components).
- The *effects on vital organs* must be assessed. The *effects are anatomical* (e.g. mediastinal tumours affect *the airway*, intracranial haematoma), *physiological* (e.g. *anaemia* aggravates myocardial

hypoxia in patients with ischaemic heart disease, *immunoparesis* predisposes to infection, or *abnormal clotting* (increased or decreased) causing hypoxia), *pharmacological* (e.g. the decision to reverse the effect of anticoagulants or when to reinstate anticoagulation).[27][28] Please see your surgery and pharmacology notes regarding pre- and postoperative management of the anticoagulated patient.

- *The procedure* may be surgical, radiological intervention (e.g. embolization of bleeding tumours, endovascular repair of large arteries such as the aorta) or diagnostic (e.g. endoscopy, lymph node biopsy, bone marrow biopsy, etc.)
- *The anatomical, physiological, and pharmacological aspect of blood components must be assessed.* Whenever you detect an abnormal blood count, you must consider clotting function and immunological function, and vice versa. *Special investigations* include a full blood count (attend to all the cell components; are they increased, decreased, or abnormal), blood biochemistry (plasma proteins, electrolytes, NPN), and radiological investigations (radiological investigations of the thorax).
- *The anaesthetic plan* will be determined by the *procedure*, the underlying *cause* of the abnormality (e.g. a patient with atrial fibrillation and a mechanical mitral valve, or a patient with a mediastinal mass presenting for a biopsy), the *clotting profile* (general vs. neuraxial anaesthesia; nasotracheal vs. orotracheal intubation). The immediate *availability of blood components* must be considered.

The anaemic patient (see also Chapters 14 and 18)
Anaemia is not a disease but an indicator of underlying pathology. In adults, anaemia is usually defined as a haemoglobin (Hb) concentration < 115 g L^{-1} (11.5 g/dl), a haematocrit (Hct) < 35%, or a haematocrit that decreases > 1% per 24 hours. The Hb may be decreased due to:
- Blood loss
- Dilution
- Haemolysis: Immune (incompatible transfusion), spherocytosis, red cell enzyme defects (G6PDH, pirovate kinase, etc.), haemoglobinopathies (Hb sickle cell disease)
- Decreased production: Bone marrow failure (leukaemia, lymphoma), kidney failure, iron deficiency, megaloblastic, aplastic (Fanconi, Diamond-Blackfan etc.), chronic disease (infection, liver disease, malignancy, autoimmune disease, HIV, diabetes mellitus), etc.
- Haemoglobinopathies: MetHb, Hb sickle cell disease, thalassaemia, etc.

The decision to administer blood perioperatively depends on the following (also see Chapter 18):
- The *cause* of the anaemia (see above)
- The *degree* of anaemia and if the patient *can tolerate the anaemia*, i.e. all patients with either a low systemic blood flow (cardiac failure) or low regional perfusion (ischaemic heart, cerebrovascular or peripheral arterial disease), or all patients with a low PaO$_2$ (lung disease), or a high oxygen consumption (neonates), and the extremes of age.
- The *duration* of anaemia (acute or chronic). Remember, a chronic anaemia is not necessarily a reason not to transfuse. In anaesthetic practice, the Hct can decrease rapidly. The anaesthetist must observe trends in Hct and intervene before it reaches unacceptably low levels (see Chapter 18).
- *Intravascular volume state*; is there dilution or haemoconcentration
- The *urgency* of surgery
- Can a transfusion *cause harm*, e.g. malignancy, isoimmunisation in patients awaiting organ transplant
- Does the *patient refuse* transfusion (religious considerations)

The polycythaemic patient[29]
A patient is polycythaemic if the Hct is > 50% (Hb > 170 g L^{-1}). Perioperative outcome is poorer if the Hct is > 55% in men and > 52% in women. Polycythaemic is often accompanied by iron insufficiency – especially after flebotomy. Polycythaemia is complicated by hyperviscosity (hypertension, thrombosis, ischaemia of the heart, brain, limbs, etc) and abnormal haemostasis (thrombosis or bleeding). Polycythaemia may be appropriate (response to hypoxaemia) or inappropriate (hypoxaemia absent):

Appropriate polycythaemia (hypoxaemic polycythaemia)
- *Lung disease*. Chronic cigarette smoking causes a chronic hypoxaemia (PaO$_2$< 60 mm Hg) and an increase in carbon monoxide (often > 5%; normal < 2.5%). Both these factors cause tissue hypoxia, which stimulates erythrocyte production.
- *High altitude*
- *Hypoventilation*: sleep apnoea
- *Cyanotic heart disease*: In these diseases, hyperviscosity causes thrombosis. Platelet concentrations are also often decreased due to decreased production and consumption due to a state of chronic thrombosis.

Inappropriate polycythaemia (non-polycythaemic polycythaemia)
- *Endocrine disease*: Cushing syndrome and phaeochromocytoma

- *Surreptitious use of anabolic steroids and erythropoietin* by athletes and body builders may cause severe polycythaemia with hyperviscosity when they become dehydrated. Anabolic steroids are also hepatotoxic and increase the incidence of ischaemic heart disease.
- *Malignancy*: Primary polycythaemia (polycythaemia vera) is a rare malignancy of haematopoietic stem cells (mostly in the liver and spleen, which enlarge massively) and is accompanied by a thrombocytosis, and leukocytosis. The disease is complicated by ischaemia (hyperviscosity, thrombosis) and bleeding (abnormal platelets). Renal carcinoma may also secrete erythropoietin.

Therefore, if the patient presents with polycythaemia, consider
- The *cause*
- *Complications* (ischaemia, thrombosis, bleeding)
- Whether *treatment* (phlebotomy or exchange transfusion) is necessary. In *non-hypoxaemic* polycythaemia, the Hct should be decreased to *< 46%,* and in *hypoxaemic polycythaemia to < 52%.*

Perioperative management of the patient with abnormal haemostasis
In this section emphasis is placed on neuraxial anaesthesia in the patient with abnormal haemostasis, patients receiving antihaemostatic agents (anti-factor and antiplatelet agents) preoperatively, intraoperative anticoagulation (heparinisation and reversal of heparin), and intraoperative coagulopathy.

The patient may be bleeding, clotting, require intraoperative anticoagulation (cardiovascular procedures), or reversal of anticoagulation. *Remember the Virchow triad of thrombosis*. It describes the three broad categories of factors that contribute to thrombosis, namely hypercoagulability, haemodynamic changes (stasis, turbulence), and endothelial dysfunction or injury (trauma, immune-mediated, atherosclerosis, etc.)

The problems in managing antihaemostasis perioperatively are:
- *Stress, tissue trauma, and immobility* cause hypercoagulability.
- *The disease necessitating antihaemostasis* is often of such a nature that interruption of antihaemostatic agents predisposes to thrombosis and embolism, e.g. mechanical cardiac valve prostheses, coronary stents, and atrial fibrillation.
- *Continuation* of anticoagulants or *bridging* of oral anticoagulants with heparin increases the risk of intra- and postoperative bleeding.
- The management of perioperative antihaemostasis is *controversial* since it is largely based on observational studies or consensus. Antihaemostasis should be *individualised* (benefit vs. risk; Tables 3 and 4) and should *be monitored* whenever possible.[28 30.]

Table 3 The CHADS scoring system: Risk for arterial (systemic) embolism in patients with atrial fibrillation when stopping warfarin[28]

Conditions	Score
Congestive cardiac failure	1
Hypertension	1
Age > 75 years	1
Diabetes mellitus	1
Stroke or TIA history	2
	Total = 6.

High risk 5 to 6 or history of stroke or TIA
Moderate risk 3 to 4 without stroke or TIA history
Low risk 0 to 2 without stroke or TIA history

Surgery and the patient on anticoagulants
Although pre- and postoperative management of antihaemostasis is the responsibility of the surgeon/interventionist, it may become your responsibility in smaller centres.

The normal platelet count is 150×10^9 L^{-1} to 350×10^9 L^{-1}. In pregnancy, about 6% of patients presenting for caesarean section has a platelet count of $< 150 \times 10^9$ L^{-1}, while 1% of patients have a count of $< 100 \times 10^9$ L^{-1}. In pre-eclamptic patients, about 30% of patients have a platelet count of $< 100 \times 10^9$ L^{-1}. For adequate haemostasis, an platelet count of 100×10^9 L^{-1} is needed, with the minimum count of *normal* platelets to sustain clotting being 50×10^9 L^{-1}. The maximum international normalized ratio (INR), which reflects adequate coagulation factor function, is 1.5 (normal up to 1.2). Procedures where bleeding is not readily accessible, require an INR ≤ 1.5.

The patient receiving warfarin poses a problem: stopping the treatment increases the risk for thrombosis and embolism (Tables 3 and 4); continuing warfarin increases the risk of bleeding and

contraindicates spinal anaesthesia. Therefore, the *principle of bridging* is usually applied. (Although there is some agreement regarding bridging, practice between hospitals and in hospitals may vary. Please see Tables 3 and 4)

Table 4 Risk stratification for arterial or venous thromboembolism when stopping warfarin28 [31]

Risk	Indication for warfarin		
	Mechanical heart valve	**Atrial fibrillation**	**VTE**
High	Mitral valve prosthesis Caged-ball or tilting AVP Stroke or TIA < 3 months	CHADS 5 or 6; Stroke or TIA < 3 months Rheumatic valvular heart disease	VTE < 3 months Severe thrombophilia, e.g. low protein C, protein S, antithrombin; antiphospholipids antibodies
Moderate	Bileaflet AVP **and** AF or any CHADS	CHADS 3 or 4	VTE 3 – 12 months Non-severe thrombophilia, e.g., heterozygous FV Leiden Recurrent VTE Cancer (treated < 6 months or palliative)
Low	Bileaflet AVP, **No** AF, **No** CHADS	CHADS 0 to 2 **and no** previous stroke or TIA	Single VTE > 12 months **and no** other risk factors

AVP aortic valve prosthesis; TIA transient ischaemic attack; AF atrial fibrillation; VTE venous thromboembolism

Bridging refers to stopping the warfarin and starting with heparin. Remember, warfarin has a very long $t_{1/2}$. Therefore, it must be stopped well in advance of the procedure. Once the effect of warfarin starts to fade, it must be replaced with an anticoagulant that has a shorter effect and is titratable to effect. It takes 4 days for an INR of 2.5 to decrease to 1.5, and 5 days for an INR of 3 to decrease to 1.5, but there is large inter-patient variability in the rate at which the INR decreases. Keep the period of subtherapeutic oral anticoagulation to a minimum.

Who should be bridged?
- *This depends on the procedure, the risk of thrombosis and embolism* (Tables 3 and 4)*, and patient and clinician preferences.*
- *The risk of bleeding with bridging exceeds the risk of thrombosis and embolism* (pulmonary or arterial), but the consequences of the thrombosis and embolism are so grave, e.g. clotting of a heart valve or cerebral embolism with stroke, that both doctor and patient usually accept the risk of bleeding and the inconvenience of bridging.
- *For superficial surgery* reversal is unnecessary, e.g. dental surgery, extra-capsular cataract removal, skin biopsy, etc. These patients *do not stop taking warfarin.*
- *Diagnostic* arthroscopy and gastrointestinal endoscopy, with or without biopsy, but not polypectomy, sphincterotomy, can be done with an INR ≤ 2.5.
- *High risk patients* must be bridged with therapeutic doses of heparin.
- *Moderate risk patients* may receive prophylactic doses of heparin.
- *Low risk patients* may stop their warfarin or may be bridged with prophylactic doses of heparin – with the proviso that warfarin is not withheld for more than 7 days.

How to bridge warfarin
- *Warfarin is stopped 5 days preoperatively.*
- *Heparin is started 60 hours after the last dose of warfarin*; that is the third morning after the last evening dose of warfarin.
- *Start with UFH or LMMH two days before surgery until 24 hours before surgery.*
- *The heparin dose* is either *therapeutic* for high risk patients, *prophylactic* for moderate risk patients, or prophylactic *or no bridging* for low risk patients (Table 5).
- *The INR is checked* 1 to 2 days before surgery. If the INR is > 1.5, vitamin K 1 mg to 2 mg is given per os. If the INR is 1.6 or 1.7 on the morning of surgery, give vitamin K 1.0 mg per os; if the INR is ≥ 1.8 on the morning of surgery, give vitamin K 2.0 mg per os.
- *Do not give fresh frozen plasma* for elective surgery, since it may reverse anticoagulation abruptly to unacceptable levels, which predisposes to thrombosis and embolism.

Restarting anticoagulation
- Restarting anticoagulation *depends on the procedure* and the degree of haemostasis.
- Start with *warfarin 12 hours to 24 hours postoperatively*. Warfarin starts to affects coagulation after about 48 hours.
- *LMMH and UFH* are started *24 hours after minor procedures* and if haemostasis was adequate. If the *risk of bleeding is high*, start therapeutic UFH or LMMH *24 hours* after surgery, *or start with prophylactic doses* postoperatively.
- Continue bridging *until the INR has increased to 2*.

Table 5 Therapeutic and prophylactic (low dose) UFH and LMMH for bridging[28]

Heparin	Therapeutic	Prophylactic (low dose)
Enoxaparin	1 mg kg^{-1} SC every 12 hours (A) or 1.5 mg kg^{-1} SC daily(B)	30 mg (0.4 mg kg^{-1}) SC every 12 hours(A) or 40 mg (0.57 mg kg^{-1})SC daily (A)
Deltaparin	120 IU kg^{-1} SC every 12 hours (A) or 200 IU kg^{-1} SC daily (B)	2500 to 5000 IU (35 IU kg^{-1} to 70 IU kg^{-1}) SC daily (A)
Nadroparine	85 IE kg^{-1} SC daily every 12 hours (A)	38 IU kg^{-1} to 57 IU kg^{-1} daily (A)
UFH	333 IU kg^{-1} IVI once, then 250 IU kg^{-1} SC every 12 hours (C)	5000 IU SC every 8 hours

SC subcutaneously; A Final dose 24 hours before surgery; B The day before surgery, only half of the total daily dose is given 24 hours before surgery; C This is effective (without dose titration based on coagulation testing) for the treatment of acute VTE

Regional anaesthesia in the patient receiving antihaemostatic agents[26][32]

Performing regional anaesthetic blocks in patient receiving antihaemostatic agents must be considered carefully, since haematomas following the block may have serious complications. This specifically applies to neuraxial blocks (spinal and epidural). An epidural haematoma should be suspected in any patient who complains of severe back pain a few hours or days following any neuraxial block, or with any prolonged or abnormal neurological deficit. ___*An immediate neurosurgical referral is indicated.*___ Risk factors associated with the development of spinal epidural haematomas are summarized in Table 6.[33] Several antihaemostatic agents are on the South African market (Table 7).

Remember that any combination of factors (e.g. renal failure) or drugs that affect haemostasis are at least additive. Renal and liver dysfunction do not only affect haemostasis, but also pharmacokinetics of antihaemostatic agents. In these circumstances, neural blockade, especially neuraxis blocks or removal of catheters should probably be avoided. The guidelines regarding neuraxial block are given in Tables 8, 9, 10, and 11.[34][32]

Table 6 Risk factors associated with spinal and epidural haematoma[33]

Factor	Condition
Patient-related	Elderly Female Inherited coagulopathy Acquired coagulopathies (liver/renal failure, malignancy, HELLP syndrome, DIC, etc.) Thrombocytopenia Spinal abnormalities (spinal bifida/stenosis, spinal tumours, ancylosing spondylitis, osteoporosis)
Procedure-related	Catheter insertion/removal Traumatic procedure (multiple attempts) Presence of blood in the catheter during insertion/removal Indwelling epidural catheter > single-shot epidural block > single-shot spinal block
Drug-related	Anticoagulation/Antiplatelet/Fibrinolytic Immediate (pre- and post- CNB) anticoagulant administration Dual anticoagulant/antiplatelet therapies

HELLP haemolysis, elevated liver enzymes, low platelet count; DIC, disseminated intravascular coagulation, CNB, central neuraxial block.

Table 7 Antihaemostatic agents

Agent or group of agents	Generic name	Trade name

Vitamin K antagonists	Warfarin	Warfarin
UFH	Heparin sodium	Heparin sodium-Fresenius, Heparin Novo
LMMH	Heparin calcium Enoxaparin Deltaparin Nadroparin	Calciparine Clexane Fragmin Fraxiparine
Selective FX inhibitors	Fondaparinux Rivaroxiban	Arixtra (subcutaneous) Xarelto (oral)
Thrombin inhibitors	Desirudin Lepirudin Ximelagatran Dabigatran (oral)	Revasc Refludin Exanta Not on the South African Market
Low dose acetyl-salisylic acid	Acetyl-salisylic acid	Ecotrin, Bayer Aspirin Cardio, Lo-aspirin, Myoprin
Dipyridamole	Dipyridamole	Persantin, Plato, Asasantin (with aspirin)
Platelet ADP antagonists	Clopidogrel Ticlopidine	Plavix Ticlid
Platelet glycoprotein IIb/IIIa antagonists	Absiximab Eptifibatide Tirofiban	ReoPro Integrilin Aggrastet
Fibrinolytic/thrombolytic agents	Streptokinase Alteplase Tenecteplase	Streptase Actilyse Metalyse

Table 8 Laboratory investigations and neuraxial block

Test	Acceptable	Individualise (benefit/risk)*
Prothrombin time	Increased by < 50% of upper limit of normal	40% to 50%
INR	≤ 1.4	1.4 to 1.7
aPTT	Upper limit of normal	Exceeding upper limit by 1 s to 4 s.
Platelet count	$\geq 100 \times 10^9$ L^{-1}	50×10^9 L^{-1} to 80×10^9 L^{-1}

aPTT Activated partial thromboplastin time. *Individualise means that, not doing the block will have more complications than not doing the block. Therefore, you must have very good reason to do the block; be careful!

Table 9 Summary of recommended time intervals before and after neuraxis needle or catheter insertion and removal of catheters

Antihaemostatic agent	Before insertion or removal	After insertion or removal	Investigations
UFH	aPTT and/or ACT normal range	1 hour	Platelet count if > 5 days
UFH intraoperative†	Night preoperatively	aPTT and/or ACT normal range	
LMMH (prophylactic) ††	12 hours	4 hours	Platelet count if > 5 days
LMMH (therapeutic) ††	24 hours	4 hours	Platelet count if > 5 days
Fondaparinux	36 hours	12 hours	
Rivaroxiban	18 hours	6 hours	
Warfarin	INR ≤ 1.4	After catheter removal	
Aspirin	12 h in patients on secondary prevention* 3 days in others; 1 week at doses >1 g daily	Resume as soon as possible after surgery	
NSAIDS	See Table 9	2 hours	
Ticlopidine‡	10 days	After catheter removal	
Clopidogrel‡	7 days	After catheter removal	
Epifibatide, tirofiban	8 hours to 10 hours	2 hours to 4 hours	Platelet count
Abciximab	24 hours to 48 hours	2 hours to 4 hours	Platelet count
Dipyridamole	No interval	No interval	
Hirudins	8 hours to 10 hours	2 hours to 4 hours	
Ximelagatran	8 hours to 10 hours	2 hours to 4 hours	
APC (drotrecogin alfa)	unknown	12 hours	
Streptokinase	24 hours	At least 2 hours**	Fibrinogen levels
Alteplase	6 hours	At least 2 hours**	Fibrinogen levels
Tenecteplase	24 hours	At least 2 hours**	Fibrinogen levels

aPTT Activated partial thromboplastin time; ACT activated clotting time; APC Activated protein C
† If surgery requires intraoperative UFH > 70 IU kg^{-1}, consider inserting the epidural catheter evening before. ††In a patient with an indwelling epidural catheter and simultaneous LMMH or other antihaemostatic treatment, non-selective NSAIDs should be avoided when catheter manipulation is planned; COX-2 inhibitors safer. ‡Five days after discontinuing clopidogrel or ticlopidine 450% of platelets have regenerated which is sufficient for primary haemostasis. * In patients with unstable angina and after stroke/TIA, MI, PCI or CABG. ** Clots are not completely stabilized until about 10 days, and risk of bleeding is probably increased if any thrombolytic drug is given before 10 days

Table 10 Half-lives and recommendations regarding discontinuation of NSAIDs

Drug	$T_{1/2}$ (hours)	Recommended interval from last dose until neuraxial block
Diklofenac	1 to 2	12 hours
Ibuprofen	2	12 hours
Ketoprofen	2	12 hours
Indomethacin	4.5	24 hours
Ketorolac	4 to 6	24 hours
Naproxen	10 to 17	48 hours
Lornoxicam 4 h 24 h	4	24 hours
Piroxicam 10–70 h 2 weeks	10 to 70	2 weeks
Tenoxicam 72 h 2 weeks	72	2 weeks
COX-2-specific inhibitors		Do not affect platelets

Table 11 Properties of commonly used antihaemostatic agents[34]

Drug	Target	Peak effect	Plasma $t_{1/2}$	Effect	Monitoring	Antidote
UFH (IV)	II, X (1:1)	< 30 min	1 - 2 h	Moderate/severe	aPTT	Protamine
LMMH (SC)	II, X (1:3)	3 h - 4 h	4 - 7 h	Moderate/severe	Anti-Xa activity	(Protamine)
Fondaparinux	X	2 h - 3 h	17 - 20 h	Moderate/severe	Anti-Xa activity	-
Apirin	Platelets (irreversible)	1 h	30 min*	Mild	Platelet function	DDAVP**
ADP blockers†	Platelets (irreversible)	3 - 7 days	8 h*	Moderate	Platelet function	Platelets
NSAIDS	Platelets (reversible)	See Table 10	See Table 10	Mild	Platelet function	DDAVP**
Warfarin	II, VII, IX, X	5 days	35 h, variable	Moderate INR 2 to 3; severe INR>3	INR	Vit K, factors, plasma

*Anti-platelet effect >>> plasma $t_{1/2}$; **Desmopressin; †Ticlopidine, clopidogrel

Intraoperative heparinisation
Some cardiovascular procedures require anticoagulation. This is accomplished with intravenous unfractioned heparin (UFH). UFH is antihaemostatic via antithrombin III (ATIII), which inhibits mainly factors IIa and Xa, but also factors IXa, XIa, and XIIa. Inherited absence of ATIII as well as several pathological conditions cause heparin resistance. The latter include venous thromboembolism, preeclampsia, cirrhosis, nephrotic syndrome, DIC, heparin pre-treatment, oestrogen therapy, and cytotoxic agents (L-asparaginase).

The dose of heparin
The antihaemostatic activity of heparin is measured in international units (IU). One IU of heparin anticoagulates 1 ml of blood for one hour. Therefore, for a procedure that needs anticoagulation for about an hour, the dose of heparin is about 1 IU per ml of blood. Remember, the blood volume in adults is about 70 ml kg^{-1}, or about 5000 ml in an adult. Therefore, the dose of heparin is about 5000 IU. Heparin is often administered as a mg kg^{-1} dose: 100 IU = 1 mg. If the surgeon requests heparinisation for vascular procedures, 0.7 mg kg^{-1} to 1 mg kg^{-1} is usually administered. For cardiac procedures requiring cardiopulmonary bypass, the dose is much higher, namely about 5 mg kg^{-1}.

Although it has been criticised and is influenced by several variables, the anticoagulant effect of heparin is measured intraoperatively using the activated clotting time (ACT). The normal ACT is 80 s to 120 s. The ACT is usually measured once the heparin has circulated (about 3 minutes after administration). The ACT measures the traditional intrinsic and common coagulation paths (from factors XII to X and from X to I). Blood is added to celite or kaolin (silicon compounds) that causes contact activation of factor XII.

Before heparinisation, a baseline ACT is measured. After heparinisation, the ACT is repeated. For vascular procedures, an acceptable ACT after heparinisation is about two to three times the baseline ACT. For cardiac surgery, an ACT of more than 400 s is usually regarded as safe to initiate cardiopulmonary bypass. After an adequate ACT has been reached, it should be repeated every 30 minutes.

How much heparin is administered if the ACT is not high enough or decreases? Look at the following example:

Baseline ACT = 100 s. The target ACT is, say 300 s. After 1 mg kg^{-1}, the ACT increased to 200 s, but you want it 300 s. One mg kg^{-1} heparin increased the ACT with 200 s – 100 s = 100 s. How much heparin is needed to increase the ACT to 300 s? 1 mg kg^{-1} increased the ACT by 100 s. Therefore [(300 s – 100 s)/100 s] × 1 mg kg^{-1} would increase it from 100 s to 300 s = 2 mg kg^{-1}. Therefore, you must give another 1 mg kg^{-1}.

Heparin's (an acid) effect is reversed with protamine sulphate (an alkali). Before reversal, an ACT is measured and the dose of protamine is calculated. This is done in the same way as the calculation of additional heparin. Since protamine has several adverse effects (hypotension due to histamine release, anaphylaxis, and rarely catastrophic pulmonary vasoconstriction), it should be administered over at least 5 minutes and at a dose that will just neutralise residual heparin. You can easily give more if necessary.

What is the dose of protamine?
A safe dose is in the region of 1 mg protamine for each 1 mg (100 IU) heparin left; we usually start with 0.8 mg protamine for each 1 mg heparin left. How much heparin is left? Look at the following example:
The ACT before neutralisation is say 250 s, while the baseline was 100 s. Therefore, you must neutralise "250 s – 100 s" of heparin = 150 s of heparin. To increase the ACT from the baseline of 100 s to 300 s, i.e. an increase of 200 s, you needed 2 mg kg^{-1} heparin.
Therefore, the amount of heparin that would increase it to 250 s would be
[(250 s – 100 s)/(300 s – 100 s)] × 2 mg kg^{-1} = 150/200 × 2 mg kg^{-1} = 1.5 mg kg^{-1} of heparin.
Therefore, the dose of protamine is between 0.8 and 1.0 × 1.5 mg kg^{-1} = between 1.2 mg kg^{-1} and 1.5 mg kg^{-1}.

Remember to *administer protamine via a crystalloid containing line* and not with plasma or blood, since protamine is an alkali and blood and plasma contains sodium citrate, which is also an alkali. Therefore, the protamine may precipitate.

This above dose-calculating method is based on the *Bull heparin titration graph*. Although the ACT and the Bull method are oversimplifications of anticoagulation and neutralisation of heparin, it is still widely used due to availability and simplicity of the test.

Although the ACT is affected by several variables, it remains a useful intraoperative tool to assess coagulation. The ACT *is prolonged by severe thrombocytopaenia* ($< 50 \times 10^9$ L^{-1}) and thrombocytopathy due to antiplatelet agents. Remember, platelets release platelet factor 4 (PF4), which neutralises heparin. Therefore, a thrombocytopaenia prolongs the ACT. On the other hand, platelet activation and platelet lysis causes the release of PF4. This contributes to the thromboplastic response to surgery and anaesthesia. These factors decrease the ACT.

Intraoperative management of the bleeding trauma patient
Although guidelines (Table 12) have been recommended for abnormal bleeding in the trauma scenario, surgery may cause bleeding via the same pathogenesis (see Chapter 23). Blood loss by the trauma patient is caused by bleeding (externally and internally), while loss of clotting function is due to loss of clotting factors and platelets. Factors are either lost with blood, is diluted (internally or externally), are consumed, are inactivated (hypothermia, acidosis), or the clots are broken down (hyperfibrinolysis of trauma).

Blood component therapy during massive trauma therapy is controversial, but the following guidelines[35] are useful (see also Table 12):
- Packed red cells to maintain an adequate haematocrit
- Transfuse 2 units of FFP for every 3 units or packed red cells, or 1:1.
- Transfuse 6 units of platelets (that is one megaunit/pheresis unit/pooled unit) for every 8 units of packed red cells
- FFP contains fibrinogen, but with hyperfibrinolysis, one unit of cryoprecipitate per 10 kg body mass may be given.
- With massive blood loss, the above recommendations become a replacement ration of 1:1:1.
- Do not forget hypocalcaemia.
- Monitor haemostasis with platelet counts, INR, PT, and thromboelastography if available. A ACT is also useful.

Antifibrinolytics agents have been used to prevent bleeding associated with fibrinolysis, including cardiac surgery. Although concerns (massive thrombosis) have been expressed regarding the use of the use of the lysine analogues, such as tranexamic acid, vascular occlusive events did not differ in patients with trauma-associated coagulopathy who had receive or not received tranexamic acid. A safe dose of tranexamic acid to decrease fibrinolysis is about 5.0 mg kg^{-1} followed by 5 mg kg^{-1} h^{-1}.[36]

Table 12 Summary of therapeutic options in massive haemorrhage[37]

1. Stabilisation of concomitant factors (prophylaxis and therapy)	Cardiac output Core temperature $\geq 34°C$ pH ≥ 7.2 Ionised Ca^{2+} ≥ 0.9 mM
2. Substitution of oxygen carriers	pRBC (functionally, Hb 6–8 g/dL; but in coagulopathy aim for Hct $\geq 30\%$ or Hb$\approx$10 g/dL*
3. Substitution of coagulation factors (for on-going, severe bleeding)	Transfuse 2 units of FFP for every 3 units of packed red cells, or 1:1 Or FFP ≥ 20 (rather 30) ml kg^{-1}
4. Substitution of platelets for primary haemostasis	6 units (1 megaunit/pheresis unit/pooled unit)/8 units of pRBC Aim for 100×10^9 L^{-1}
5. Fibrinogen and inhibition of possible (hyper-) fibrinolysis (always before fibrinogen!)	One unit of cryoprecipitate per 10 kg body mass. Or fibrinogen (2–)4(–6) g (aiming at ≥ 1.50 g L^{-1}) Tranexamic acid initial 1 g in 10 min + 1 g over 8 h or 2(–4) g (15–30 mg kg^{-1})
6. Suspecting thrombocytopathy	DDAVP 0.3 µg kg^{-1} over 30 min

pRBC packed red blood cells; DDAVP desmopressin (enhance platelet adhesion + endothelial release of vWF and FVIII); *Red blood cells enhance platelet function.

CHAPTER 20

BLOOD GAS AND ACID-BASE EVALUATION

Key points
- The aim of this Chapter 9s to give some *background regarding acid-base homeostasis*. You must look for blood gas or acid-base abnormalities when you evaluate the following aspects of your patient: *Anatomical, physiological, and pharmacological*
- The *hydrogen ion concentration*: pH
- *Acids and bases*
- *Buffers*
- *"Anatomical" and chemical buffers"*
- Acid-base *and temperature*
- PO_2 and SO_2, *PCO_2 and bicarbonate*: Metabolic and respiratory *acidoses and alkaloses*
- *The base excess* (BE): The actual BE (ABE), the standard BE (BEecf, SBE)
- The plasma *anion gap* (AG)
- AG, SBE, and the Chloride/sodium ratio
- The strong ion difference (Stewart-Fencle)
- Steps in *evaluation of the acid-base state*

The aim of this Chapter 9s to give some background regarding acid-base homeostasis. Several pathophysiological principles are discussed. Extra material is presented to allow you to understand a topic, which is extremely important, but often not well understood, and therefore neglected. Furthermore, *all clinicians* (GPs and specialists) need to be able to manage critically ill patients and treat common diseases, e.g. hypertension and diabetes mellitus, trauma, etc. The lives of patients treated by an emergency department doctor or GP are just as valuable as those managed by a (so-called) specialist. You must be able to *suspect, identify, and manage the acid-base abnormalities, including the electrolyte disturbances, which often complicate these conditions.*

As is discussed in Chapter 17 (Endocrine disease), you must always link an abnormal blood gas or acid-base state to the origin of the problem. *Vice versa*, you must look for blood gas or acid-base abnormalities when you evaluate the following aspects of your patient:
- Anatomical abnormalities
- Physiological abnormalities
- Pharmacological treatment

Remember, that these aspects interact; it is highly unlikely that one of these will not affect the others to some extent. Blood gas and acid-base analyses form part of the monitoring aspect of disease and treatment. Therefore, if you detect an abnormality in the patient, look for acid-base and blood gas abnormalities and if you find acid-base and blood gas abnormalities, go back and look for its origin: anatomy, physiology, pharmacology.

All body functions are to some extent dependent on the chemical and physical environment. These functions include the activity of enzymes, hormones, membranes, etc. The chemical and physical environments of body fluids are, amongst others, determined by temperature and the concentrations of the following components: electrolytes (including hydrogen) and proteins. In this chapter, the focus will be on the hydrogen concentration in body fluids and its interaction with electrolytes, non-electrolytes, and buffers. The discussion will follow the order often found on the report of the so-called blood gas analysis.

As introduction, consider the *steps used when evaluating the acid-base state of blood*. This is followed by a discussion of the fundamentals of acid-base physiology and evaluation.

STEPS IN EVALUATION OF THE ACID-BASE STATE

Step 1: Identify the obvious abnormalities
pH: 7.35 to 7.45
PCO_2: 35 mm Hg to 45 mm Hg (31 mm Hg to 39 mm Hg in Pretoria)
Cations: Na^+ 135 mM to 147 mM, K^+ 3.3 mM to 5.3 mM
Anions: Cl^- 98 mM to 107 mM, HCO_3^- 19 mM to 29 mM
Albumin: 42 g L^{-1}
SBE: 0 ± 2 mM
Anion gap: 12 ± 4 mEq L^{-1}

Step 2
What is the pH?
Within normal limits = normal, compensated or mixed abnormality
On the alkaline side = alkalosis
On the acid side = acidosis

Step 3
Look at the PO_2 and SO_2

Step 4
Determine if the PCO_2 fits in with the pH:
Alkalosis + $PCO_2 < 40$ mm Hg = respiratory alkalosis
Acidosis + $PCO_2 > 40$ mm Hg = respiratory acidosis

Step 5
If the PCO_2 does not fit in with the pH → look at the SBC
Alkalosis + SBC > 24 = metabolic alkalosis
Acidosis + SBC < 24 = metabolic acidosis
Calculate the BE (unmeasured anions) to determine the effect of Na^+, Cl^-, and albumin

Step 6
Calculate the serum AG
Acidosis + AG > 16 mM = High AG metabolic acidosis (normal Cl^- + ↓ ABC)
Acidosis + AG normal = Low AG metabolic acidosis (↑ Cl^- + ↓ ABC)
Correct the AG for albumin

Step 7
Determine the degree of compensation (Table 8)

Table 8 Compensations for acid-base abnormalities

Primary abnormality	pH	Compensation	Expected response*
Metabolic acidosis: ↓ ABC or ↑ H^+	↓	↓ $PaCO_2$	$\Delta PaCO_2 = \Delta ABC \times$ **1.2**
Metabolic alkalosis: ↑ ABC or ↓ H^+	↑	↑ $PaCO_2$	$\Delta PaCO_2 = \Delta ABC \times$ **0.7**
Respiratory acidosis: ↑ $PaCO_2$	↓	↑ ABC	*Acute:* $\Delta ABC = \Delta PaCO_2 \times$ **0.1**
			Chronic: $\Delta ABC = \Delta PaCO_2 \times$ **0.3**
Respiratory alkalosis: ↓ $PaCO_2$	↑	↓ ABC	*Acute:* $\Delta ABC = \Delta PaCO_2 \times$ **0.2**
			Chronic: $\Delta ABC = \Delta PaCO_2 \times$ **0.4**

$\Delta PaCO_2 = PaCO_2 - 40$ mm Hg; $\Delta ABC = 24 - ABC$ mM. If these changes do not approximately correspond to the observed $PaCO_2$ or ΔABC, there is a mixed abnormality.

Step 8
Look at the metabolites
Lactate
Glucose

Step 9
Look at the haematological variables
Haematocrit
Haemoglobin
Abnormal haemoglobins

THE HYDROGEN ION CONCENTRATION: pH

The normal hydrogen ion (H^+) is expressed as hydrogen activity, namely [H^+]. The normal [H^+] in extracellular fluid is 35 nM to 45 nM. [H^+] is expressed as a negative logarithm, namely pH (potency of hydrogen):

pH = -log[H^+]

If the [H^+] is 40 nM, the pH is calculated as follows:
pH = -log(40 nM) = -log(40 × 10^{-9}) = -(log40 + log10^{-9}) = -(1.6 – 9) = -1.6 + 9 = 7.4
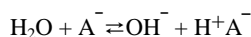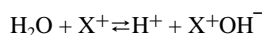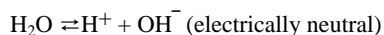
The normal *pH of extracellular fluid* is 7.35 to 7.45. A disadvantage of the pH scale is that the change in [H^+] is not reflected in the change in pH, e.g. a doubling of the [H^+] from 40 nM to 80 nM causes a change of only 0.3 in the pH, namely from 7.4 to 7.1. Likewise, a halving of the [H^+] from 40 nM to 20 nM increases the pH from 7.4 to 7.7.

Intracellular pH is about 6.8. It should however be appreciated that this pH is neutral, i.e. [H^+] = [OH^-] – since the dissociation of water (and other electrolytes) increases with an increasing temperature. Therefore, neutral pH at room temperature (20°C) is 7.0, but 6.8 at body temperature (37°C). Intracellular pH is about 0.3 to 0.6 pH units lower than extracellular pH, depending on the organ. The impact of temperature changes on the acid-base status as well as on the interpretation of acid-base investigations should be appreciated.

Acids and bases
According to Arrhenius *an acid* releases H^+ ions, while *a base* releases OH^- ions. A Brønsted-Lowry acid is a proton donor, while a base is a proton acceptor. Strong anions (acids) do not accept H^+ easily, while strong cations (bases) do not accept OH^- easily.
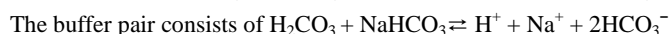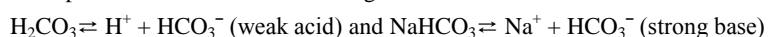
Strong acids and bases dissociate easily:

HA $\rightleftharpoons$ H^+ + A^- and BOH $\rightleftharpoons$ B^+ + OH^-

H_2O $\rightleftharpoons$ H^+ + OH^- (electrically neutral)

H_2O + X^+ $\rightleftharpoons$ H^+ + X^+OH^-

H_2O + A^- $\rightleftharpoons$ OH^- + H^+A^-

Cations are bases (Na^+, K^+, Mg^{2+}, Ca^{2+})
Anions are acids (Cl^-, SO_4^{2-}, Cl^-, $H_2PO_4^-$, ketones, lactate)

Buffers
During acid base disturbances, homeostatic mechanisms try to keep the pH of the body fluids as near normal as possible. This is called compensation. Buffers play an important role in compensation during acid-base abnormalities. *A buffer* is a substance that *prevents a change in pH* if a strong acid or base is added to the solutions. A buffer consists of a weak acid and its conjugate strong base (salt) or of a weak base and its conjugate strong acid (salt), which dissociates in water. The weak anion of the weak acid accepts a H^+ easily, while the weak cation of the weak base accepts OH^- easily. Therefore, a buffer makes a weak acid or base from a strong acid or base, respectively. If the [H^+] increases, it will accept H^+ ions, while it will release H^+ ions when the [H^+] decreases.

Example of a weak acid and its strong base:

H_2CO_3 $\rightleftharpoons$ H^+ + HCO_3^- (weak acid) and $NaHCO_3$ $\rightleftharpoons$ Na^+ + HCO_3^- (strong base)

The buffer pair consists of H_2CO_3 + $NaHCO_3$ $\rightleftharpoons$ H^+ + Na^+ + $2HCO_3^-$

If a strong acid (many free H^+), e.g. aceto-acetic acid (HAc, one of the ketones present during a diabetic keto-acidosis or starvation) is added to the body fluid (intra- or extracellular), the law of mass action determines that if a component is added to the left of the equation, it must be removed. This happens by driving the reaction to the right to maintain equilibrium. Therefore, the buffering will be as follows:

H^+ + Na^+ + $2HCO_3^-$ + **H^+** + Ac^- (strong acid, completely dissociated) $\rightleftharpoons$ $2H_2CO_3$ + NaAc
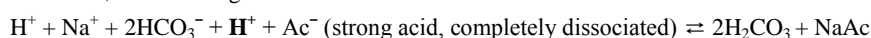
Now what happens to the $2H_2CO_3$ + NaAc? The carbonic acid (H_2CO_3) dissociates (catalysed by carbonic anhydrase):
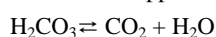
H_2CO_3 $\rightleftharpoons$ CO_2 + H_2O
Both CO_2 and **H^+** stimulate ventilation and is excreted by the lungs (therefore, CO_2 is called a volatile acid), while sodium aceto-acetate (NaAc) is excreted by the kidneys. Can you see that the H^+ has disappeared, and that the lungs and the kidneys

took part in the elimination?

You can test the urine for the presence of ketone bodies. Most organic acids are called fixed acids, since they are not excreted by the lungs. However, some acids, particularly the ketones are also excreted by the lungs. Therefore, these substances can be smelt in the breath of diabetic and starved patients.

Example of a weak base and its strong acid:

$NH_4OH \rightleftharpoons OH^- + NH_4^+$ (weak base) and $NH_4Cl \rightleftharpoons NH_4^+ + Cl^-$ (strong acid)
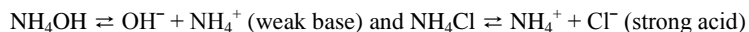
The buffer pair consists of $NH_4OH + NH_4Cl \rightleftharpoons OH^- + 2NH_4^+ + Cl^-$

If a strong base, e.g. NaOH is added, the following will happen:

$OH^- + 2NH_4^+ + Cl^- + Na^+ + \mathbf{OH^-} \rightleftharpoons NaCl + 2NH_4OH$
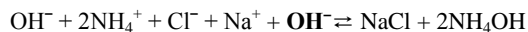
The ability of a buffer (remember, a buffer consists of a buffer pair) to maintain a particular pH is dependent on the *buffer capacity* of the buffer, its concentration, and its pKa. The pKa of a buffer refers to the pH at which the buffer is 50% dissociated ([weak acid] = [salt of weak acid]). A weak acid dissociates only in a relatively alkaline solution. Therefore, the weaker the acid, the higher the pKa. The ideal physiological buffer is one with a pKa as near as possible to the physiological pH, i.e. 7.4 extracellularly and about 6.8 intracellularly at 37°C. Why? Because a low pKa means that the anion of an acid does not accept H^+ at 'n higher pH of around 6.8 to 7.4. If the pKa of the acid is too high, it will release H^+ at higher pHs.

At physiological pH, lactic acid (pKa = 3,4) is completely dissociated. Therefore, lactate is a strong anion but a poor buffer. Carbonic acid (H_2CO_3) has a pKa of 6.1. Therefore, H_2CO_3 is a weak acid and HCO_3^- is a better buffer than lactate at a pH of 7.4.

The ability of a buffer to bind H^+ or OH^-, also depends on the buffer concentration as well as the number of binding sites in the buffer molecule. *Therefore, proteins (intracellular and extracellular) are excellent buffers, since their pKas are near physiological pH, they occur in high concentrations, and they have multiple binding sites.* Of these, haemoglobin (intracellular) and albumin (extracellular) are of the most important. The *histidine residues* in the proteins contain an α-imidazole group. The amino acids are poli-anions; they accept H^+ when an acid must be buffered and release H^+ when a base must be buffered. The pKa of the histidine residues is in the region of 7.4 (7.0 to 7.7).

The pH of the buffered solution depends on the ratio between the [salt] and the [acid], i.e. [salt]/[acid], e.g. the H_2CO_3-$NaHCO_3$ buffer pair:

pH = pKa + log[salt]/[acid]

What must the [salt]/[acid] ratio of the H_2CO_3-$NaHCO_3$ buffer pair be to maintain a pH at 7.4?

pKa of the H_2CO_3-$NaHCO_3$ buffer pair is 6.1.

∴ $7.4 = 6.1 + \log([HCO_3^-]/0.03 \times PCO_2)$

∴ $\log([HCO_3^-]/0.03 \times PCO_2) = 1.3$

∴ $([HCO_3^-]/0.03 \times PCO_2)$ = antilog of 1.3 = 20.

Therefore, in order to maintain a pH at 7.4, the $[HCO_3^-]/0.03 \times PCO_2 = 20/1$.

If the $[HCO_3^-]$ is normal (24 mM), 0.03 mM mm $Hg^{-1} \times PCO_2 = (1/20) \times 24 = 1.2$ mM

∴ $PCO_2 = 1.2$ mM/0.03 mM mm $Hg^{-1} = 40$ mm Hg

Look at the above example. Now you must read slowly: If the anion (salt) part of the buffer pair increases relative to the acid part (the ratio increases), the pH increases. Likewise, if the acid part of the buffer pair increases relative to the salt, the ratio decreases, and the pH will also decrease. Therefore, if you would inject only the salt part of the buffer pair, the patient becomes alkalotic, e.g. the administration of $NaHCO_3$ increases the pH. However, if you would hyperventilate the patient (decrease PCO_2), the ratio will also increase. Likewise, a decrease in $NaHCO_3$ (e.g. if HCO_3 binds strong acids) and an increase in PCO_2 cause a decrease in the [salt]/[acid] ratio and consequently a decrease in pH, i.e. an acidosis.

What about other buffer pairs? Let us look at the albumin (A) buffer pair:

Albumin is a weak acid. The buffer pair consists of HA (the weak acid) and its salt NaA. If you would remove albumin (A), the [NaA]/[A] ratio increases, with a consequent increase in pH. Therefore, a hypoalbuminaemia causes an alkalosis (*primary hypoalbuminaemic alkalosis*), while a hyperalbuminaemia (dehydration, e.g. cholera) contributes to an acidosis. A hypoalbuminaemia may therefore mask a metabolic acidosis. Hypoalbuminaemia is a very common condition.

The most important physiological buffers are summarized in Table 1. It is not necessary that you know the pKas, but you must know that abnormal levels of the buffers are usually accompanied by acid-base abnormalities. Abnormal buffer concentrations are usually accompanied by abnormalities of, and compensations for acid-base abnormalities.

Table 1 Buffer systems

Buffer	Main location	pKa (37°C)
Bicarbonate (H_2CO_3 / HCO_3^-)	Extracellular	6.1
Pi ($H_2PO_4^-$ - / HPO_4^{2-})	Intracellular, urine	6.8
Proteins (Histidine groups)	Intracellular (haemoglobin, myoglobin) Extracellular (albumin)	7.0 to 7.7

Pi = inorganic phosphate

"Anatomical" and chemical buffers

From the discussion about buffers, it should be clear that *the lungs* excrete volatile acids, while *the kidneys* excrete fixed (non-volatile) acids. What about the phosphate and protein buffers? Phosphate (Pi) occurs as $H_2PO_4^-$ and HPO_4^{2-} and is found abundantly in *bone* and intracellularly. The most important intracellular protein buffers are haemoglobin and myoglobin, while the main extracellular protein buffer is albumin. These buffers are the anions of weak acids. Therefore, high plasma concentrations of phosphate, haemoglobin (haemolysis), myolysis (myoglobin), and of albumin (cholera) will cause an acidosis. Where does albumin come from? It is manufactured in *the liver*. Therefore, a low plasma albumin (increased *gastrointestinal* loss, decreased protein absorption, decreased production by the liver, catabolism, and dilution) causes an alkalosis. What are the end-products of protein metabolism? It is ammonia (NH_3). What happens to the NH_3? It is removed by the liver through the H^+-consuming urea cycle. Furthermore, the liver is responsible for the clearance of several acidic metabolites (lactate, acetate, citrate, etc) and toxins.

It should be clear that the lungs, kidneys, liver, gastro-intestinal tract, blood, and bone form an integral part of the "buffering" systems. All these organs rely on an adequate supply of nutrients (substrate for organ function). Remember that all buffer ions of a buffer pair are associated with a cation (usually K^+, Na^+) or and anion (Cl^-). *Therefore, all vital organ dysfunction, as well as electrolyte disturbances are often associated with abnormal buffering function, and consequently an abnormal acid-base state – an alkalosis or acidosis. If you make the diagnosis of vital organ dysfunction, you must look for acid-base disturbances. If you detect an acid-base disturbance, you must look for vital organ dysfunction. If your patient is on any therapy that affects buffering systems, electrolytes, or vital organs ("anatomical" buffers), an acid-base derangement may be present.*

Buffer systems and temperature

Blood gas and acid base analyses are read at 37°C. That means that you do not adjust the temperature setting of the gas analyser. Therefore, if the patient's temperature is, say 34°C, you read the results as though the patient has a temperature of 37°C. This is called the *α-stat* approach. If you set the analyser to read the results at the patient's real temperature, we call it the *pH stat* approach. These two approaches have to do with the buffer characteristics of blood at different temperatures.

The "α" in α-stat refers to the α-imidazole group in the amino acid histidine in protein – intra- and extracellular. Haemoglobin and albumin have 34 and 16 histidine molecules, respectively. The α-imidazole group can bind or release hydrogen ions. It is a buffer with unique buffering characteristics at different temperatures. The uncharged α-imidazole side chain of histidine reversibly binds H^+. It has a pKa value that depends on the local protein environment, temperature, and composition of the solvent. Regarding the ionisable side chains, histidine differs from the other 19 amino acids; in proteins, histidine has a pKa of between 5.5 and 8.5 (usually between 7.0 and 7.7). The C α-NH2 groups next to the N-terminal are the major buffer groups. They contribute to hydrogen ion buffering at physiological pH in globins and other polypeptides and has a pKa of between 7.25 and 8.0 in human haemoglobin A.

The "stat" refers to the maintenance (keep static) of the acid-base state (pH) for that temperature. Theoretically, the α-stat strategy is physiologically better (the patient becomes *poikilothermic like a reptile*) since this system *maintains a pH, which is normal (neutral) for that temperature*.

The *pH-stat strategy* reads the results at the patient's actual temperature. This approach keeps the pH between 7.35 and 7.45 and the PCO_2 between 31 mm Hg and 39 mm Hg (35 mm Hg to 45 mm Hg at sea level). If the analyser is adjusted to the low temperature setting, the PCO_2 will appear low and the pH will be high. The anaesthetist may then interpret this result as a respiratory alkalosis and adjust the ventilation downwards to retain CO_2. This is what happens in hibernating mammals. There is only *one instance where the pH-stat approach is applied*, namely during procedures that may jeopardized brain perfusion, e.g. complex cardiovascular surgery. The patient is then cooled to about 18°C before circulation and ventilation is stopped during the critical period of brain ischaemia. We call this deep hypothermic arrest. During cooling, the pH-stat strategy is applied and CO_2 is added to the blood to keep CO_2 and pH within the *normal limits for 37°C* (*keep pH static*). This high $[CO_2]$s causes cerebral vasodilatation and ensures more homogenous cooling of the brain before circulatory arrest is instituted. If you are interested, ask the anaesthetist to explain this in more detail to you.

PO$_2$ AND SaO$_2$

The partial pressure of oxygen in arterial blood (PaO_2) gives an indication of the efficacy of the respiratory system to oxygenate pulmonary arterial blood. Pathology of *any part of the respiratory or cardiovascular system* can, depending on its severity, cause a low PaO_2 (hypoxic hypoxia) and hypercapnia. Abnormalities of PaO_2 and SaO_2 are discussed in Chapter 14.

The SO_2 is the degree (%) to which haemoglobin is saturated with oxygen. The normal arterial SO_2 is between 92% and 99%. It decreases (lower affinity for O_2) with a rightward shift of the oxygen-Hb dissociation curve (decreased pH, increased temperature), and increases (higher affinity) with a leftward shift of the curve (increased Hb, low temperature, foetal Hb).

Hb is about 90% saturated with O_2 at a PO_2 of about 60 mm Hg. Thereafter, the curve flattens and at about 100 mm Hg, SO_2 is nearly 100% saturated. The SO_2 reflected on the blood gas analyses is the percentage of oxygenated Hb (HbO_2) of the oxygenated plus deoxygenated Hb (HHb):
$$SO_2 = [HbO_2/(HbO_2 + HHb)] \times 100$$

Since SO_2 (%) reflect only two Hb species, it may differ from the percentage that HbO_2 occupy if other Hb compounds are present, namely carboxy Hb (HbCO) and methaemoglobin (MetHb). If these abnormal compounds are present in high concentrations, the gap between HbO_2 (%) and SO_2 increases, since
$$HbO_2 \, (\%) = [HbO_2/(HbO_2 + HHb + MetHb + HbCO)] \times 100.$$

When all the different Hb compounds are taken into account, it is called *co-oximetry*. Always look for these results on the blood gas analyses since it may reveille important causes of hypoxia, such as carbon monoxide toxicity and methaemoglobinaemia.

Remember that an abnormal PO_2 may have the following effects on acid-base homeostasis:
- A low PaO_2 (< 60 mm Hg) stimulates the peripheral chemoreceptors in the aortic arch and carotid body, which stimulates ventilation with a subsequent *decrease in the $PaCO_2$*. Therefore, any cause of a low PaO_2 in the spontaneously breathing patient is accompanied by a low $PaCO_2$ (hypocapnia). When the patient cannot maintain the increased ventilation (work of breathing) any longer, ventilation will fail and the $PaCO_2$ will increase (hypercapnia).
- If oxygen supply (see Chapter 14) decreases to the extent that aerobic metabolism fails, production of lactic acid increases. Therefore, *hypoxia* of any cause may led to a *lactic acidosis*.
- Chronic hypoxic hypoxia stimulates erythropoietin secretion. Therefore, if a patient is polycythaemic, look for a low PO_2.
- If a patient is chronically hypercapnic, the $[H^+]$ in the cerebrospinal fluid (CSF) is buffered (neutralized) by the HCO_3^-. The chemoreceptors in the brainstem will therefore no longer be stimulated and ventilation will decrease. These patients are dependent on stimulation of the peripheral chemoreceptors (hypoxic drive) to stimulate ventilation. That is why patients with chronic hypercapnia stop breathing when they receive additional oxygen (high PaO_2).

The diagnosis of respiratory failure is made when the PaO_2 is less than 60 mm Hg or the $PaCO_2$ is more than 50 mm Hg. If an **acute lung insult** decreases the PaO_2/FiO_2 ratio to < 300 mm Hg, the patient suffers from acute lung injury (ALI); a ratio of < 200 mm Hg is called an acute respiratory distress syndrome (ARDS).

PCO₂ AND BICARBONATE

PCO₂
The main cause of CO_2 is aerobic metabolism. It diffuses out of the cells into the interstitial fluid and from there to blood plasma.
You must understand the difference between the *partial pressure* of a gas in a fluid (the unit is mm Hg or kPa) and the *concentration* of the gas in the fluid (the unit is ml L^{-1} or ml dl^{-1}). What does PCO_2 mean? Gasses dissolve in fluids. If the fluid is in a closed container, some of the gas particles in the fluid escape to the space above the fluid, while some of the gas particles return to the fluid where they re-dissolve. At some stage, the number of particles leaving the fluid will equal the number returning to the fluid; equilibrium is reached. The partial pressure of the gas above the fluid at this equilibrium reflects the amount of gas dissolved in the fluid, and is called the partial pressure of the gas in the fluid. Therefore, a PCO_2 of, say 40 mm Hg in blood, means that if the blood is put into a container,

the partial pressure of CO_2 in the space above the blood at equilibrium will be 40 mm Hg.

If the fluid is cooled, the kinetic energy of the fluid and the gas particles decrease. Therefore, the gas particles are less prone to escape from the fluid (the *solubility of the gas increases*). Since less gas particles escape to the space above the fluid, the partial *pressure of the gas will be lower but the concentration will increase*.

This phenomenon has the following very important implications. This you must know. Firstly, when you put a blood sample into a blood gas analyser, the analyser measures the *partial pressure* of the gasses (CO_2 and O_2). If you would tell the analyser that the temperature of the blood is, say 35°C (hypothermic), it looks in its algorithm what the partial pressure of the gas at this temperature is. As explained above, the *partial pressure will be lower at hypothermia*.

Secondly, the analyser measures the partial pressures of CO_2 and O_2 with their respective electrodes. The CO_2 in blood in the analyser equilibrates with the fluid in the electrode. The CO_2 in the electrode fluid associates with water in the following reaction:

$$CO_2 + H_2O \rightleftarrows H_2CO_3 \rightleftarrows H^+ + HCO_3^-$$
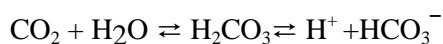
The CO_2 electrode measures the $[H^+]$ in this reaction. Since the $[H^+]$ in the electrode is proportional to CO_2, the gas analysis reports PCO_2. At low temperatures, less CO_2 molecules escape from the blood sample, and the dissociation of carbonic acid (H_2CO_3) to form H^+ decreases. Therefore, hypothermia causes a decrease in PCO_2. Therefore, a low PCO_2 has an alkalizing effect:

According to the law of mass action,
pH = pKa + log($[HCO_3^-]/[CO_2]$)
where pKa is the dissociation constant of H_2CO_3 = 6.1 and $[CO_2]$ = $PCO_2 \times$ solubility of CO_2.

Therefore,
pH = pKa + log($[HCO_3^-]$)/($PCO_2 \times$ solubility)
$\quad$ = 6,1 + log($[HCO_3^-]$)/(0,03 mM mm $Hg^{-1} \times PCO_2$) (This is the *Henderson-Hasselbalch equation*.)
If $[HCO_3^-]$ = 24 mM and PCO_2 = 40 mm Hg,
pH = 6.1 + log[24/(0.03 × 40)] = 6.1 + log(24/1.2) = 6.1 + log20 = 6.1 + 1.3 = 7.4

Except during cooling for deep hypothermic arrest, blood gas and acid-base analysers are always set to report results at 37°C.

A primary increase in $PaCO_2$ (hypercapnia) is called a *respiratory acidosis*. This may be due to:
- An *increased production of CO_2* without an accompanying increase in pulmonary ventilation. This is often the case in patients that are being ventilated:
  - Administration of HCO_3^-
  - Buffering of acids (lactate, ketones) by HCO_3^-
  - Malignant hyperthermia
- Normal production of CO_2 and *hypoventilation* (see Chapter 13).

A *respiratory acidosis is compensated* by an increased $[HCO_3^-]$. The response to an acute hypercapnia is due to the increased production of HCO_3^- – especially by the red blood cells ($H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$). *Sustained (chronic) hypercapnia* causes an increased reabsorption of HCO_3^- by the kidney, which increases the $[HCO_3^-]$ further

A primary decrease in $PaCO_2$ (hypocapnia) is called *respiratory alkalosis*. Hypocapnia follows when the pulmonary ventilation is relatively larger than the production of CO_2 (hyperventilation). In spontaneously ventilating patients, hyperventilation is caused by *central* stimulation (emotional, pain), or *peripheral* (carotid body and aortic chemoreceptors) by a *lowPaO_2* (lung pathology), or a *metabolic acidosis* (lactate, ketones, aspirin toxicity, etc.). In mechanical ventilated patients, hypocapnia is

caused by inappropriate ventilator settings.

In the *acute phase*, a respiratory alkalosis is *compensated* by a decrease in $[HCO_3^-]$ production by mainly the red blood cells ($H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$). *Sustained (chronic) hypocapnia* causes a decreased reabsorption of HCO_3^- and decreased secretion of H^+ by the kidneys (metabolic acidosis). After several days the metabolic acidosis may return the pH to about normal levels; the $[HCO_3^-]$ may be as low as 12 mM.

Bicarbonate (HCO_3^-)
HCO_3^- is produced in all body fluids from CO_2 by the following carbonic anhydrase catalysed reaction:

$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$

Look at the Henderson-Hasselbalch equation: $pH = pKa + \log\{[HCO_3^-])/(PCO_2 \times solubility)\}$

The normal $[HCO_3^-]$ is about 24 mM. When CO_2 production increases, PCO_2 increases. CO2 reacts with H_2O to form H_2CO_3. The latter dissociates to form water and bicarbonate. The acid-base analyser measures pH and CO_2 and calculates $[HCO_3^-]$. This $[HCO_3^-]$ is the real $[HCO_3^-]$ in the blood and is called the *actual bicarbonate*. It is abbreviated as *HCO_3 (act) or ABC*. Therefore, *a primary (that means, it was first) increased PCO_2 (respiratory acidosis) is always accompanied by an increased ABC*. The primary respiratory acidosis is followed (compensated) by an increased $[HCO_3^-]$ and is called a *compensated respiratory acidosis*. The compensation tends to rectify the pH.

A primary decreased [HCO_3] is called a metabolic acidosis. A metabolic acidosis (increased $[H^+]$ stimulates ventilation with a decreased $PaCO_2$. Thus a metabolic acidosis is *compensated by a low PaCO_2*. This compensation is rarely complete. *The mechanisms* and causes of a metabolic acidosis are as follows:
- *Addition of H^+*
  o Increased production: ketoacidosis, lactic acidosis, toxins (ethanol, methanol, salicylate, ethylene glycol)
  o Decreased renal excretion: renal failure, obstructive uropathy, renal tubular acidosis, mineralocorticoid deficiency
- *Loss of HCO_3^-*
  o Extrarenal losses: acute diarrhoea, pancreatic fistulae, uretero-enterostomy
  o Renal losses: renal tubular acidosis

During *diarrhoea*, fluid containing high $[HCO_3^-]$ and $[K^+]$ is excreted. The low $[HCO_3^-]$ in the glomerular filtrate leads to an increased reabsorption of Cl^-. Therefore, diarrhoea is complicated by a *hypokalaemic hyperchloraemic metabolic acidosis with a normal anion gap* (see later)

Obstruction of urine excretion (*obstructive uropathy*), e.g. due to an enlarged prostate, back-pressure decreases the glomerular filtration rate. This causes a decreased secretion of H^+, K^+, and decreased reabsorption of HCO_3^-. This leads to a hyperkalaemic metabolic acidosis.

If the urinary bladder is removed, the ureters are implanted into the ileum (*uretero-enterostomy*). The urine drains into the gut. The Cl^- and NH_4^+ in the urine are reabsorbed in exchange for HCO_3^- and K^+ respectively. This is complicated by a hyperchloraemic hypokalaemic normal anion gap (see later) metabolic acidosis.

A primary increased [HCO_3^-] or primary decreased [H^+] is called a metabolic alkalosis. There is decreased stimulation of ventilation, which leads to CO_2 retention. Therefore, a metabolic alkalosis is *compensated by an increased PaCO_2*. *The mechanisms* and causes of a metabolic alkalosis are as follows:

- *Administration of alkali:*
  - Oral intake of acid-neutralizing medication, including HCO_3^-
  - Intravenous administration of $NaHCO_3$
- *Increased production of HCO_3^-:*
  - Clearance of organic acids during resuscitation, e.g. of lactate (due to hypoxia) and citrate (in banked blood)
  - Oral intake of the salts of organic acids in anti-indigestion preparations. These salts are metabolised to HCO_3^- ($MgCO_3$, acetate, citrate, tartrate, etc.)
- *Increased loss of H^+ or decreased loss of HCO_3^-*
  - *H^+-Na^+ exchange in the kidney.* This is caused by hypokalaemia and all conditions that increase the secretion of aldosterone.
  - *Gastric outlet obstruction*, e.g. pyloric stenosis. HCl secretion by the parietal cells causes an equivalent production of $NaHCO_3$. Normally this is followed by duodenal secretion of $NaHCO_3$. If vomiting occurs with free communication between the duodenum and the stomach, the HCO_3^- is neutralized by the H^+. The acid-base disturbances are therefore mainly due to loss of volume and electrolytes (Na^+, K^+, and Cl^-). The alkalosis and loss of Na^+ and K^+ decreases the secretion of H^+, while the urinary Cl^- causes increased loss of filtered HCO_3^-.
  - *Hypochloraemia*, e.g. due to diuretics and cystic fibrosis (see later)

How does one differentiate whether an increased [HCO_3^-] is due to a primary hypercapnia (respiratory acidosis, $PaCO_2 > 45$ mm Hg) or to a metabolic alkalosis?
- Remember the Henderson-Hasselbalch equation: *if the PCO_2 increases*, log{([HCO_3^-])/($PCO_2\times$ solubility)} decreases, with a decrease in pH. However, the increased CO_2 will bind to H_2O to form H_2CO_3, which dissociates to H^+ + HCO_3^-. Therefore, if a low pH (<7.4) is accompanied by a high PCO_2 with an increased [HCO_3^-], the primary abnormality is an increased PCO_2, i.e. a *respiratory acidosis*.
- However, that does not exclude the co-existence of a metabolic alkalosis, which may also increase [HCO_3^-]. Now, the acid-base analyser calculates what the [HCO_3^-] would be if the PCO_2 was normal (40 mm Hg) at 37°C (it standardizes the extracellular PCO_2 at 40 mm Hg) but also take into account the effect the most important buffer in the extracellular fluid, namely haemoglobin. Since equilibrium exists between the interstitial and intravascular components of the extracellular fluid, the plasma acid-base state reflects the situation in the interstitium.
- However, the main buffer in blood is haemoglobin is limited to blood and does not distribute to the interstitium, but influences the acid-base state of the interstitium. Therefore, the blood gas analyser "dilutes" the haemoglobin in the whole extracellular compartment, which is about 3 times larger than the plasma volume. Most blood gas analysers use a haemoglobin concentration of about a 1/3 of the normal haemoglobin of about 15 g dl^{-1} = 5 g dl^{-1}. *This entity is the standard or extracellular bicarbonate ($HCO_3(S)$, SBC or BC_{ecf}) and is independent of PCO_2.*

Remember that haemoglobin has an important buffer in blood due to its high buffer capacity. It owes its high buffer capacity to high concentration in blood; many –COOH and –NH_3 groups; and most importantly the 36 histidine residues. Histidine contains an imidazole group, which dissociates over a pH range of 7.0 to 7.7. This range covers the whole physiological pH range. Oxygenated haemoglobin is a stronger acid than deoxygenated haemoglobin. Some analysers use the actual haemoglobin saturation, while others use fully saturated haemoglobin in their algorithms. SBC is calculated using the Van Slyke formula (it is not necessary that you memorize the equation, but note the importance of haemoglobin):

$$SBC = [ABC - (0.34 \times Hb + 7.7)(pH - 7.4)] \times (1 - 0.0034 \times Hb),$$

where ABC is the actual HCO_3^- in mM, pH is at 37°C, and Hb in g dl^{-1}.[38]

Remember, that haemoglobin and albumin buffers do not distribute into the interstitial fluid compartment (about 110 ml kg^{-1}) since they are limited to the plasma (about 40 ml kg^{-1}) and red cells (about 30 ml kg^{-1}). If one would allow all the interstitial and intravascular fluid to mix in one compartment, the haemoglobin concentration would not be distributed in the blood volume (30 + 40 ml kg^{-1}), but in the blood volume + the interstitial volume (110 ml kg^{-1}) = about 180 ml kg^{-1} = nearly 3 × blood volume. Therefore, the haemoglobin concentration would be about 1/3 of the blood haemoglobin concentration. If the blood gas analyser reports the buffer status of extracellular fluid, it uses the above Van Slyke calculation (or some modification thereof) but will adjust the haemoglobin to its concentration to about 1/3 of the

measured value or use a default concentration of the normal haemoglobin of about 15 g dl^{-1}, i.e. 5 g dl^{-1}. Therefore, the above formula can be simplified to the following, which is mostly used by blood gas analysers:

$$SBC = 0.93(ABC) + 14.84(pH - 7.4)$$

- If the ABC is high (> 24.4 mM), while the SBC is about normal, you know that the increased HCO_3 is mainly due to the increased PCO_2. The pH will be low (<7.35). This is a *uncompensated respiratory acidosis*. However, if both the ABC and SBC are increased (ABC > SBC), there is an co-existing metabolic increase in [HCO_3^-], i.e. a co-existing metabolic alkalosis. The pH is usually in the low normal range of 7.35 to 7.40. This is called a *compensated respiratory acidosis*.
- If the PCO_2 is increased, ABC is in the normal range, and the SBC is decreased (< 24 mM), it points to an underlying metabolic decreased [HCO_3^-], i.e. an underlying metabolic acidosis, which co-exists with the respiratory acidosis. In this case, the pH is usually clearly indicative of an acidosis, namely << 7.35. This is a *mixed respiratory and metabolic acidosis*.

How does one differentiate whether a decreased [HCO_3^-] is due to a primary hypocapnia (respiratory alkalosis (PaCO$_2$< 35 mm Hg)) or to a metabolic acidosis?
- Again, look at the Henderson-Hasselbalch equation: *if thePCO$_2$ decreases*, log([HCO_3^-])/(PCO_2× solubility) increases, with an increase in pH. Therefore, if a high pH (> 7.40) is accompanied by a low PCO_2, the primary abnormality is a decreased PCO_2, i.e. a *respiratory alkalosis*. However, that does not exclude the co-existence of a metabolic acidosis. Now, the acid-base analyser calculates the SBC. If ABC is low (< 24 mM), while the SBC is about normal, you know that the decreased HCO_3 is mainly due a decreased PCO_2. The pH will be > 7.45 and is called an *uncompensated respiratory alkalosis*.
- However, if both the ABC and SBC are decreased, there is an co-existing decrease in [HCO_3^-], i.e. a co-existing metabolic acidosis. The pH will be between 7.40 to 7.45 and is called a *compensated respiratory alkalosis*.
- If PCO_2 is decreased, ABC in the normal range, and SBC increased (> 24 mM), it points to an underlying increased [HCO_3^-], i.e. a co-existing metabolic alkalosis. In this case, the pH will be very high, namely >> 7.45. This is a *mixed respiratory and metabolic alkalosis*.

How does one differentiate whether an increased [HCO_3^-] is due to a primary increased [HCO_3^-] (metabolic alkalosis, [HCO_3] > 24 mM) or due to a respiratory acidosis (increased PaCO$_2$)?
- According to the Henderson-Hasselbalch equation, the pH increases if *[HCO_3^-] increases*. Therefore, if a high pH (> 7.45) is accompanied by a high [HCO_3^-] and a normal PCO_2, the primary abnormality is an increased [HCO_3^-], i.e. an *uncompensated metabolic alkalosis*.
- However, that does not exclude a co-existing respiratory acidosis (increased PCO_2), which may also increase the [HCO_3^-]. The acid-base analyser calculates the SBC. If both PCO_2 and ABC are increased, while SBC > ABC but > N, you know that the ABC is mainly due to a primary increased [HCO_3^-]. The pH will be on the high side (between 7.40 and 7.45). This is a *compensated metabolic alkalosis*.
- However, if the PCO_2 is decreased, ABC in the normal range, while the SBC is normal, there is an co-existing decreased PCO_2, i.e. a co-existing respiratory alkalosis. The pH may be very high, i.e. >> 7.45. This is called a *mixed metabolic and respiratory alkalosis*.

How does one differentiate if a decreased [HCO_3^-] is due to a primary decreased [HCO_3^-] (metabolic acidosis, [HCO_3] < 24 mM]) or due to a respiratory alkalosis (PCO$_2$< 35 mm Hg)?
- Look at the Henderson-Hasselbalch equation: *if the[HCO_3^-]decreases*, log([HCO_3^-])/(PCO_2× solubility) decreases, with a decrease in pH. Therefore, if a low pH (< 7.35) is accompanied by a low [HCO_3^-] but a normal PCO_2, the primary abnormality is a decreased [HCO_3^-] , i.e. an *uncompensated metabolic acidosis*.
- The pH will be < 7.35. That does however not rule out a co-existing respiratory alkalosis (low PCO_2). The SBC is calculated. If both PCO_2 and ABC are decreased, while the ABC <SBC but SBC < normal, you know that the decreased [HCO_3^-] is due to both a primary decreased [HCO_3^-] as well as a low PCO_2. The pH will be between 7.35 and 7.40 and is called a *compensated metabolic acidosis*.

- However, if the PCO_2 and ABC are increased, while SBC is normal in the normal range, there is an co-existing increase in PCO_2, i.e. a co-existing respiratory acidosis. The pH will be $\ll 7.35$ and is called a *mixed metabolic and respiratory acidosis*.

In this part, the role of bicarbonate was discussed. It is important that the student understands the relationship between PCO_2 and $[HCO_3^-]$. Similar processes occur with other buffer pairs. However, bicarbonate is very important due to its concentration and the ease to monitor it.

THE BASE EXCESS (BE)

Another way to quantify an acid-base abnormality is the BE. This entity gives an indication of how much the ABC and the SBC deviate from the normal level of 24.4 mM.

The actual BE (ABE)
The actual BE [ABE, BE blood, BE(B)] is the difference between the ABC and the normal value of 24.4 mM: ABE = ABC − 24,4 mM.

The standard BE (SBE)
This is the equivalent of the SBC. It is the BE of extracellular fluid (interstitium, plasma) and refers to the amount (mmol) of strong base that must be added or taken away (strong acid added) to return the pH to 7.40 at a temperature of 37°C, a PCO_2 of 40 mm Hg (therefore, SBE is independent of PCO_2) and normal mean extracellular haemoglobin concentration of about 50 g l^{-1}. The normal value is 0 ± 2 mM.

Blood gas analysers use different algorithms to calculate SBE. If the BE is low (negative), it means that there is a shortage of HCO^-, and it is called a *base deficit* (BD). Therefore, there is an ABE and a SBE. An example of an equation to calculate SBE is:

$$SBE = 0.93(ABC) + 14.84(pH − 7.4) − 24.4, \text{ or more difficult,}$$
$$SBE = [ABC − 24.4 + (0.34 \times Hb + 7.7)(pH − 7.4)] \times (1 − 0.0034 \times Hb).$$

Why are the BE and BD useful entities?
The BE and BD quantifies the extent to which HCO_3^- has buffered acids. In other words, the lower the BE (the higher the BD), the more unmeasured strong acids (consisting of H^+ and strong anions) have been buffered. These anions are called unmeasured strong anions (UA). Therefore, BE and BD give an indication of the main extracellular buffer, namely HCO_3^-. If the pH is low and the BE is low, there is too little HCO_3^- to neutralise strong acids (metabolic acidosis); if the pH is high and the BE is also high, there is too much HCO_3^- (metabolic alkalosis).

The SBD is used to calculate the dose of $NaHCO_3$ needed to treat a *metabolic acidosis*. The HCO_3^- is intended to neutralize (buffer) acid in the extracellular space. Remember, total body water = 0.6 L kg^{-1} lean body mass; intracellular = 0.4 L kg^{-1} and extracellular = 0.2 L kg^{-1} (60%, 40% and 20%* respectively). Therefore, the dose (mmol) of $NaHCO_3$ to correct the SBD of extracellular fluid* = SBD $\times$ lean body mass in kg $\times$ 0.2 L kg^{-1}*.

Example:
Body mass = 80 kg; SBE = -15 mM (SBD = 15 mM) Remember mM = millimolar = mmol L^{-1}. Dose of $NaHCO_3$ = 15 mmol $L^{-1} \times$ 80 kg $\times$ 0.2 L kg^{-1} = 240 mmol. A $NaHCO_3$ 8.4% injection contains 1 mmol of HCO_3^- per ml. Usually, only half this dose is administered, the acid-base state reassessed and more $NaHCO_3$ is administered if necessary. Since $NaHCO_3$ precipitates calcium to form $CaCO_3$, it must be administered in a *calcium-free infusion*, e.g. NaCl 0.9%. $NaHCO_3$ 8.4% injection should not be administered into *lines containing catecholamines (adrenaline, noradrenaline, dobutamine)* since it inactivates these compounds.

When is administration of NaHCO₃ indicated? There is no clear answer since it is uncertain whether it is the acidosis (H^+) *per se* that is detrimental, or the strong anions of the strong acids, or the pathology causing the increase in strong acids, e.g. lactate and keto-acids. You are in good company if you do

not administer NaHCO$_3$ at all. You may administer NaHCO$_3$ for a metabolic acidosis if the pH is < 7.1 (no literature supports this figure). If the acidosis is caused by free haemoglobin (haemolysis), myoglobin (rhabdomyolysis), or acidic toxins (e.g. glycols), the administration of NaHCO$_3$ is probably indicated to facilitate the renal excretion of the substances. A severe acidosis may also occur in the presence of renal and hepatic failure when acids cannot be metabolised or excreted. *The most important modality of the treatment of a metabolic acidosis is treatment of the cause, which often includes fluid resuscitation or organ replacement therapy, e.g. dialysis.*

Remember that in the presence of a metabolic acidosis due to the presence of organic acids, the HCO$_3^-$ binds (buffers) the H$^+$ to form CO$_2$ and H$_2$O. Therefore, you must be on the lookout for an *increased PCO$_2$*. If the patient is breathing spontaneously, the increasing PCO$_2$ stimulates ventilation. Therefore, the PCO$_2$ will be normal and pH low (uncompensated metabolic acidosis). However, the high [H$^+$] (low pH) also stimulates ventilation and the PCO$_2$ decreases further, which will now increase the pH towards normal (compensated metabolic acidosis). However, in the ventilated patient, these ventilatory compensations must be done by the anaesthetist by changing the ventilator settings to avoid an increased PCO$_2$ (respiratory acidosis). Another problem with the administration of NaHCO$_3$ 8.4% injection, is the high [Na$^+$]. It contains one mmol Na$^+$ per ml and may therefore *cause a hypernatraemia*, *hyperosmolality,* and *fluid overload.*
Therefore, regarding the administration of NaHCO$_3$:

- It is used for the treatment of a *metabolic acidosis*.
- The most important treatment of a metabolic acidosis is treatment of *the cause*.
- The pH threshold is about *< 7.1* (controversial).
- Administer it with a calcium-free infusion, e.g. NaCl 0.9%.
- Do not administer it into a catecholamine-containing line.
- Be on the lookout for an increased PCO$_2$ and increase the ventilation.
- Look for a hypernatraemia, hyperosmolality, and fluid overload.

Abnormal PCO$_2$, ABC, SBC, ABE, and SBE are summarized in Table 2. Mixed acid-base derangements occur commonly (Table 3). *You must not memorise this table, but to work it out.*

Table 2 Bicarbonate and acid-base abnormalities

Abnormality	pH	PCO$_2$	ABC	SBC	ABE	SBE
Respiratory acidosis						
Uncompensated respiratory acidosis	< 7.35	↑	↑	N	↑	N
Compensated respiratory acidosis	7.35 – 7.40	↑	↑↑	↑	↑↑	↑
Mixed respiratory and metabolic acidosis	<< 7.35	↑	±N	↓	±N	↓
Respiratory alkalosis						
Uncompensated respiratory alkalosis	> 7.45	↓	↓	N	↓	N
Compensated respiratory alkalosis	7.40 – 7.45	↓	↓↓	↓	↓↓	↓
Mixed respiratory and metabolic alkalosis	>> 7.45	↓	±N	↑	±N	↑
Metabolic alkalosis						
Uncompensated metabolic alkalosis	> 7.45	N↑	↑	↑	↑	↑
Compensated metabolic alkalosis	7.40 – 7.45	↑	↑↑	↑	↑↑	↑
Mixed respiratory and metabolic alkalosis	>> 7.45	↓	±N	↑	±N	↑
Metabolic acidosis						
Uncompensated metabolic acidosis	< 7.35	N↓	↓	↓	↓	↓
Compensated metabolic acidosis	7.35 – 7.40	↓	↓↓	↓	↓↓	↓
Mixed respiratory and metabolic acidosis	<< 7.35	↑	±N	↓	±N	↓

Table 3 Mixed acid base abnormalities

Abnormality	pH	PCO$_2$	ABC	Examples
MAc + RAc	↓↓	↑	↓	Cardiac arrest Respiratory failure Cyanotic heart lesions
MAlk + RAlk	↑↑	↓	↑	Congestive cardiac failure (secondary hyperaldosteronism, diuretics, hyperventilate due to pulmonary oedema) Gastric outlet obstruction (MAlk) + hyperventilation due to pain (RAlk) Hepatic failure (increased NH$_3$ stimulates ventilation, decreases acid-forming urea synthesis and increases reabsorption of HCO$_3$)
MAlk + RAc	N	↑↑	↑↑	Diuretics + chronic obstructive lung disease Vomiting + chronic obstructive lung disease
MAc + RAlk	N	↓	↑	Renal failure (MAc → RAlk) Congestive cardiac failure (MAc → RAlk) Salicylate overdose stimulates the respiratory centre (RAlk) and interferes with intermediary metabolism (MAc) In septic shock Gram-negative bacteraemia stimulates the respiratory centre (RAlk) + tissue hypoperfusion (shock) results in a lactic acidosis (MAc).
MAc + MAlk	N	N	N	Diuretic therapy (MAlk) + ketoacidosis (MAc) Vomiting (MAlk) + ketoacidosis (MAc) Vomiting (MAlk) + renal failure (MAc) Vomiting (MAlk) + dehydration (lactic acidosis)

M, metabolic; R, respiratory; Alk, alkalosis; Ac, acidosis

The SBE adjusted for the main extracellular cation (Na$^+$), anion (Cl$^-$), and protein anion (albumin).
The effect of unmeasured acids (anions) is called the BE adjusted for unmeasured anions (UA), or BE(UA). This concept also introduces another dimension to the evaluation of acid-base status, namely the influence of strong electrolytes (always dissociated) and the main unmeasured weak ions.
Recall the following:
- Albumin is a weak acid (anion). A low albumin level causes an increase in the pH and may therefore mask the presence of metabolic acidosis caused by unmeasured strong anions (acids).
- The weak acid and its strong base:

  $H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$ (weak acid)

  $NaHCO_3 \rightleftharpoons Na^+ + HCO_3^-$ (strong base)

  The buffer pair consists of $H_2CO_3 + NaHCO_3 \rightleftharpoons H^+ + Na^+ + 2HCO_3^-$
- Na$^+$ retention or increased [Na$^+$] is associated with a metabolic alkalosis.
- The weak base and its strong acid:

  $NH_4OH \rightleftharpoons OH^- + NH_4^+$ (weak base)

  $NH_4Cl \rightleftharpoons NH_4^+ + Cl^-$ (strong acid)

  The buffer pair consists of $NH_4OH + NH_4Cl \rightleftharpoons OH^- + 2NH_4^+ + Cl^-$
- An increased [Cl$^-$] is associated with a metabolic acidosis and a low [Cl$^-$] with a metabolic alkalosis. This is due to the movement of HCO$_3^-$ and Cl$^-$ in opposite directions over erythrocyte and renal tubular cell membranes. *Therefore, a primary change in [Cl$^-$] is followed by an opposite change in [HCO$_3^-$]*. Therefore, resuscitation with NaCl 0.9% or colloids dissolved in NaCl 0.9% have the side-effect of a hyperchloraemic acidosis.
- Any metabolic alkalosis that results from a primary loss of Cl$^-$ improves when treated with Cl$^-$ (NaCl or KCl), and is called a *chloride- (or saline-) responsive metabolic alkalosis*. These patients are *usually hypovolaemic and have a low urine [Cl$^-$] (< 10 mM)*. This type of alkalosis is caused by loss of Cl$^-$ from the gastrointestinal tract, skin, or kidney:
  - *From the kidney,* e.g. loop diuretics such as furosemide, Bartter syndrome, low [K$^+$], low [Mg^{2+}]. The urine [Cl$^-$] is high.
  - *From the gastrointestinal tract,* e.g. gastric outlet obstruction such as pyloric stenosis, vomiting, gastric suctioning. The urine [Cl$^-$] is low.
  - *In sweat* in patients with cystic fibrosis. The urine [Cl$^-$] is low.
- Any metabolic alkalosis that results from an increased Na$^+$ retention or increased [Na$^+$] is called a *chloride non-responsive metabolic alkalosis*. This is caused by conditions that are accompanied by increased levels of aldosterone (primary or secondary). Remember, aldosterone fine-tunes sodium levels by increasing Na$^+$ reabsorption and K$^+$ and H$^+$ secretion in the distal renal tubuli. These patients are usually *normo- or hypervolaemic and have a urine [Cl$^-$] > 20 mM*.

The formula for BE(UA) takes into account the acid-base effects of the concentrations of the main strong cation (Na^+), strong anion (Cl^-), and albumin:

$$SBE = (\text{effect of } Na^+ \text{ and } Cl^-) + (\text{albumin effect}) + BE(UA)$$
$$\therefore BE(UA) = SBE - (\text{effect of } Na^+ \text{ and } Cl^-) - (\text{albumin effect})$$

At a pH of 7.4 the effect of albumin, Na^+, and Cl^- on the BE are as follows:
- Albumin effect = 0.25(albumin – 42 g L^{-1}). If the albumin is normal, i.e. 42 g L^{-1}, the albumin effect = 0.
- Effect of Na^+ and Cl^- = [Na^+] – [Cl^-] – 38. If the [Na^+] and [Cl^-] are normal, i.e. 140 mM and 102 mM, respectively, the effect of Na^+ and Cl^- = 38 – 38 = 0 mM.
- Therefore,

$$\textbf{BE(UA)} = \textbf{SBE} - \textbf{[Na}^+\textbf{]} + \textbf{[Cl}^-\textbf{]} + \textbf{38} - \textbf{0.25(42} - \textbf{albumin g L}^{-1}\textbf{)}$$

It can be seen that if the albumin term is eliminated, BE increases (more positive, i.e. less acidotic). However, if the effect of a low albumin is taken into account, the BE will decrease (more negative) and an acidosis is revealed.

The formula for BE(UA) says that in the presence of an *metabolic acidosis*, the presence of a high [Cl^-] (common) and/or a high [albumin] (less common) must be excluded. Therefore, if BE(UA) and SBE are low (negative), while *[Na^+], [Cl^-], and [albumin] are all normal*, the acidosis is due to the presence of other *unmeasured* strong anions such as SO_4^{2-}, ketones, lactate, and acetate and weak anions such as Pi, albumin, and poligeline (in Haemaccel and Gelofucin). If the BE(UA) is normal, and SBE is low (negative) or normal, a *high [Cl^-] or a high [albumin]* is causing the metabolic acidosis.

The reverse is true for a *metabolic alkalosis*: When the *BE(UA) is high (positive)*, SBE is close to zero, while the [Cl^-] and [albumin] are normal, the alkalosis is caused by increased cations (mainly Na^+ ions, since they are present in large numbers, as opposed to K^+, Ca^{2+}, and Mg^{2+}). If the patient is alkalotic, *BE(UA) is normal, SBE is high*, and [Na^+] is normal, the alkalosis is caused by a low *[Cl^-]*. If the patient is alkalotic, *BE(UA) is high, SBE close to zero*, and both [Na^+] and [Cl^-] are normal, the alkalosis is caused by a *low [albumin]*.

The causes of *some* of the BE(UA) abnormalities are summarized in Table 4. You must play around with the formula and see how different combinations of abnormalities may change the BE(UA). I must admit that this may be a confusing exercise, but hopefully will encourage you to look deeper into acid-base abnormalities; to find abnormalities, even if the "blood gas analysis" appears to be normal at first sight. Something you must have noticed, is the relationship between [Na^+] and [Cl^-]. This issue will be discussed later on under *strong ion difference. So, prepare yourself for some more confusion!*

Table 4 BE(UA) and metabolic acid-base abnormalities

Diagnosis	BE(UA)	SBE	[Na^+]	[Cl^-]	Albumin	Origin
Metabolic acidosis	↓	↓	N	N	N	↑UA
	N	↓	N	↑	N	↑[Cl^-]→↓[HCO_3^-]
	↓	N	N	N	↑	↑[Albumin]
Metabolic alkalosis	↑	N	↑	N	N	↑[Na^+]
	N	↑	N	↓	N	↓[Cl^-]→↑[HCO_3^-]
	↑	N	N	N	↓	↓[Albumin]
	N	↑	N	N	N	↑[HCO_3^-]

Example:
A patient from the intensive care unit presents with a SBE of –1.0 mM (still within normal limits). Closer inspection of the special investigations reveals an albumin of 18 g L^{-1} (hypoalbuminaemia is very common in ICU patients). The [Na^+] and [Cl^-] are within normal limits. Therefore,

$$BE(UA) = SBE + Na^+ - Cl^- - 38 + 0.25(\text{albumin} - 42 \text{ g } L^{-1})$$
$$BE(UA) = -1 + 140 - 102 - 38 + 0.25(18 - 42) = -1 + 38 - 38 - 6 = -7 \text{ mEq}$$

This patient clearly has a metabolic acidosis, which was obscured by the associated low albumin, which is a common cause of a metabolic alkalosis. If the acid-base analyser measures the lactate and glucose levels and you have an idea what the albumin is, you can come very close to the cause of the acidosis, e.g. ketoacidosis or exogenous acids (toxins). *You should again see how important it is to depart from the notion of "blood-gas analysis", and look at all the other components of the analysis and their origin.* Can you recall the causes of a high [lactate]?

THE PLASMA ANION GAP (AG)

Thus far you might have noticed an emerging concept, namely the relationship between measured positive (cations) and negative charges (anions), and of course, that of electrical neutrality. An entity that quantifies this principle is the *gap (difference) between the main cations and the main anions,*

which is called the anion gap (AG). The AG consists of other unmeasured anions, especially protein and lactate:

$$AG = (Na^+ + K^+) - (Cl^- + ABC)$$

The normal AG depends on the method of measurement of the different components and is usually indicated on the analysis results. Some analysers have a normal value of 6 ± 3 mEq L^{-1}, others (in our hospital) of 12 ± 4 mEq L^{-1} (Figure 1). Please note, that although the unit reported is mostly mM, we work with *charges* and the unit is strictly speaking mEq L^{-1}.

You must, as with the previous indicators of the acid-base state, interpret it with the patients anatomical pathology, pathophysiology, and pharmacotherapy in mind. Furthermore, as with the other indicators, a normal AG does not mean that the acid-state is normal; just as a normal body mass is an indication of the absence of serious pathology.

Limitations of the AG:
- The classification of acidoses according to the AG is very artificial since several mechanisms of the acidoses occur simultaneously, e.g. an intoxicated trauma patient (hypovolaemia, ischaemia, toxins) who is receiving NaCl-rich fluid (Voluven, saline) and β agonists. *This is no exaggeration; this is the typical patient on the emergency operation list.*
- The $[HCO_3^-]$ decreases independently during hyperventilation.
- A high Pi is not measured.
- It does not differentiate between changes in albumin and Pi.
- A low albumin obscures a high AG. Therefore, the AG is corrected in the same way as BE, namely AG corrected for albumin = AG + 0.25(42 - albumin g/l). Example: The patient is acidotic with an AG of 14 mEq L^{-1}, which is normal. The albumin is 14 g L^{-1}. The corrected AG = 12 + 0.25(42 - 14) = 12 + 0.25(28) = 12 + 7 = 19 mEq L^{-1}. Can you see that the high AG acidosis is revealed?
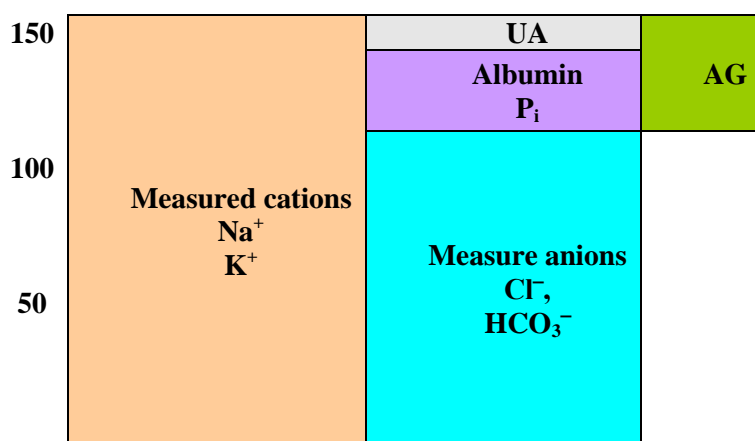
Figure 1 The anion gap

Causes of a high AG acidosis:
This type of acidosis is often caused by UAs. These substances are buffered by HCO_3^-, which is changed to CO_2.
- High [UA], e.g. lactate, ketones (DM, starvation), toxins (aspirin, glycols, alcohol).
- Although lactate per se is not toxic, it serves as a marker of severe illness. A high [lactate] is caused by the following conditions:
- Hypoxia (increased anaerobic metabolism);
- Inhibition of mitochondrial function (antiretroviral drugs),
- Stimulation of glycolysis (β agonists like adrenaline, dobutamine, salbutamol);
- Increased glycolysis, especially in patients with renal impairment (biguanides such as metformin);
- Thiamine is necessary for the decarboxylation of α-keto acids such as pyruvate. Re-feeding in

alcoholics or critically ill patients may develop an acute thiamine deficiency with the accumulation of pyruvate and lactate;
- Decreased clearance (renal failure, liver failure).
- High albumin and Pi

Causes of a low (normal) AG acidosis:
- Hyperchloraemia
- Renal failure often causes an acidosis with increased [Pi], increased [SO_4^{2-}], and low albumin.
- Renal tubular acidosis is defined as an inability of the kidneys to clear acid in the presence of adequate glomerular filtration. This condition is inherited or secondary to disease or drugs. Inability of the proximal tubuli to reabsorb HCO_3^- is inherited (renal tubular acidosis, RTA) or is caused by the carbonic anhydrase inhibitor *acetazolamide.* This drug causes a decreased HCO_3 reabsorption by the proximal tubuli, natriuresis, and kaliuresis. An inherited functional (RTA), secondary functional (*trimethoprim*), or absolute (*diabetes mellitus nephropathy*) renin/aldosterone deficiency impairs Na^+/K^+ and H^+ exchange in the distal tubuli and causes a natriuresis but retention of K^+ and H^+ (amiloride-like action). The antibacterial agent trimethoprim is present in cotrimoxazole and used in the treatment of *Pneumocystis carinii* pneumonia (occurs commonly in HIV patients).
- Increased unmeasured cations, e.g. Mg^{2+}, Ca^{2+}, Li+, myeloproteins (myeloma). These cations bind Cl^-. They also replace the main positive charges Na^+ and K^+.
- Decreased UAs, albumin, and Pi
- Pseudohyponatraemia (hyperlipidaemia, hyperglycaemia)
- Severe hypernatraemia (measurement error)
- Hyperviscosity (measurement error)
- Increased concentrations of halides: $\uparrow$[triglycerides] $\rightarrow$ $\uparrow$[Cl^-] (measurement error); Iodine radiocontrast $\rightarrow$ $\uparrow I^-$

Remember, a low AG can obscure a high AG acidosis.

AIDS and the AG
- Low albumin: emaciation, malnutrition (diarrhoea), HIV nephropathy proteinuria
- High [Ca^{2+}]: chronic granulomatous lesion (tuberculosis, fungal infections) produce $1,25(OH)_2VitD$, which is unaffected by the normal negative feedback on renal 1αhydroxylase.
- Increased triglycerides $\rightarrow$ increased [Cl^-] (measurement error)
- Increased [lactate] due to antiretroviral drugs
- Starvation ketosis

AG, SBE, AND THE CHLORIDE/SODIUM RATIO

As has been pointed out, the indicators of acid-base disturbances must be read together. An entity which comes in very handy to identify the aetiology of an abnormality is the Cl^-/Na^+ ratio (Table 5). The normal Cl^-/Na^+ ratio is between 0.74 and 0.78.

Table 5 The Cl^-/Na^+ ratio

Abnormality	Cl^-/Na^+	SBC, SBE	AG	Origin	Remark
Acidosis	N	↓	↑	↑UAs	UA acidosis
	↑	↓	N	↑[Cl^-]	Hyperchloraemic acidosis
	↑	↓	N	↑[Cl^-], ↑UAs	Mixed acidosis
Alkalosis	↓	↑	N	↓[Cl^-]	Hypochloraemic alkalosis

Example: A patient is acidotic and has a low SBC and SBE, a normal AG and [lactate], is normoglycaemic, and has no ketones or other acids. The [Na^+] = 135 mM (within normal limits), the [Cl^-] = 107 mM (within normal limits). The patient is being ventilated and the $PaCO_2$ is normal. Where does the acidosis come from? What you do know, is that the patient has received *one litre of*

Voluven (dissolved in NaCl 0.9%). *The Cl⁻/Na⁺ = 107/135 = 0.79*, which points to a *relative hyperchloraemia*, probably due to the Voluven transfusion. *This is a very common cause of a metabolic acidosis. So, pleeeeeeeeeeeeeeeease, do not miss it!*

THE STRONG ION DIFFERENCE (STEWART-FENCLE)

The indicators of acid-base state discussed thus far all give an indication of the degree of the disturbance, but give a very limited picture:
- *The pH* tells if there is predominantly an acidosis or an alkalosis.
- *PCO_2* is an indication of the *respiratory* component.
- *The ABC, SBC, ABE, and SBE* identify a *non-respiratory* component.

These variables do not address acid-base abnormalities associated with other substances, e.g. chloride and unmeasured weak anions (Atot). We discussed two variables, which address these components:
- *The AG* identifies the contribution of *chloride and unmeasured anions*.
- *The BE(UA)* takes into account the influence of the main extracellular electrolytes (Na^+ and Cl^-) and protein (albumin).

The *strong ion approach* considers these substances take several components into account. All these variables have been addressed, but this approach (interpretation) does it from a different viewpoint. This method is based on the principles of *electrical neutrality* and of *three chemically independent factors* that determine plasma pH. *These three factors are PCO_2, apparent or measured strong ion difference (SIDa), and Atot: Although they are chemically independent, they are not physiologically independent*:
- PCO_2 (HCO_3^- is not an independent variable; neither is it a strong anion)
- Atot is the non-volatile buffers. It represents the weak acids, of which albumin and Pi are the most important, including albumin and Pi (Atot).
- *Strong* ion difference (SID) (Figure 2)
  SID = (*completely* dissociated cations) – (*completely* dissociated anions)
     = ($Na^+ + K^+ + Ca^{2+} + Mg^{2+}$) - ($Cl^- + lactate + SO_4^{2-} + ketones + fatty acids, etc.$)

Acid-base analysers do not measure Mg^{2+}, SO_4^{2-}, ketone, fatty acids, etc. Therefore, the following formula is often used:
SID = ($Na^+ + K^+ + ionised Ca^{2+} + Mg^{2+}$) - ($Cl^- + lactate$) = *apparent or measured SID (SIDa, SIDm)* (Figure 2).
The normal value is 40 ± 2 mEq L^{-1} (e.g. 140 + 4 + 2 + 2 - 100 - 1 = 39 mEq L^{-1})
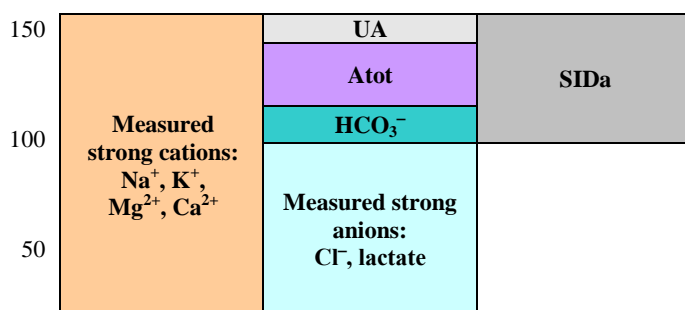
Figure 2 The strong ion difference

The three factors have been combined in one formula. (It is not necessary for you to memorize the formula.):

$$pH = pK_1 + \log \frac{[SIDa - Atot/(1+10^{pKa - pH})]}{S \times PCO_2}$$

This formula describes pH as a function of:
- Three chemically independent variables
  - PCO_2
  - SID
  - Atot, and
- Three constants:
  - *S* the solubility of CO_2 (0.03 mEq L^{-1} mm Hg)
  - K_1 the dissociation constant for H_2CO_3 (6.1)
  - Ka the effective dissociation constant of Atot). The Ka for human plasma ([Atot] = 20 mEq L^{-1}, Ka = 3.0 x 10^{-7} mEq L^{-1})

I shall simplify the formula. Can you see that it resembles the Henderson-Hasselbalch equation. Perhaps you (may) remember it. But I think you must remember the principle:

$$pH = 6.1 + \log \frac{(SIDa – Atot \times B)}{S \times PCO_2}$$

Since acid-base disturbances are caused by PCO_2, SIDa, and Atot independently, six primary disturbances can be distinguished (Tables 6 and 7, Figure 3):

- Respiratory acidosis and alkalosis
- Strong ion acidosis and alkalosis
- Atot acidosis and alkalosis

Table 6 Primary sources of acid-base disturbances

Disturbance	Respiratory	Metabolic		
	PaCO$_2$	SIDa	Atot	
			Albumin	Pi
Acidosis	↑	↓	↑	↑
Alkalosis	↓	↑	↓	↓

Table 7 Abnormalities in *SIDa* and acid-base disturbances

Disturbance	Water deficit or excess	Imbalance of SIDa
Alkalosis	Concentration	Cl⁻ deficit
Acidosis	Dilution	Cl⁻ excess, presence of UA

Figure 3 Relationship between pH and SIDa

Although the three components of the Stewart approach are regarded chemically independent, they are not physiologically independent. Therefore, remember the following:
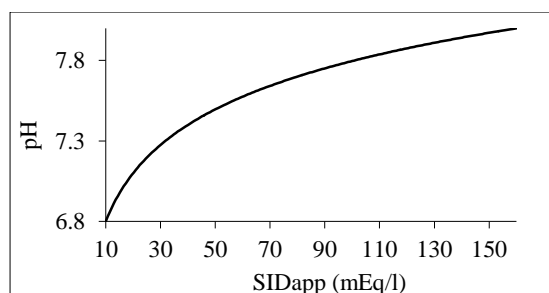- Although the proponents of this approach regard the three determinants of acid-base state as being independent, it is not the case. PCO$_2$ and SID affect each other, while the factors in the SIDa do not change independently; from the concept of electroneutrality – an increase in a cation must be accompanied by the increase of an anion, or decrease of another cation, and *vice versa* for changes in anion concentrations. These changes cause a change in the SIDa.
- Some of these changes, e.g. acute haemodilution and concentration, only occur with large and sudden changes in volume and concentrations, but are relatively short-lived.
- The lungs, kidneys, and non-HCO$_3$ buffers (intracellular and bone) play a pivotal role in the relative concentrations/changes of cations (Na$^+$, K$^+$, and H$^+$), anions (Cl⁻, HCO$_3$⁻), and PCO$_2$.
- Albumin is a buffer but its concentrations do not change to compensate for changes of the other species.

The advantage of the Stewart approach (SID and Atot) is that it draws the attention to other causes of acid-base disturbances. A low SIDa reveals a metabolic alkalosis (low Atot) in patients with a normal pH and normal SBE. The transfusion of 0,9 % NaCl and 5% dextrose solutions causes a metabolic acidosis. The SID of 0,9 % NaCl and of 0.5% dextrose is 0 mEq L^{-1}. An acidosis develops especially when large volumes of saline or dextrose are administered, which dilute other plasma components. These solutions decrease the [Na$^+$] more than [Cl⁻], resulting in a lower SIDa. When Atot is normal, the ΔSID = ΔBE. The treatment of this low SID acidosis is the transfusion with a solution with a high SID, e.g. NaHCO$_3$ injection.

But how does an acute volume load with 0,9 % NaCl and 0.5% dextrose cause an acidosis (dilutional acidosis)? Both of these solutions cause a dilution of HCO$_3$⁻ and CO$_2$. Since the PCO$_2$ decreases with acute dilution by HCO$_3$⁻-free fluids, patient will hypoventilate to correct the PCO$_2$. CO$_2$ is also replenished by the CO$_2$ production by the tissues. Therefore, the patient will develop a combined metabolic and respiratory acidosis. The administration of 0,9 % NaCl has an additional effect: The relative *hyperchloraemia* increases the Cl⁻ delivered to the cortical collecting ducts in the kidney. These Cl⁻ ions are exchanged for HCO$_3$⁻, which is lost in the urine. Acute volume load with buffer-free fluid also increases the glomerular filtration rate, which decreases the efficacy of HCO$_3$⁻ reabsorption.

A large volume of dextrose solution also lowers the plasma [Na$^+$]. Less Na$^+$ is delivered to the kidney. The low [Na$^+$] in the tubular fluid causes retention of H$^+$ and K$^+$. Therefore, the *acute* acid-base disturbance is a metabolic acidosis. However, this effect is eliminated by the secretion of aldosterone, which enhances the reabsorption of Na$^+$ and excretion of H$^+$ and K$^+$. The reverse happens in hypochloraemia and *acute volume contraction*, which causes an *alkalosis*.

For an interesting review regarding the validity of the Stewart approach, the student is referred to Kurts et al.[39]

CHAPTER 21

OBSTETRIC ANAESTHESIA

Key points
- Physiological changes of pregnancy
- General approach to the obstetric patient
- Anaesthesia for labour and vaginal delivery
- Anaesthesia for caesarean section
- Regional anaesthesia
- General anaesthesia
- Contraindications and complications related to spinal/epidural anaesthesia and their management
- The possible complications related to general anaesthesia and their management
- Considerations in the hypertensive conditions of pregnancy

Physiological changes in pregnancy

During pregnancy, various organs undergo physiologic changes (Table 1). These changes have important implications for the anaesthetist as they increase the anaesthetic risk.

Table 1 Physiological changes in pregnancy

Organ system	Changes
Haematological	• in plasma volume by 45% • in total blood volume by 35% • Dilutional anaemia (Hct = 35%) • Platelets ↑10% • ↑ Clotting factors 30% to 250%
Cardiovascular	• ↑ in cardiac output by 30% to 50% • ↑ stroke volume up to 30% • Aorta-cava compression occurs in 10% • Heart rate increases 15% to 30% • ↓ Systolic BP 5% and diastolic BP 15% • ↓ Peripheral vascular resistance 15%
Ventilation and metabolism	• Congestion of the airways predispose to bleeding during the placement of nasopharyngeal airways, nasogastric and endotracheal tubes. • ↑ Minute ventilation (50%) • ↑ Tidal volume 40%, RR ↑ 15% • ↓ FRC (20%) • O2 consumption ↑ by 20 – 50%; patient is more prone to hypoxaemia • PaO2 ↑10%, PaCO2 ↓15%, HCO3 ↓15%
Gastrointestinal	• Delayed stomach emptying • ↓ Tone of lower oesophageal sphincter with gastro-oesophageal reflux
Altered response to drugs	• ↓ Requirements of inhalants (↓ MAC with as much as 40%) • ↓ local anaesthetic required for epidural or spinal

General approach to the obstetric patient

A high majority of patients entering the obstetric unit potentially require anaesthesia, whether *planned or emergent*. Patients definitely requiring anaesthetic care (for labour or caesareans section) should undergo a *focused pre-anaesthetic evaluation* as early as possible. This should include a maternal health history (age, parity, duration of pregnancy, etc.); underlying co-morbidities, anaesthesia related obstetric history, blood pressure measurement, airway assessment and examination of the back for regional anaesthesia.

All patients in labour should be managed with *intravenous fluids* to prevent dehydration. Blood should be sent for group and screening in patients at high risk of haemorrhage or a borderline acceptable haematocrit. All patients are considered to have a *full stomach regardless* of the time of last oral intake. Ideally, patient monitoring should include *cardiotocography*. The supine position should be avoided. About 90% of patients prefer the left lateral position to prevent supine hypotension

syndrome (*aorta-cava compression*); about 10% prefer the right lateral position. During caesarean section the table is tilted to the side the patient prefers.

Anaesthesia for caesarean section
General anaesthesia
General anaesthesia has been associated with higher maternal mortality.
Regional (neuraxial) anaesthesia (see also Chapter9)
- Subarachnoid (spinal) anaesthesia
- Epidural anaesthesia
- Combined spinal and epidural anaesthesia (CSE)

Neuraxial anaesthesia is the *anaesthetic of choice* for caesarean section. *Advantages* are:
- Decreased risk of maternal *pulmonary aspiration*
- Less exposure of the *foetus to depressant drugs*
- The mother is *awake at the birth* of her child
- *No uterine relaxation* by anaesthetic vapours
- The possibility to provide *postoperative pain relief*

REGARDING NEURAXIAL ANALGESIA AND ANAESTHESIA, THERE ARE SOME IMPORTANT ISSUES. BEFORE DOING A NEURAXIAL BLOCK FOR ANALGESIA OR ANAESTHESIA, ALL THE FOLLOWING MUST BE COMPLIED WITH:
- You must have been *trained to perform the procedure* and to *manage complications*.
- The most important patient factor for neuraxial analgesia and anaesthesia to succeed is an *informed, motivated, and cooperative patient*.
- The *procedure must be explained to the patient*, including what it entails, other options, and possible complications. She must *sign informed consent* for the procedure.
- It must only be done in a *well-equipped unit*: immediate availability of equipment for CPR, i.e. oxygen, suction, a bed that can be tilted, defibrillator, airway management, and drugs. *Minimal monitoring* requirements include blood pressure (cycling on 1 minute), ECG and pulse oximetry.
- Well-trained, motivated and reliable *staff*
- *IF EVEN ONE OF THESE FACTORS IS NOT FULFILLED, DO NOT PROCEED!*

Subarachnoid anaesthesia (usually called a "spinal") for caesarean section
- *Preparation, positioning, and surface anatomy to do the spinal*
  - *The theatre and anaesthetic equipment must be complete and tested.*
  - The obstetricians, sisters, and doctor to receive the neonate must be present and ready.
  - The anaesthetist must have a *competent assistant*.
  - Good *venous access* is essential (a minimum of an 18 G cannula, preferably a 16 G).
  - *Start preloading* with Ringer lactate so that a volume of about **10 ml kg^{-1}** has been infused by the time the spinal has been done.
  - *A vasopressor* such as phenylephrine (*first choice*), diluted to 50 μg ml^{-1}, must be immediately available. You can prepare it by adding 10 mg of phenylephrine to 200 ml of saline (10 mg in 200 ml = 10 000 μg in 200 ml = 10 000 μg/200 per ml = 50 μg ml^{-1}).
  - *Everything must be prepared for a general anaesthetic*, i.e. the anaesthetic machine must have been tested, laryngoscopes, endotracheal tubes, tube stylet, oral laryngeal mask, suction, functioning theatre table.
  - *All neuraxial procedures involve the spinal cord, including breaching of the spinal meninges. There, the anaesthetist must follow sterile techniques (mask, scrubbing, sterile gown, gloves).* The patient is placed in the *sitting or lateral* decubitus position. The procedure is easier if the patient is sitting and bending forwards. The *spinous processes* are usually palpable over the spine and help define the *midline*. *A line* between the highest points of both *iliac crests* (Tuffier's line) usually crosses either the *body of L4 or the L4-L5 interspace.* This is the ideal *insertion level* for a spinal and epidural since the spinal cord stops at about the second lumber vertebra. Therefore, a spinal injection is always done below this level.
  - If the patient is sitting, make a horizontal impression with a thumb nail between the spinous

processes between which you plan to insert the needle. Palpate the spinous processes with of your left and right thumbs and make a vertical impression on both sides of the horizontal impression. Now, you should see an *H-shaped marking on the skin*. The midpoint of the horizontal bar of the H is the entry point of the needle.

- *Draw up the following drugs:*
  - Draw up 5 ml of *lignocaine 2% injection* and attach a needle no longer than 23 mm (in South Africa, at present this is a 23 G blue needle). The *purpose of this injection is two-fold*: to *anaesthetise the skin* and *identify the direction of the interspinous space* (soeknaald). If you cannot enter the space with this needle, you will definitely not manage with the spinal (or epidural needle). The direction of the needle at this level is usually slightly cephalad. Once you have identified the interspinous space, inject another 2 ml of lignocaine. Remember, the distance between the skin and the dura varies between **2 cm and 8 cm**; if a longer needle is used to identify the interspinous space and administer the local anaesthetic, **you may puncture the dura**.
  - *Drugs used for spinal anaesthesia*
    Local anaesthetics: Hyperbaric bupivacaine 10 mg to 12.5 mg (2 ml to 2.5 ml of a 0.5% injection)

Hyperbaric solutions contain glucose and have a density higher than that of CSF. Therefore, the solution will gravitate to the lowest point; if the patient is put head down, the block will be more cephalad (usually to the thoracic kyphosis at T4), but if the patient is put head up, the solution will gravitate to the sacral area (saddle block, S1 to S5). *An isobaric solution* has the same density as CSF and stays at the level of injection (around L2 to L5 if the injection is given at level L3/4 or L4/5). If the *ready-made* heavy bupivacaine is not available, it *can be prepared* by adding 0.5 ml of a glucose 50% injection to 4.5 ml of a bupivacaine 0.5% injection (plain; without glucose).

An opioid (sufentanil 2.5 μg or fentanyl 12.5 μg) *may be added* to the bupivacaine. It facilitates and potentiates the block. Unfortunately, spinal opioids are associated with generalized pruritis, especially in the neck and chest ereas.

  - ***In our hospital we use the following:***
    *Hyperbaric 0.5% bupivacaine injection (5 mg ml^{-1}).*The volume is calculated according to the patients length (in metres); the taller the patient the larger the dose, and *vice versa.**The volume to be injected is (1 ml m^{-1}× height in m) + 0.4 ml.***

    Example: A parturient with a length of 1.6 m is scheduled for a caesarean section under spinal anaesthesia. What volume of the hyperbaric 0.5% bupivacaine must be administered?
    The volume is (1 ml m^{-1} × height in m) + 0.4 ml
    = (1 ml m^{-1} × 1.60 m) + 0.4 ml = 1.6 ml + 0.4 ml = **2.0 ml**
    This 2.0 ml contains 2.0 ml × 5 mg ml^{-1} = 10 mg of bupivacaine

    <div align="center">***OR***</div>

    If an opioid is added to the bupivacaine, the following mixtures are used: Hyperbaric bupivacaine 15 mg (that is 3 ml of a 0.5% injection) plus either sufentanil 5 μg (that is 1 ml of a 10 μg in 2 ml injection) or fentanyl 25 μg (that is 0.5 ml of a 100 μg in 2 ml injection). Of this total of 4 ml (or 3.5 ml if fentanyl is used) *the dose of this mixture is (1 ml m^{-1} × height in m) + 1.1 ml*

    Example: A parturient with a length of 1.6 m is scheduled for a caesarean section under spinal anaesthesia. What volume of the bupivacaine + sufentanil mixture must be administered? The volume is about (1 ml m^{-1} × height in m) + 1.1 ml = (1 ml m^{-1} × 1.60 c) + 1.1 ml = 1.6 ml + 1.1 ml = **2.7 ml**
    This volume contains (2.7/4.0) × 15 mg = 10.1 mg of bupivacaine and
    (2.7/4.0) × 5 μg = 3.4 μg of sufentanil
    Although the doses given above take height into account, one must remember that the

difference in height between persons is influenced more by the length of the legs than the length of the spine.[i]

The correlation between the spread of local anaesthetic solutions volume and block height is very poor. For term parturient, one study suggested a dose of 6 mg of bupivacaine per metre height. For the above patient of 1.6 m tall, the dose will be 1.6 m $\times$ 6 mg m^{-1} = 9.6 mg, which is contained in 9.6 mg/5 mg ml^{-1} = 1.92 ml $\approx$ 2 ml. **Therefore, you will not be wrong if use the following doses for all patients: 2 ml of hyperbaric bupivacaine 0.5% or 2.5 ml of a mixture consisting of 2 ml hyperbaric bupivacaine 0.5% and 2.5 µg of sufentanil (0.5 ml of an injection containing 10 µg in 2 ml).**

- *Inserting the spinal needle and injecting the local anaesthetic*
  The layers breached to achieve a spinal are as follows: skin, subcutaneous fat, supraspinous ligament, interspinous ligament, ligamentum flavum (first loss of resistance), epidural space, dura and arachnoid mater (second loss of resistance) and then the subarachnoid space is entered (Figure 1). *A spinal needle 25 G or thinner* is inserted (usually through a thicker guide needle). The *guide needle* is usually packed with these thin needles. *Inserted the guide needle* up to a depth of not more than 2 cm where you have identified the interspinous space. The *spinal needle is passed through the guide needle*. The stylet inside the spinal needle is withdrawn every 3 mm to 5 mm to inspect for backflow of cerebrospinal fluid. Once free flow of CSF is obtained, the syringe containing the local anaesthetic is attached to the spinal needle and the *planned volume is injected.* The needle *stylet is reinserted* into the spinal needle and the needle is removed. The *needle is inspected* to see if it is complete.
- The colour of the SCF must be noted in the anaesthetic record (clear, blood stained, xanthochromatic) and whether root pain was elicited necessitating repositioning of the needle.
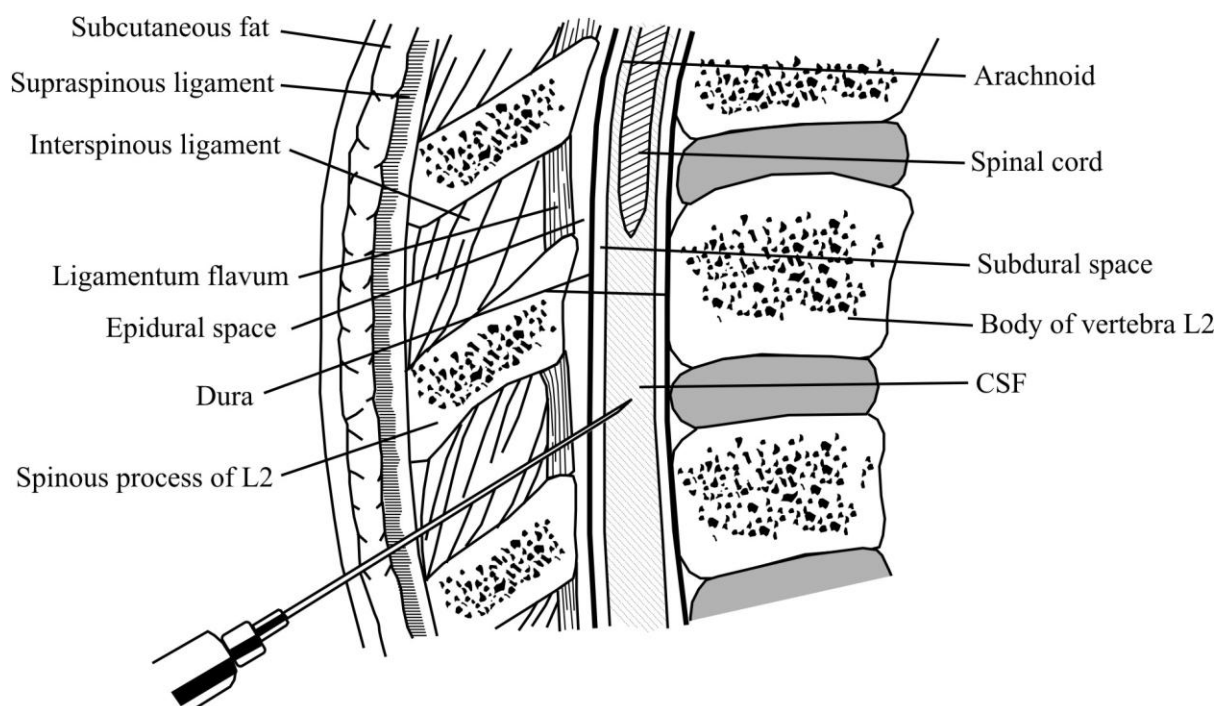
Figure 1 Anatomy of the epidural and subarachnoid spaces

- *Positioning for the caesarean section*
  o The *patient is immediately placed in the supine position*. Since the *head must be higher* than the lowest point of the thoracic kyphosis (about T4) where the hyperbaric bupivacaine accumulate, the head should be supported on a pillow.
  o In the last trimester a patient in the supine position can have a 30-56% decrease in cardiac output due uterine compression of the aorta and inferior vena cava (IVC). Since the pressure in the IVC is lower than in the aorta, the IVC is compressed more than the aorta. Compression of

the IVC results in decreased venous return to the heart, a decrease in cardiac output, dizziness, paleness, hypotension, sweating, and a reflex bradycardia or tachycardia. Not only does maternal cardiac output decrease, but also uterine perfusion and foetal oxygenation. This is called the *aorta cava compression syndrome*. Therefore, all patients should be nursed on their sides and in theatre the patient must be positioned in a *left lateral tilt (about 10% of women prefer right lateral tilt)*. Therefore, the *table tilted 15° to the side* the patient prefers. During a cardiac arrest in the parturient, the *lateral tilt is essential during CPR*, since compression of the IVC may make CPR less effective.

- *Monitoring*
  The *ECG, oxygen saturation and blood pressure* must be monitored closely. Administer oxygen if the saturation decreases below about 98%. The *first indication of a decrease in blood* pressure justifies administration of *phenylephrine* 50 μg.[xxvi] *If the hypotension is accompanied by a bradycardia*, inject *ephedrine* 0.1 mg kg (usually 5 mg). You can prepare this by diluting ephedrine 50 mg to 10 ml; this dilution contains 5 mg ml^{-1}. Alternatively, *adrenaline* 100 ng kg^{-1} is administered (usually 5 μg to 10 μg). You can prepare this by diluting 1 ampoule of adrenaline (1 mg) to 200 ml; this dilution contains 1 mg in 200 ml = 1000 μg in 200 ml = 1000 μg/200 per ml = 5 μg ml^{-1}. For example, if the patient has a body mass of say 80 kg, the dose is 100 ng kg^{-1} × 80 kg = 8 000 ng = 8 μg = 0.5 ml to 1.0 ml of the dilution.

  Monitor the development of the spinal block. It takes about 5 minutes for an adequate level of anaesthesia. During this time, you must *keep contact with the women*; ask her to *move the hands* to identify a high spinal and *speak to her* to identify decreased consciousness. *Nausea* may be a sign of hypotension and must not be disregarded.

- *Delivery of the foetus*
  o *Administer oxygen* and accept a saturation of about 97% since it seems as though hyperoxia causes placental vasoconstriction.
  o *Test the level of the block (at least up to T6, i.e. level of the xyphisternum)*
  o The *patient is draped* and the operation may begin.
  o Once the last foetus is being removed, the obstetrician requests a uterotonic agent, usually *oxytocin* (see below).

- *Fluid replacement*
  o Patients presenting for *elective section* are usually *well hydrated* but those who have been in labour for some time and present for *emergency* section, are often *dehydrated*. Therefore, *preloading* (see above) should commence as soon as possible.
  o Since a caesarean section is a relatively short procedure, fluid therapy usually consists of *replacement of blood loss*. *Blood loss* during a caesarean section is 600 ml to 1 000 ml, but is usually well compensated for by autotransfusion from the contracting uterus. It is however necessary to replace excessive blood loss (see Chapter 18).
  o Be careful *not to overload pregnant patients – especially preeclamptic patients*. Fluid management in preeclamptic patients is controversial and difficult (see your obstetrics notes).

- **<u>The use of uterotonic agents during caesarean section</u>**[40]
  After delivery of the last foetus, uterotonic agents are injected to facilitate uterine contraction. *Oxytocin is the first-line agent* to prevent and treat uterine atony and postpartum haemorrhage (PPH). **<u>Slow</u>** *administration of a 2 IU bolus* of oxytocin usually suffices to increase uterine tone and reduce oxytocin side effects. The World Health Organization recommends an infusion of oxytocin consisting of 20 IU in 1 L crystalloid administered at 1 ml per minute for 2 hours. This infusion delivers 0.02 IU per minute. (Using a 60 drops per ml administration set, this is 60 drops per minute.). If patient has received oxytocin to augment uterine contractions or if she was receiving tocolytics before caesarean section, higher doses may be needed to contract the uterus.

[xxvi] Instead of 50μg boluses, you can start with about 50 μg min^{-1}. This is done by adding 10 mg of phenylephrine to 200 ml saline, and administer it at 1 ml per min (using a 60 drop per ml infusion set, this is 60 drops per minute). You can start this infusion as soon as you start doing the block.

Oxytocin has a narrow therapeutic range. Therefore, the lowest dose should be administered slowly. The most common *cardiovascular side effects* are hypotension and tachycardia, but other dysrhythmias and myocardial ischaemia also occur. Cardiovascular effects of oxytocin may be poorly tolerated in patients with cardiac disease, and preeclamptic patients. In contrast to vasodilatation in the systemic vasculature, oxytocin can cause coronary vasoconstriction (ST segment elevation) with rapid injection of large doses (> 5 IU), and this is aggravated by the simultaneous administration of 0.2 mg ergometrine.

Oxytocin has a structure similar to that of vasopressin. Therefore, large doses or prolonged administration may cause *water retention and hyponatraemia*, which may be complicated by seizures and coma. The drug may cause *nausea and vomiting*, especially after bolus injection.

Complications of spinal blocks in obstetrics

- *High spinal blockade* may occur if excessive doses/volumes of drugs are used or if there is unusual sensitivity or spread of local anaesthetic. If spinal anaesthesia ascends to the cervical levels severe hypotension, bradycardia and respiratory insufficiency may ensue (high/total spinal). Patients may initially complain of dyspnoea and have numbness and weakness in the upper extremities. Once recognized, reassure patient, provide supplemental oxygen, and correct bradycardia and hypotension. If the block progresses any higher than the upper limbs, intubation and mechanical ventilation may be necessary. Support the circulation with intravenous fluids, vasoconstrictors, and positive inotropes (see above).
- *Hypotension is the most common adverse effect of spinal anaesthesia.* The hypotensive response will be much more pronounced if left lateral tilt is not adequate. Therefore, all patients should be maintained in a left lateral tilt position. During administration of a spinal for a lower segment caesarean section, a noticeable increase in the heart rate of often heralds the hypotension. *Immediate treatment of hypotension is essential* as utero-placental circulation may be severely affected to the detriment of the foetus. Growth retarded and "sick" foetuses have been known to develop severe metabolic acidosis immediately after delivery, in mothers where the blood pressure markedly dropped after the spinal. *Measures to prevent hypotension* consists of intravenous fluid with 1 000 ml to 1 500 ml Ringer lactate or 300 ml to 500ml colloid before (preloading) or while doing the spinal (co-loading), ephedrine (if bradycardic), phenylephrine (if tachycardic), and adrenaline (see above). Administer oxygen by mask.
- *Sever bradycardia and hypotension* may be followed by *cardiac arrest.* This is thought to be caused by a Bezold-Yarisch cardiac reflex.
- *Urinary retention* caused by blockade of segments S2 to S4, which decreases urinary bladder tone and inhibits the voiding reflex. Therefore, all patients should have a urinary catheter *in situ*; if a catheter has not been inserted, the patient should be observed postoperatively for bladder distension and voiding.
- *Inadequate anaesthesia and analgesia* (failed spinal)
- *Direct neurological injury* can result from spinal cord or nerve root injury. Any sustained paraesthesia should alert the clinician to redirect the needle. Injections should be immediately stopped and the needle withdrawn if they are associated with pain. Direct injection into the spinal cord can cause paraplegia. Apart from direct neurological injury, the spinal cord can also be affected by the tonicity of the injection or direct toxicity of the components of the injection. These complications include *cauda equina syndrome, transient neurological symptoms, and anterior spinal cord syndrome.*
- *Spinal haematoma* can occur, particularly in the presence of abnormal coagulation (bleeding disorders, anticoagulant therapy). The pathological insult to the spinal cord and nerves are due to a mass effect compressing neural tissue and causing direct pressure injury and ischaemia. Rapid diagnosis and intervention (surgical decompression within 8 h) is of paramount importance to prevent permanent neurological squeals.
- *Meningitis and arachnoiditis* can be caused by contaminated equipment or injected solutions, or as a result of organisms tracking in from the skin**.** Therefore, this procedure should be undertaken in

an aseptic manner.

- *Backache*
- *Post-dural puncture headache (PDPH)* is a common, unfortunate side effect of dural puncture in young patients, especially when *needles thicker than 25 G* are used. Onset is usually within 12 h to 72 h, but may also be seen immediately. *Typically*, PDPH is bilateral, frontal, retro-orbital, occipital and extends into the neck. It may be throbbing or constant and associated with photophobia and nausea. *The hallmark* is that the headache worsens when the patient sits up and improves when lying down. *The pathogenesis* is thought to be due to a leakage of CSF from the dural defect, which causes a decrease in intracranial pressure (ICP). The decreased ICP causes traction on the pain-sensitive basal meninges – especially if the patient sits up.
  - o *Modifications of technique* and *new technology needles* have decreased PDPH to acceptable levels. These include: using needles not thicker than *25 G*, penetrating the dura with the *bevel of the needle* parallel to the spinal cord (split rather than cutting the longitudinal dural fibres), and use of *pencil point needles.* (There is still uncertainty about the latter two factors.)
  - o Management of PDPH consists of clinical exclusion of meningitis, bed rest, simple analgesics, caffeine, and oral (coffee) or intravenous fluids. If the headache persists for more than 24 hours, an epidural blood patch should be done. The epidural blood patch consists of injection of 15 ml of the patient's blood into the epidural space at the level where the spinal was done. This procedure is done in an operating theatre under sterile technique by two doctors. One performs the epidural, while the second takes blood in a sterile manner from the patient. Once the epidural the epidural space is identified, the blood is injected slowly into the epidural space. Typically, this provides instant relief of headache. Back ache is a common complication of this procedure.

Epidural anaesthesia for caesarean section

This is similar to epidural analgesia for labour, but larger volumes of the local anaesthetic are used and onset of anaesthesia is much slower than with spinal anaesthesia. The dose is about 20 ml if bupivacaine 0.5%. This is injected in fractions of 5 ml until an adequate level of anaesthesia (T4) is reached. Another reason to inject epidurals in fraction of about 5 ml, is to exclude unintended intrathecal placement of the epidural catheter; if a dense high block develops after about 5 minutes after injecting 5 ml, the catheter is probably intrathecal and not epidural. This is no catastrophe; take note of it and proceed as if you have done a spinal in the first place. Complications are the same as for intrathecal injections.

*Reminder***:**
- ***SPINAL (Intrathecal) ANAESTHESIA is preferred for CAESARIAN sections.***
- ***EPIDURALS are used for LABOUR ANALGESIA, or when a SLOWER ONSET BLOCK is desired, e.g. in patients with cardiac disease and preeclampsia.***

Contraindications to neuraxial blockade (spinals, epidural, analgesia, or anaesthesia)
- *Absolute contraindications*
  - o *Inexperienced* operator
  - o *Patient* refusal, uncooperative patient, inability to communicate with patient (see below)
  - o Infection at the site of injection
  - o Any *coagulopathy* (bleeding diathesis or anticoagulant therapy) (See Chapter 19)
  - o Severe *hypovolaemia*
  - o Increased *intracranial pressure*
  - o *Fixed cardiac output states*[xxvii] (valve stenoses, constrictive pericarditis, etc.)
- *Relative contraindications*
  - o Systemic sepsis
  - o Active *neurological disease*, e.g. demyelinating lesions, motor neuron disease, etc. If you

---

[xxvii] Fixed cardiac output means that the cardiac output cannot increase if the demand for an increased output would arises.

decide to do it, the neurological function must be noted and the benefit risk must be considered.
- o Prior *back surgery* at the site of needle placement or *deformities* such as scoliosis.
- o *Complicated surgery*: major blood loss anticipated (placenta praevia, abruptio placentae, extra-uterine pregnancy), prolonged surgery, manoeuvres that compromise respiration, severe foetal abnormalities)

General anaesthesia for caesarean section
- **Preparation**
  - o *The theatre and anaesthetic equipment must be complete and tested.*
  - o The obstetricians, sisters, and doctor to receive the neonate must be present and ready.
  - o The anaesthetist must have a *competent assistant*.
  - o Very good *venous access* is essential (preferably a 16 G cannula) and *start preloading* with about 10 ml kg^{-1} of Ringer lactate.
- **Positioning**
  - o Tilt the patient to the side she prefers to alleviate *aorta-caval compression* (to the left in about 90% of cases).
  - o If the patient has large breasts, put one pillow behind the scapulae, one behind the back, and another one behind the head if necessary to ensure the sniffing position.
- **Induction**
Induction of anaesthesia and *airway management* (rapid sequence induction with cricoid pressure) are the same for elective and emergency caesarean sections.
  - o If the patient has pain, give fentanyl about 1 μg kg^{-1} or alfentanil 10 μg kg^{-1}, keeping in mind that is may suppress the neonate's ventilation.
  - o *Preoxygenate* with 80% of oxygen in air for 3 minutes.
  - o *Induce* with either propofol 1.5 mg kg^{-1} to 2 ml kg^{-1}, or thiopentone 2.0 mg kg^{-1} to 2.5 ml kg^{-1}, or ketamine 1.5 mg kg^{-1} to 2 ml kg^{-1}.
  - o The assistant must apply *cricoid pressure* as soon as the patient loses consciousness.
  - o Inject *suxamethonium* 1.0 mg kg^{-1}. Wait for 30 seconds for relaxation (fasciculations are not always apparent in pregnant patients).
  - o *Intubate* with half a number endotracheal tube smaller as you would in a non-pregnant patient and inflate the cuff.
  - o Ensure *bilateral air entry* by listening in the axillae and see of the *capnogram* is normal.
  - o Only now may the assistant *relieve cricoid pressure*.
  - o Inject a *vasoconstrictor* if the blood pressure decreases < 100 mm Hg.
- **Maintenance of anaesthesia**
  - o *Ventilate* with 50% of oxygen and accept a saturation of about 97% since it seems as though hyperoxia causes placental vasoconstriction. Set the ventilator at a tidal volume of about 7 ml kg^{-1} and a rate of between 10 min^{-1} and 15 min^{-1}. *Avoid hyperventilation and high oxygen* concentrations, as they cause placental vasoconstriction.
  - o Maintain anaesthesia with a *volatile anaesthetic*, keeping in mind that the MAC in pregnancy may be lower. Therefore, 0.75 MAC may be enough. Since awareness is more common during caesarean section, you may add *nitrous oxide* 50% to the gas mixture. The other reason to keep the dose or volatile anaesthetics at the lower side is their tocolytic effect (they relax the uterus).
  - o By now the obstetrician should have opened the uterus and must be busy *delivering the neonate*.
  - o Once the last foetus is being removed, the obstetrician requests a uterotonic agent, usually *oxytocin* (see above).
  - o If the suxamethonium has worked out, the patient may breathe spontaneously.
- *Fluid replacement: As for spinal anaesthesia*
- *Emergence and extubation*
  - o When the obstetrician has closed the uterus, you may *start lightening the anaesthetic*.
  - o When the skin wound has been sutured halfway, *switch off the vapour and nitrous oxide* and administer *80% of oxygen* in air.
  - o *Suction* the throat.

o *Extubate the patient when she is fully awake* and able to protect the airway.

Facts to remember for anaesthesia in obstetrics patients
- *General anaesthesia for caesarean section should be avoided if possible.*
- There should be *no difference in the pre-operative preparation between emergency and elective* cases and whether *neuraxial or general anaesthesia* is planned.
- *Acid aspiration and aspiration pneumonitis*
  During general anaesthesia there is a higher risk of regurgitation and acid aspiration than in the non-pregnant population. Eighty per cent of aspiration is due to passive regurgitation and 20% due to active vomiting.
  o *Various factors contribute to the pregnant woman's risk to aspirate*
    The large uterus increases the intraabdominal and therefore the intra-gastric pressure. The *cardio-oesophageal angle* changes in late pregnancy due to the large uterus. Increased release of *progesterone* by the corpus callosum and the placenta causes relaxation of the intestinal smooth muscle that decreases stomach emptying. There is an increased production of *gastrin*, which increases the volume and acid content of gastric secretions. Decreased *motilin* secretion causes delayed stomach emptying. Stomach emptying is also delayed due to pain, anxiety and narcotic analgesics. *Anticholinergic drugs* lower LOS tone. *Antacids that contain particles* can worsen the pneumonitis if aspiration occurs.
  o *Symptoms of reflux usually disappear* once the baby has been delivered, but the risk of aspiration remains for 48 hours postpartum. The acid content of gastric fluid decreases rapidly after labour due to a decrease in gastrin levels.
  o *Factors which limit regurgitation and aspiration*
    The mother should *not eat* (or drink?) from the start of labour. Few or no *opiates* should be given. Good *airway evaluation* by anaesthetist is essential. *Avoid general anaesthesia.* If general anaesthesia is indicated, a *rapid sequence induction* (RSI) with cricoid pressure and endotracheal intubation is indicated. Avoid induction in the lithotomy position. Prescribe *prophylaxis against regurgitation of acid stomach content.*
  o *Prophylaxis against acid pneumonitis in the event of aspiration consists of all of the following:*
    Sodium citrate (0.3M) is a clear antacid. Give 25 ml 30 min preoperatively.
    Metoclopramide increases body emptying and lower oesophageal sphincter tone. It is also antiemetic. Give 10 mg orally 1 hour preoperative.
    Ranitidine is an H_2-receptor antagonist, which lowers gastric acid content. Give 150mg orally the evening before and 2 hours before caesarean section.
- *Tracheal intubation pregnant patient is more difficult* due to increased thickness of airway mucosae, airway oedema in preeclampsia, and obesity. Complications of difficult or failed intubation are the same as in non-pregnant patients, including hypoxia and pulmonary aspiration. Do not forget the laryngeal mask if unable to intubate, but keep in mind the increased risk of aspiration with a laryngeal mask.
- *Difficult intubation is the most feared complication of anaesthesia.* Incidence of failed intubation is about 1:500. Many of these cases could have been identified with pre-operative evaluation. *The complications of difficult or failed intubation are* **hypoxia** *and* **aspiration.** Currently, the most common cause of obstetric-related death involving general anaesthesia is aspiration pneumonitis. Maternal mortality reported due to hypoxia is caused by repeated unsuccessful attempts at endotracheal intubation and oesophageal intubation. Remember that numerous attempts to intubate without oxygenating the patient in between attempts, increases the risk of hypoxic brain damage.
- *Anaesthetists should be au fait with the "failed intubation drill".* If intubation is not possible for *an elective caesarean section,* the patient is *woken up* and alternatives are considered. A failed intubation may occur in an *emergency*, e.g. foetal distress and the foetus has to be delivered quickly, the following protocol should be followed (see also Chapter 3):
  o Maintain cricoid pressure
  o Insert oropharyngeal airway and manually ventilate the patient with the bag of the anaesthetic circuit. Adequate chest movement and oxygen saturation must be maintained.
  o If manual ventilation is not adequate with an oropharyngeal airway and mask, a *laryngeal mask*

airway may be helpful (see Chapter 3 on basic airway management). Remember though that *cricoid pressure makes placement of the LMA more difficult.*

- o Allow the surgeon to deliver the baby.
- o When the muscle relaxant has worn off, the patient will be able to breathe spontaneously until the conclusion of the operation.
- o In case of the cannot intubate-cannot ventilate scenario, a emergency surgical airway must be created – usually a crico-thyroidotomy.

- *Intra-operative awareness* due to an insufficient level of anaesthesia. *Intra-operative awareness* remains a source of concern during a general anaesthetic when given for a caesarean section.

- *Air embolism during caesarean section*
Subclinical air embolism probably occurs during a caesarean section very often (29%). Rarely, these emboli may be large enough to cause severe haemodynamic compromise. Patients may present with sever hypotension, a precordial "millwheel" murmur, desaturation and sudden decrease in the end-tidal CO_2. Some patients complain of chest pain during caesarean sections done under regional anaesthesia. The condition is treated by immediate flooding of the surgical field with isotonic fluid (not water) and compressing the open vessels with wet swabs. The anaesthetist must immediately start with CPR in an attempt to force the air out of the heart. Nitrous oxide must immediately be discontinued and the patient must be ventilated with 100% of oxygen.

  Air emboli may appear at *any time from uterine incision to uterine closure*. The *majority* of emboli seem to present *while the uterus is being sutured. Manual removal of the placenta* and *exteriorisation of the uterus* may predispose to air embolism, but are not sited in every case.

- *Amniotic fluid embolism* occurs when this fluid enters the uterine veins. This is complicated by sudden cardiovascular collapse (anaphylaxis of foetal matter, pulmonary hypertension, right sided cardiac failure), pulmonary oedema (ARDS), and a bleeding diathesis (activation of coagulation cascade). Treatment consists of cardiovascular support, ventilation, and correction of the coagulopathy [plasma, platelets, cryoprecipitate (fibrinogen)]. The mortality is > 50%.

Anaesthesia for the hypertensive obstetric patient (see also your obstetric notes)
The American College of Obstetrics and Gynaecology divided hypertensive conditions during pregnancy into 4 groups:
- *Chronic hypertension* is the presence of continued hypertension prior to pregnancy extending into the pregnancy.
- *Super-imposed pre-eclampsia on chronic hypertension.* These patients develop an increase in blood pressure, proteinuria and/or oedema during their pregnancy. They suffered from hypertension prior to the pregnancy.
- *Transient pregnancy induced hypertension* that refers to the development of hypertension without proteinuria or oedema in a previous normotensive pregnant patient. Normotension is restored by day 10 post-partum.
- *Preeclampsia or pregnancy-induced hypertension (PIH)* remains the most common, serious and the least explainable form of hypertension. It is *defined as the triad* of hypertension, proteinuria, and generalised oedema. Preeclampsia develops around week 20 of gestation. The postulated theory is a disturbance between the balance of two prostaglandins, namely thromboxane (vasoconstrictor) and prostacyclin (vasodilator). Daily ingestion of a low dose aspirin has been shown to markedly decrease the incidence of PIH in woman with a propensity to develop this disease. Doppler flow studies have shown that lumbar epidurals are of benefit to these patients, as uterine-placental blood flow is improved. It is safe to do an epidural on a patient who has received magnesium sulphate.

Patients with chronic hypertension may be hypovolaemic. Rehydration of these hypovolaemic patients is essential prior to starting antihypertensive therapy or doing regional anaesthesia. Catastrophic decreases in blood pressure may otherwise occur. The drug of choice during a general anaesthetic for the prevention of a hypertensive response pre-induction or intra-operatively, is esmolol, a shorter acting β-blocker.

Problems unique to the preeclamptic patient make their management difficult. The patients may be very ill. Patients are hypovolaemic secondary to the general vasoconstriction. Decrease in glomerular filtration rate can lead to oliguria. Patients may develop hypertensive cerebral haemorrhage and pulmonary oedema (capillary leak).

Decrease in uterine perfusion is often seen depending on the grade of the condition. Preeclampsia is often complicated by *placental insufficiency* and abruptio placentae occur more commonly.

Antihypertensive therapy should be instituted to decrease the generalised vasospasm with an increased peripheral vascular resistance. Methyldopa and hydralazine may be used. Methyldopa is not considered safe in porphyrics.

Albuminuria results in a decrease in colloid osmotic pressure. Generalised oedema and cerebral oedema may occur. Pharyngeal oedema may cause a problem with intubation.

Preeclampsia may be complicated by a *coagulopathy*. This is caused by both a thrombocytopaenia, thrombocytopathy, and hypofibrinogenaemia. These abnormalities cause a prolonged bleeding time, PT, PTT, and clotting time.

Patients usually receive magnesium sulphate as part of their acute management. Magnesium is a vasodilator, negative inotropic, and tocolytic. This is due to its effect as physiological calcium blocker and increases prostacyclin. It is also sedative, anticonvulsant, and relaxes skeletal muscle (decreases prejunctional release of ACh). Since $MgSO_4$ is *excreted by the kidneys*, magnesium levels should be monitored. The normal level is 0.7 mM to 1 mM and the therapeutic level is 2 mM. Tendon reflexes decrease at 4 mM to 5 mM, respiration is depressed at 6 mM, while asystole occurs at 12 mM. The antidote is calcium chloride (6 mg kg^{-1}) or calcium gluconate (18 mg kg^{-1}). Magnesium *potentiates the effects of both suxamethonium and non-depolarising muscle relaxants*.

When *anaesthetising the preeclamptic patient*, the pathophysiology should be taken into account. Of particular concern are the cardiovascular changes, fluid and volume abnormalities, and coagulopathy. Fluid status must be optimised but guard against fluid overload. Patients must continue taking their antihypertensives. Intraoperatively, blood pressure must be managed as in non-pregnant patients, i.e. keep the blood pressure within 20% to 30% of the preoperative blood pressure. The choice anaesthetic technique is epidural anaesthesia if the clotting profile is acceptable (see Chapter 19). If a general anaesthetic is indicated, the response to laryngoscopy and intubation should be attenuated with one of the following: nitro-glycerine (1 μg kg^{-1}), esmolol (0.5 mg kg^{-1} to 1.0 mg kg^{-1}), alfentanil (15μg/kg 2 minute before induction), or remifentanil (0.2 μg kg^{-1} min^{-1}).

Analgesia during labour and vaginal delivery
Pain pathways during labour (sensory supply to uterus)
- *Latent and first stage*: mostly *visceral* pain (*T10 to L1*). T10 supplies the fundus of the uterus and L1 the groin.
- *Second stage*: onset of *perineal pain* (pudendal nerve; S2 to S4 pudendal nerve). Therefore, pain during the second stage of labour involves segments *T10 to S4*.
- *Caesarean section requires a T4* (nipple level) sensory level since innervation of the visceral peritoneum is much wider than the parietal peritoneum.

Psychological and non-pharmacological techniques
Patient *education and positive conditioning* about the birthing process are central to such techniques. Less common *non-pharmacological* techniques include hypnosis, transcutaneous electrical nerve stimulation, biofeedback and acupuncture. The success of all these techniques varies considerably between patients, but *most patients require additional analgesia*.

Pharmacological management
Parenteral agents are still widely used and often include *opioids and sedatives.* Almost all opioid analgesics and sedatives readily *cross the placenta* and can affect the foetus. Therefore, concern over foetal depression limits the use of these agents to the early stages of labour. *Pethidine* is the most commonly used opioid, and can be given in doses of 10 mg to 25 mg intravenously or 25 mg to 50 mg intramuscularly every six hours. *Morphine* is less commonly used since equianalgesic doses appear to cause *greater respiratory depression* in the foetus and parturient.

Promethazine 25 mg to 50 mg intramuscularly or *hydroxyzine* 50 mg to 100 mg intramuscularly can be used alone or on combination with pethidine. In addition, *both these antihistamines* reduce anxiety, opioid requirements, and the incidence of nausea without adding appreciably to neonatal depression.

Patient controlled analgesia devices are advocated by some clinicians early in labour because this technique appears to reduce total opioid requirements.

Pudendal nerve block
Combined with perineal infiltration of local anaesthesia, this technique provides acceptable perineal anaesthesia during the second stage of labour. This nerve block is not commonly done. If it is used, it is done by the obstetrician.

Neuraxial analgesia
Epidural analgesia is the most popular method employed by anaesthetists to provide pain relief during labour and delivery. Epidural analgesia should generally be *initiated when the parturient wants it* (on demand) and the obstetric team approves it. However, an obstetric epidural service is very *labour intensive*. *Contraindications* and complications are as for spinal anaesthesia (see below).

The advantages of epidural analgesia are:
- Epidural anaesthesia eliminates the risk of general anaesthesia with failed intubation and aspiration, should caesarean section be required.
- There is less *drug-induced depression* in the foetus.
- Maintains *intervillous flow* and decreases *foetal acidosis* with prolonged labour.
- *Mother involved* in the birth**.** Epidurals provide excellent pain relief, yet allow the mother to be awake and cooperative during labour.
- Mother awake and *pain free post-operatively*.

- Earlier *breast-feeding* promoted.

Specific indications for epidurals in obstetrics are:

- *Pre- eclampsia*, if the *platelet count* is more than $100\ 000 \times 10^9\ L^{-1}$.
- During *premature labour*, the epidural allows controlled delivery of the baby.
- If *caesarean section is foreseen*, the epidural can be used for analgesia, and converted to epidural anaesthesia if the epidural catheter is already in situ. In diabetics, epidural analgesia is advantages since babies are often big, and prolonged labour more likely. Furthermore, it increases intervillous blood flow, and decreased postoperative complications.
- *Heart valve* lesions.

Drugs used for epidural analgesia during labour

Dilute mixtures of local anaesthetics (0.0625-0.125% bupivacaine), with or without opioids (sufentanil 0.2 μg ml^{-1} to 0.5 μg ml^{-1}), can be used to provide analgesia during a lumbar epidural (*but there are several recipes, including patient-controlled epidural analgesia*). These drugs work synergistically, which allows for lower concentrations of drug used and a decreased incidence of side effects.

Example: For epidural analgesia using 200 ml of a solution of 0.1% bupivacaine solution with 0.2 μg ml^{-1} sufentanil, do the following:

- An epidural catheter is inserted at level L3/4 or L4/5.
- Ideally the hospital pharmacy should *prepare the solutions sterilely*.
- *Bupivacaine*: A 0.1% solution contains 0.1 g bupivacaine = 0.1×1000 mg = 100 mg in 100 ml. In 200 ml there is 2×100 mg bupivacaine = 200 mg bupivacaine. Bupivacaine is marketed as 10 ml ampoules containing 0.5% bupivacaine and 20 ml ampoules containing 0.5% bupivacaine as well as adrenaline 0.002 μg ml^{-1}. A bupivacaine 0.5% injection contains 0.5 g = 500 mg in 100 ml = 5 mg ml^{-1}. Therefore, 200 mg is contained in 200/5 = 40 ml of the bupivacaine 0.5% injection.
- *Sufentanil*: In 200 ml of a solution containing sufentanil 0.2 μg ml^{-1}, there is 200 ml × 0.2 μg ml^{-1} = 40 μg sufentanil. Sufentanil injection contains 10 μg in 2 ml. Therefore, (40 μg/10 μg) × 2 ml = 8 ml sufentanil injection containing 10 μg in 2 ml.
- *The total volume of additions* is 40 ml of bupivacaine + 8 ml of sufentanil = 48 ml. You remove 48 ml from a bag containing 200 of *saline*. Then 40 ml of bupivacaine 0.5% and 8 ml (4 ampoules) of sufentanil is added sterilely.
- *__Label the bag clearly as follows__*:

EPIDURAL INFUSION
Contains: Bupivacaine 0.1%
Sufentanil 0.2 μg per ml
Infuse ***__EPIDURALLY__*** at 10 ml per hour.
Prepared by Dr IN Kraam
Time: 10:00 11 September 2012
Contact number: 078 910 1112

- *Dose*: After a *bolus* dose of 10 ml, the solution is *infused epidurally* at a rate of 8 ml h^{-1} to 12 ml h^{-1}.

CHAPTER 22

PAEDIATRIC ANAESTHESIA

Educational objectives:
- Babies are not very small adults
- Anatomy and physiology of the infant
- Physiology/pathology of prematurity
- Pharmacological differences
- Premedication and NPO periods
- Monitoring
- Induction.
- Small babies may have little reserve during intubation and may desaturate
- Intravenous Access
- Airway management and ventilation
- Maintenance
- Intra-operative fluid requirements
- The ambient temperature is very important when anaesthetizing small babies
- Pain relief

Paediatric anaesthesia encompasses anaesthesia for *neonates* (first 30 days of life), *infants* (1 month to 1 year), and *children* (1 year to 12 years). Paediatric patients have unique *anatomical, physiological, and pharmacological characteristics* that differ from those in adults. Although the principles are the same, these differences necessitate some modifications in anaesthetic management.

The aim of this Chapter 9s not to cover the whole spectrum of paediatric anaesthesia, but only to discuss the general principles. For a discussion of the anaesthetic management of specific paediatric medical and surgical diseases, you must consult standard anaesthesiology text books.

- **Anatomic and physiological differences**
  - *Body surface area (BSA) and thermoregulation*
  Body surface areas in infants are relatively larger than in adults; the head of an infant contributes substantially to the BSA of an infant. Therefore, naked infants should never be left exposed unless the ambient temperature is at least 23°C for term neonates and 28°C for premature infants (it is 1°C in adults). These are the *critical temperatures* and refer to the ambient temperatures below which the core temperature of the naked patient will decrease. The temperatures at which the body consumes the least oxygen (neither sweating nor thermogenic) are the *neutral temperatures* (Table 1).

Table 1 Critical and neutral ambient temperatures

Patient	Critical	Neutral
Premature infant	28°C	34°C
Term infant	23°C	32°C
Adult	1°C	28°C

Infants younger than 3 months do not shiver. Therefore, they are dependent on *non-shivering thermogenesis* to maintain normothermia. Lipolysis followed by consumption of AcCoA (oxidative phosphorylation) in *brown fat* is responsible for non-shivering thermogenesis. In neonates, about 4% of the body mass consists of brown fat. Brown fat of neonates is rich in mitochondria, and has a rich sympathetic nervous system innervation. It is distributed *superficially* over the shoulders, neck, and between the scapulae. *Deep brown fat* is occurs in the mediastinum and retroperitoneally around the kidneys. Metabolism of brown fat is limited in premature infants. Volatile anaesthetics inhibit thermogenesis in brown fat. Brown fat disappears by the age of one year.

Since infants become hypothermic easily, measures must be taken to prevent it. These include:

- *Theatre* temperature of about 26°C
- Warming and humidifying ventilatory *gasses* (circle system)
- Warming *blankets* (Bair Hugger)
- Radiant *over-head heaters*
- Warm intravenous *fluids* and warm fluids to disinfect the operating field.
- Cover the head and limbs with orthopaedic wool

o *Oxygen consumption (VO_2)*

Oxygen consumption correlates better with body surface area than with body mass. Therefore, oxygen consumption per kg is larger in infants than in larger patients. VO_2 patients of all sizes = $10 \times (kg)^{0.75}$. In an infant of 1.5 kg it is $10(1.5)^{0.75}$ = 13.6 ml min^{-1} = 16.6 ml min^{-1}/1.5 kg = 9.0 ml kg^{-1} min^{-1}. In an adult of 70 kg it is $10(70)^{0.75}$ = 13.6 ml min^{-1} = 242 ml min^{-1}/70 kg = 3.5 ml kg^{-1} min^{-1}.

o *Relative to body size, the head is larger and occiput more prominent*

In adults, a pillow is placed underneath the head to facilitate mask ventilation and intubation. In small children and babies, a rolled up towel is place behind the shoulders to compensate for the relatively large occiput (Figure 1).[41]
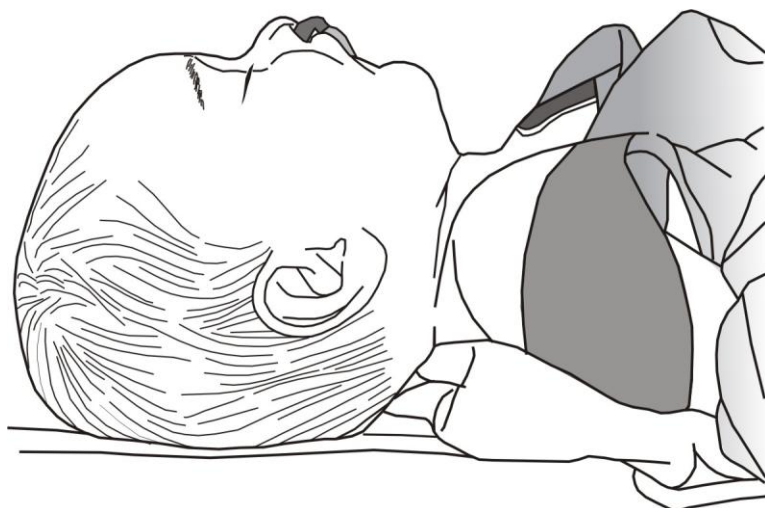
Figure 1 Elevation of the shoulders of the infant for airway management[41]

o *Narrow nasal passages*

Since infants are obligate nasal breathers, a nasogastric tube may increase the work of breathing. This effect is aggravated by oedema of the other nasal passage after nasotracheal intubation.

o *Large tongues*

Neonates and infants have relatively large tongues, which complicates mask ventilation and laryngoscopy. Laryngoscopy is further complicated by the long floppy epiglottis, short neck and more cephalad larynx (in adults the larynx is at the level of C6, in neonates at C4, and in premature babies as high as C3), making the larynx appear more anteriorly on laryngoscopy.

o *Long floppy epiglottis*

When using a curved (Macintosh) laryngoscope blade, is glided over the tongue until its tip is positioned in the vallecula (the recess between the root of the tongue anterior and the epiglottis just posterior where it flaps over the vocal cords). Due to its length in infants, the epiglottis tends to fall backwards to obscure the vocal cords when using the curved blade. To overcome this problem, ***a straight blade (Miller) is used to intubate infants – especially in neonates***. As opposed to the curved blade, which is positioned in the vallecula anterior to the epiglottis, the *straight blade is positioned posterior to the epiglottis to displace it anteriorly to expose the vocal cords*.

Since the vocal cords tend to hide behind the tongue and epiglottis, it is often necessary that

your assistant applies pressure on the cricoid ring. Furthermore, it is useful to *insert a stylet* into the ET tube to curve the tube anteriorly to guide the tip into the trachea. *Beware that the tip of the stylet does not stick out* from the ET tube since it will injure the airway.

Very often *a two-person intubation is done* in infants: the one does the laryngoscopy and manipulate the cricoid and thyroid cartilages to display the vocal cords; the assistant then intubates. Therefore, before you attempt induction and intubation of an infant (actually all patients), see to it that you have a curved and straight laryngoscope blade, a stylet, and a capable assistant.

o *Narrow cricoid ring*
The narrowest part of the airway in adults is the glottis while in children *younger than 5 years* it is *the circular to ellipsoid cricoid cartilage*. Therefore, tracheal tubes can be used to get a fairly good (but still incomplete) seal between the circular *uncuffed* tube and cricoid ring.

The following formula is used to **calculate the size (inner diameter in mm) of the uncuffed endotracheal tube** for Caucasian children:

$$(age/4) + 4.$$

A tube of half a size bigger and smaller should also be available. E.g., in an infant of 1 year, the tube size is $(1/4) + 4 \approx 4.0$, but if it is too large, insert a 3.5 mm tube; if it leeks (audible leak at an inspiratory pressure of > 25 cm H_2O), insert a 4.5 mm tube.

Usually, uncuffed tubes are used in children < 10 years. *Cuffed paediatric tubes* are available, but since the cuff takes up space around the tube, a tube of half a size (0.5 mm) smaller must be used.

o *Short trachea*
The neonatal trachea is only about 4 cm long. At 2 years, it is about 5 cm, at 3 years about 6 cm, and about 13 cm in adults. A shorter trachea makes endobronchial intubation a real concern.

In infants, the **depth** (in cm) of an oral endotracheal tube is about

$$(7.5 + 1 \text{ per kg}) \text{ at the upper alveolar ridge,}$$

e.g. in an infant of 2.5 kg, the tube is inserted to $(7.5 + 2.5) = 10$ cm. For nasotracheal intubation, 1 cm to 2 cm is added.

In children *with normal milestones* an oral tube is inserted to

$$0.6(\text{age in years}) + 11 \text{ cm or } 0.5(\text{years}) + 12 \text{ at the upper incisors,}$$

e.g. in a child of 4 years, the tube is inserted to $0.6(4) + 11$ cm $= 2.4 + 11$ cm ≈ 13.5 cm (or $0.5 \times 4 + 12 \approx 14$ cm). There is *large anatomic variability* amongst neonates and infants. Therefore, these formulae should only be used as a guide and clinical confirmation by inspection of the chest (equal expansion) and *auscultation in the axillae* (bilateral and equal air entry) is still essential. Correct placement of the tube is further confirmed by a *sustained capnogram* and acceptable airway pressures (< 25 cm H_2O in infants).

o *The thoracic cage and diaphragm*
The *ribs* are more horizontal and pliable. Since the bucket handle effect of the horizontal ribs is less effective during inspiration, babies are more dependent on diaphragmatic breathing. The *diaphragm and the intercostal muscles* contain more type II (fatigue easily) than type I muscle. Infants have *less and smaller airways*, which increases airway resistance. Although the *compliance* of the thoracic cage is higher than in adults, the compliance of the immature lungs is less since the lungs have *less alveoli* (complete at the age of eight years). Neonates, especially if premature, have less *surfactant*, which decreases compliance. Of all these differences, only the more compliant chest wall decreases the work of breathing; all the other differences increase the work of breathing.

o *Lung volumes and ventilation*
On a per kilogram basis adults and infants have similar lung volumes and capacities, i.e. tidal volumes, dead space, and functional residual capacities (Table 2). Since infants have higher

oxygen consumptions, they have higher minute volumes.

o *Work of breathing*

These anatomical and physiological factors combined with the fatigability of the ventilatory muscles, and the *higher oxygen consumption* make infants very vulnerable to hypoventilation if the work of breathing or the oxygen consumption increases. This happens with narrowing of the upper and lower airways (inflammation, secretions) and splinting of the diaphragm.

o *Control of breathing*

Infants, especially those with a *postconceptional age of less than 60 weeks* have an immature control of breathing and are prone to apnoea. The more premature the infant, the higher the likelihood to develop apnoea spells. *Apnoea spells* are defined as cessation of ventilation of $\geq$ 30 seconds and have an obstructive and a central component. The present an immature control of breathing and is aggravated by hypothermia, hypoxaemia, hypercapnia, hypoglycaemia, anaemia, sepsis, intravenous and inhalational anaesthetic agents, as well as regional anaesthesia. Elective surgery should preferably be postponed until infants are older than the critical postconceptional age of 60 weeks. If surgery is done before this age, perioperative apnoea monitoring as well as factors that may exacerbate apnoea spells must be monitored and prevented.

Table 2 Ventilatory variables in infants and adults

Variable	Infants	Adults
Oxygen consumption (ml kg^{-1} min^{-1})	6.5 to 8.5	3.5
Minute volume (ml kg^{-1} min^{-1})	100 to 150	70 to 100
Tidal volume (ml)	6 to 8 ml kg^{-1} min^{-1}	6 to 8 ml kg^{-1} min^{-1}
Respiratory rate (min^{-1})	30 to 50	12 to16
Functional residual capacity (ml kg^{-1})	30	30
Dead space (ml kg^{-1})	2 to 2.5	2
PaO2 breathing room air (mm Hg)	65-85	85-100mmHg
PaCO2 breathing room air (mm Hg)	30 to 36	35 to 45

o *Airway management and ventilation*

As is the case in adults, airway management starts with the correct positioning of the patient to optimize mask ventilation and intubation. Due to the prominent occiput in infants, this is best achieved by placing a rolled up towel beneath the shoulders.

The need for intubation is determined by the patient's underlying condition and the surgery. If the surgery is short and peripheral in nature and no muscle relaxation required, an appropriate sized laryngeal mask can be inserted.

For anaesthetic circuits for paediatric patients, please see the discussion about the Jackson Rees circuit in Chapter 4. Older anaesthetic machines are designed for adults and cannot reliably deliver the small tidal volumes and rapid ventilatory rates that are required in neonates and small children. Large tidal volumes to a child can cause barotrauma to the lungs. Therefore, the pressure-limited mode of ventilation should preferably be used in neonates, infants, and small children.

Newer anaesthetic machines allow the anaesthetist to type in the patient's mass. The ventilator then delivers a safe pressure-regulated tidal volume. In children weighing less than 10 kg, a pressure limited to 10 cm H_2O to 15 cm H_2O results in adequate tidal volumes. An adequate tidal volume clinically results in a just visible rise in the chest wall, but modern ventilators are equipped with spirometers that display the ventilation variables, i.e. tidal volume, inspiratory pressure, and minute volume.

Calculating the ventilator settings
- *The Busch method to calculate the minute volume (you must know this method)*
For each kg $\leq$ 10 kg 200 ml kg^{-1} min^{-1}
For each kg > 10 kg and $\leq$ 15 kg + 150 ml kg^{-1} min^{-1}

For each kg > 15 kg + 100 ml kg^{-1} min^{-1}

Example: A child has a body mass of 17 kg = 10 + 5 + 2 kg
Minute volume = (10 × 200) + (5 × 150) + (2 × 100) ml min^{-1} = 2950 ml min^{-1}
Tidal volume = 17 kg × 7 ml kg^{-1} = 119 ml
Ventilatory rate = 2950 ml min^{-}1/119 ml = 25 min^{-1}

Another way to calculate minute volume is as follows
The minute ventilation (when you set the ventilator for a patient) is proportional to the VO_2, and of course, the CO_2 production (VCO_2). Remember that the body produces between 0.7 ml and 1.0 ml CO_2 for each ml of O_2 consumed (that is called the *respiratory coefficient*, R). The concentration of CO_2 in alveolar gas is about 35 mm Hg, or about 5%, i.e. 35mm Hg as a fraction of ambient pressure (760 mm Hg at sea level or 650 mm Hg in Pretoria). Therefore, the minute alveolar volume (to get rid of the produced CO_2) is about $100/5 × VO_2$ or $20 × VO_2$.

Example: what are the ventilator settings for an infant of 3.5 kg?
$VO_2 = 10(3.5)^{0.75} = 25.6$ ml min^{-1}
Let us assume that the respiratory coefficient = 1.
Therefore, $VCO_2 = VO_2 = 25.6$ ml min^{-1}
Therefore, *minute alveolar volume = (100%/5%) × 25.6 ml min^{-1} = 5 × 25.6 ml min^{-}1= **512 ml min^{-1}***
However, remember, the minute volume consists of alveolar ventilation + dead space (ventilation of the airways and unperfused areas of the lung), which amounts to 40% of the minute ventilation.
Therefore, minute volume = alveolar ventilation (60%) + dead space ventilation (40%).
Therefore, minute volume = 100%/60% × ***512 ml min^{-1}*** = **853 ml min^{-1}**

The tidal volume is between 6 ml kg^{-1} and 8 ml kg^{-1}
Therefore the *tidal volume is 3.5 kg × say 7 ml kg^{-1} = 25.0 ml.*
Therefore the *ventilatory rate* is **853 ml min^{-1}**/25.0 ml = 34 min^{-1}.

The inspiratory fraction of oxygen (FiO$_2$) should be limited during ventilation, especially in premature infants, since they are prone to develop *retinopathy of prematurity*. High FiO$_2$s also aggravate lung injury. *It is recommended that the FiO$_2$ should be just enough to maintain the haemoglobin oxygen saturation between 88% and 92% in neonates. High PaO$_2$s are also possibly detrimental in older patients (neurotoxicity).*

o *Cardiovascular system*
The myocardium consists of more connective tissue than contractile elements than in adults. This makes the heart less compliant and decreases the stroke volume. Therefore, cardiac output is more *dependent on the heart rate* than in adults to increase cardiac output. There may be *residuals of the foetal circulation*, namely a patent ductus arteriosus, patent foramen ovale and a reactive pulmonary vascular bed with high vascular resistance.

Any factor that increases the pulmonary vascular resistance, e.g. hypovolaemia, hypotension, anaemia, hypoxia, acidosis, and hypothermia promotes *reinstitution of the foetal circulation*. That means that blood passes from the pulmonary artery to the aorta and from the right atrium to the left atrium. Since blood does not perfuse the alveoli, *the clinical signs of return of the foetal circulation* are hypotension, desaturation, and a decrease in the end-tidal CO_2.

If *air bubbles* would be allowed to enter the venous circulation, the air emboli may pass from the right atrium to the left atrium and from the pulmonary artery to the aorta and embolise to vital organs, especially the brain. This is called *paradoxical air embolism*. Therefore, you ensure that venous lines are free of air before you connect them to the venous cannula. You must also take care not to inject any air into a baby (actually, into any patient).

Since the cardiac output at rest is near the maximum in babies, they have a *limited cardiac re*serve. Adults can increase their cardiac output by 300% from rest, whereas infants can only increase it by 30% to 40%. The *sympathetic system and baroreceptor reflexes* are immature leading to a lower blood pressure and a limited ability of the vasculature to respond to

hypovolaemia with vasoconstriction. The *catecholamine stores* are maintained at a lower level and the response to exogenous catecholamines is blunted. The *parasympathetic system matures earlier* and therefore the heart responds to hypoxia with a bradycardia leading to severe reductions in cardiac output. The *immature heart is also more sensitive to the calcium channel blocking abilities* of the volatile anaesthetics and opioid induced bradycardia. Therefore, infants are very *vulnerable to hypovolaemia and cardiac suppression*.

o   *Haematological system*
    Premature and full-term neonates have normal *platelet-vessel interaction* but platelet aggregation is transiently impaired. Neonates have limited stores of vitamin K. Therefore, the *vitamin K dependent clotting factors* are decreased during the first few days.

    A new-born's haematocrit is 55%, decreases to 30% (physiological anaemia) at 3 months, where after it increases. The high haematocrit at birth is due to the foetal PaO2 (about 40 mm Hg). The polycythaemia and low P50 of foetal haemoglobin (19 mm Hg compared with 26.5 mm Hg in adults) ensures an adequate oxygen supply necessary for the high foetal and neonatal oxygen consumption. At 6 months of age the oxyhaemoglobin dissociation curve approximates that of adults. Therefore, anaemia in infants is defined as a haematocrit of $\leq$ 30%. When intraoperative blood loss is expected to decrease the haematocrit to below this level, blood must be available (see Chapter 18).

o   *Fluid distribution and kidney function* (see also Chapter 18)
    Total body water and extracellular fluid (ECF) are increased. In neonates the ECF is equivalent to about 40% of body weight compared with about 15% in adults. At the age of 24 months the ECF volume relative to body weight is similar to that in adults.

    Kidney function is completely developed at the age of 6 months. Patients younger than 6 months have a decreased creatinine clearance, impaired sodium retention (obligate *sodium losers*), poor dilutional and concentrating abilities, and impaired glucose excretion and bicarbonate reabsorption. On the first day, a neonate excretes a mean of 8.5 ml kg^{-1} day^{-1}, and a mean of 76 ml kg^{-1} day^{-1} on day 7, while young men excrete a mean of 20 ml kg^{-1} day^{-1}. *Therefore, infants need more fluid than children and adults.* Meticulous detail to fluid administration in the peri-operative period is imperative. Adequate exogenous sodium, glucose and water must be provided without volume overloading the child (see Chapter 18).

o   *Gastrointestinal and hepatic function*
    The ability to coordinate swallowing and respiration is fully developed at the age of about 5 months. Therefore neonates and infants have a relative high incidence of gastro-oesophageal reflux. At term the liver is relatively immature, resulting in impaired conjugation function. Neonates also have low glycogen stores and are unable to handle large protein loads.

o   *Metabolic differences*
    Neonates, especially premature neonates have *limited metabolic reserve*. They are prone to:
    - Hypothermia
    - Hypoxaemia
    - Hypercapnia
    - Hypoglycaemia (glucose < 1.5 mM in premature neonates and < 2.0 mM in term neonates younger than 3 days, and < 2.5 mM after 3 days)
    - Hypocalcaemia (total serum calcium < 1.8 mM and ionised calcium < 0.8 mM), and anaemia (haematocrit < 40% in neonates; < 30% in older infants)

    Therefore, *metabolic monitoring* is imperative pre-, intra-, and postoperatively. These metabolic abnormalities do not occur in infants only, but also in sick older patients (sepsis, malnutrition, dehydration). Patients with metabolic abnormalities present with *nonspecific signs*; the younger and the sicker, the more vague. These signs include:
    -   Apathy, apnoea, and hypotonia (hypothermia, hypoxaemia, hypercapnia, hypoglycaemia, anaemia)
    -   Irritability and convulsions (hypoglycaemia, hypocalcaemia)
    -   Hypertonia and muscle twitching (hypocalcaemia)

- Hypotension and bradycardia (hypoxaemia, hypoglycaemia, hypocalcaemia)
- Al these signs may also point to an underlying septicaemia and its sequelae, i.e. meningitis and pneumonia.
  o *Psychological*
  Each age group comes with a different degree of psychological maturation and concern. From 8 months to 4 years children suffer from separation anxiety, then from 4 years to 6 years they have misconceptions about surgical mutilation, between 6 years to 13 years they fear that they will not wake up. After 13 years of age the fear changes to fear of loss of control and body image issues. This should be taken into account when each paediatric patient and their family are approached.

Pharmacological differences

Drug dosing in the paediatric population is, as is the case in adults, based on body mass. The body mass for age at the 50th percentile can be calculated from the following equation:

$$\textit{Mass in kg at the 50th percentile} = (Age \times 2) + 9$$

Example:
What is the mass of a child aged 3 years?
Mass = (Age ×2) + 9 kg = (3 × 2) + 9 kg = 15 kg

Body mass does not reflect *body composition*, i.e. percentages of body water and fat. Remember that the neonate's body consists of about 80% water. In neonates, the extracellular component makes out about 40% of the body mass. Since water soluble drugs have larger volumes of distribution, e.g. muscle relaxants and most antibiotics, neonates and infants require larger doses. Due to the smaller in fat stores, drugs that depend on redistribution to fat tissue for the termination of their action have longer duration of action, e.g. sodium thiopental.

Plasma protein binding is decreased. Therefore, the doses of drugs that are highly protein bound, should be reduced, e.g. propofol and vecuronium. Remember, the main plasma protein in neonates is not albumin but alpha-fetoprotein. The immature liver and kidney function also contribute to changes in pharmacokinetics, especially a decreased clearance of drugs.

Infants have a higher alveolar ventilation to FRC ratio (as high as 5:1) resulting in rapid induction with and emergence from volatile anaesthetics. Therefore, the FA/FI ratio rises much steeper than in adults. The *minimum alveolar concentration* (MAC) is higher in infants than in neonates and adults (Table 2). Decreased requirements in neonates may be due to increased concentrations of progesterone and β-endorphins as well as an immature central nervous system.

The requirements of *muscle relaxants* are higher in neonates due to the increased volume of distribution and the increased number of embryonic neuromuscular receptors (extrajunctional post-synaptic nicotinic receptors). The *intravenous dose of suxamethonium in neonates* is at least 1.5 mg kg^{-1} to 2 mg kg^{-1}. Since suxamethonium often causes a bradycardia in neonates, it is advised that it is preceded by atropine 10 µg kg^{-1}, or it must be immediately available should a bradycardia follow.

Table 2 Minimum alveolar concentrations (MAC) (%) of anaesthetic vapours*

Agent	Neonates	Infants	Children	Adults
Halothane	0.87	1.1 to 1.2	0.87	0.75
Isoflurane	1.6	1.8 to 1.9	1.3 to 1.6	1.2
Sevoflurane	3.2	3.2	2.5	2
Desflurane	8-9	9 to10	7 to 8	6

*These figures are only rough guide lines; you must know the MACs in adults, and that they are higher in younger patients.

Induction and maintenance of anaesthesia

General anaesthesia can be achieved either with a volatile inhalational induction or an intravenous induction. Intramuscular induction is reserved for specific cases, such as severely combative children or children without an IV line and at risk of developing malignant hyperthermia (a group in which inhalational agent should be avoided).

Inhalational induction is the most popular method of induction in paediatric anaesthesia as it circumvents the need to cannulate small veins in an awake, uncooperative patient. The parents can be included in the process by placing the child on the mother or father's lap, providing an extra sense of security to the child.

A vapour induction for elective procedures is done in the following way: The patient is on a parent's or assistant's lap, a pulse oximeter is attached to the patient, and the tip of the capnography tubing is stuck to cheek near the nose. The Jackson Rees system is held by the assistant near to the patient's nose. The fresh gas consisting of 70% of nitrous oxide and 30% oxygen is opened to about 10 L min^{-1}. The nitrous oxide has a rapid effect. Sevoflurane (or halothane) is added to the fresh gas in 0.2 MAC increments to about 3 MAC. If the patient is peaceful, he/she can be covered with a light blanket to fill the gas in the enclosed space with vapour. Once the patient's muscle tone decreases, a mask can be placed over the mouth and airway, and, the nitrous oxide may be replace with air, and the flow decreased to appropriate levels. Older children can be placed on the theatre table and be induced using a mask. Remember to decrease the vapour concentration to about 1.5 MAC (end-tidal concentration) after induction!

As soon as the patient is under anaesthesia, an intravenous cannula can be inserted. ***Remember, do not fiddle with the patient (airway or intravenous access) during light plains of anaesthesia, since they tend to develop laryngospasm (see Chapter 3).*** Therefore, wait until the patient is in the *surgical plain of anaesthesia* before inserting an intravenous line.

If a rapid sequence induction is indicated, the patient is preoxygenated with 80% to 100% oxygen administered with a tight fitting mask for 3 minutes to 5 minutes, followed by the intravenous induction agent and suxamethonium. In a non-emergency setting, if the patient has an intravenous line *in situ*, preoxygenation is followed by an intravenous or vapour induction, followed by a non-depolarizing muscle relaxant.

Intravenous induction is done with sodium thiopental 3 mg kg^{-1}, propofol 2 mg kg^{-1} to 3 mg kg^{-1} or ketamine 2 mg kg^{-1}. Patients that are very combative or those with a history of *malignant hyperthermia* (MH) must be induced with *subcutaneous ketamine*. The *subcutaneous* dose is 10 mg kg^{-1}. Atropine 0.02 mg kg^{-1} can be administered subcutaneously to decrease secretions caused by ketamine.

Once the patient is asleep, an intravenous line is inserted where after a vapour or ketamine or propofol infusion (for MH-sensitive patients) can be used to maintain anaesthesia. As is the case with adults, opioids may be used if necessary. Keep in mind the increased sensitivity of neonates to the respiratory-suppressant effect of opioids.

Vascular access

Intravenous access can be extremely difficult in the infants. Familiarise yourself with the position of relative fixed veins on the hand, wrist, foot, ankle, and neck (see your anatomy atlas). If intravenous access is impossible, an *intraosseous needle* must be used (see Chapter 22). Special intraosseous needles are available, but an ordinary 18 G needle and can be used. The periosteum of the tibial tuberositas is numbed with lignocaine, where after the 18 G needle is inserted *sterilely* through the cortex into the epiphyseal cancellous or spongelike bone (Figure 1).[42] In infants and children up to 8 years, the preferred site is the *anteromedial surface of the tibia*, 1 cm to 2 cm below the tibial tuberositas. Here, the bone cortex is thin and easy to penetrate with a needle.[43]

Epiphysis

Diaphysis

Epiphysis

Articular cartilage
Spongy bone
Epiphyseal plate
Red marrow cavities

Compact bone

Medullary cavity

Endosteum

Yellow marrow

Periosteum
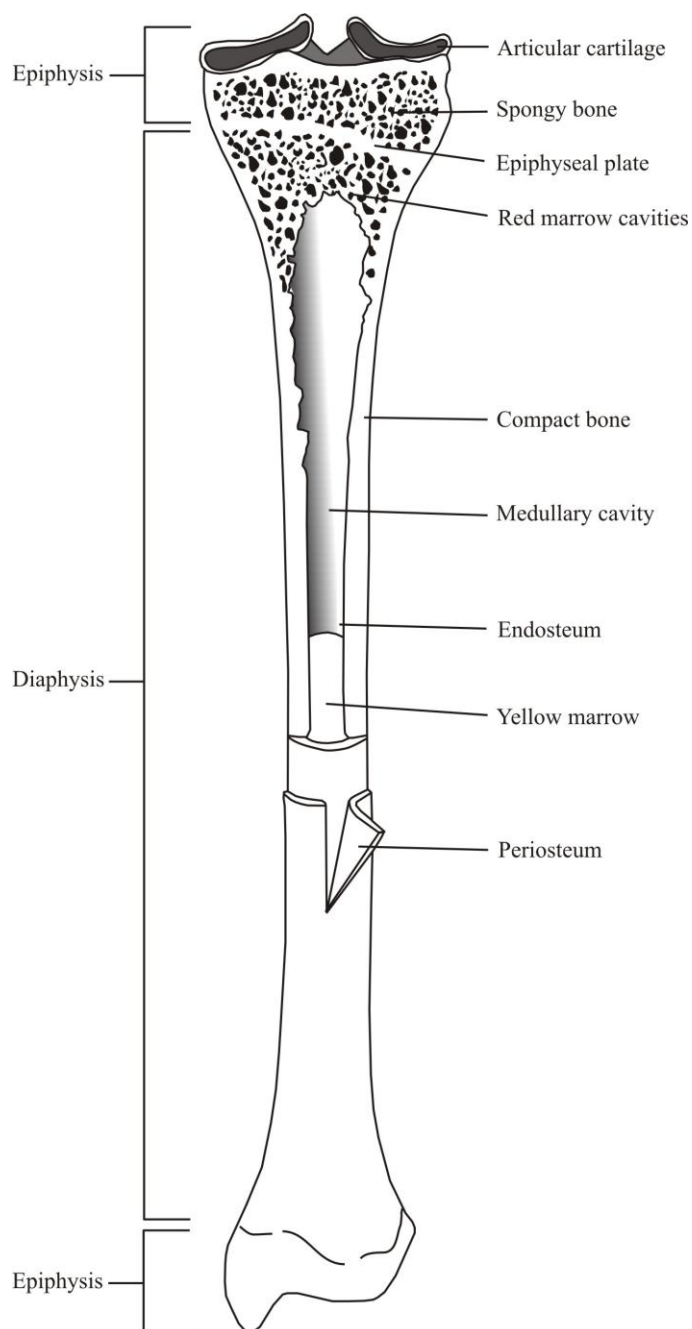
Figure 1 Tibia with epiphysis and sponge bone[42]

Premedication and nil per os periods
Nil per os (NPO) guidelines have been changed in recent years to prevent long periods of pre-operative starvation, which increases the stress response and postoperative nausea and vomiting.
Guidelines are as follows:
6 hours for solids and cow milk
4 hours for breast milk and non-clear fluids
2 hours for clear fluids

Sedative premedication can be given (preferable in children older than 1 year). Sedative premedication aims to achieve amnesia, anxiolysis, prevention of physiological stress, and analgesia. This facilitates a smooth induction of anaesthesia and separation from the parents. The oral route is generally preferred because it is more acceptable to both the child and the parents. The disadvantage of oral premedication is that it takes about 30 minutes to take effect. Premedication is given about 30

minutes preoperatively. *After the premedication has been administered, the child must not be left alone, but be monitored.*

The following oral premedication drugs are available at our Steve Biko Academic Hospital:
- *Midazolam* is a very effective sedative and amnesic. At present, only parenteral preparations (injections) are available; 15 mg in 3 ml and 5 mg in 5 ml. The dose is 0.25 mg kg^{-1} to 1mg kg^{-1}.
- *Tilidine* (Valoron drops) is an opioid dualist and effective analgesic. There is 2.5 mg of tilidine per drop. The dose is 0.7 mg kg^{-1} to 1.0 mg kg^{-1}.
- *Ketamine* is a very effective sedative and analgesic. At present only parenteral preparations are available; 10 mg per ml, 50 mg per ml, and 100 mg per ml.15 mg in 3 ml and 5 mg in 5 ml. The dose is 5 mg kg^{-1} to 10 mg kg^{-1} if given PO.
- Some anaesthesiologists routinely prescribe atropine 20 µg kg^{-1} per os. This dose decreases secretions and is antiemetic, but does not prevent intraoperative bradycardia.

Midazolam, tilidine, and ketamine taste very bitter and should mixed with sweet syrup, e.g. dextrose 50% injection or one teaspoonful of sugar and water to 10 ml. Since most surgical procedures cause substantial pain, we mix these drugs with paracetamol syrup (24 mg per 1 ml = 120 mg in 5 ml). The drug at the correct dose and smallest volume is added to an analgesic dose of paracetamol (20 mg kg^{-1}). Do *not administer these drugs as intranasal drops* since they may be toxic to the olfactory nerve endings.

Example:
Prescribe premedication of tilidine to a child of two years with a body mass of 12 kg.
Dose of tilidine: 1 mg kg^{-1}.
Therefore, the child must receive 12 kg × 1 mg kg^{-1} = 12 mg.
There is 2.5 mg drop^{-1}.
Therefore, the child must receive 12 mg/2.5 mg drop^{-1} = 4.8 drops ≈ 5 drops (or if you use a dose of say 0.8 mg kg^{-1}, (12 kg × 0.8 mg kg^{-1})/2.5 mg drop^{-1} = 9.6 mg/2.5 mg drop^{-1} ≈ 4 drops.
The tilidine drops are added to sweet syrup or to paracetamol syrup (preferable). If you use paracetamol, the dose is 12 kg × 20 mg kg^{-1} = 240 mg = 240 mg/24 mg ml^{-1} = 10 ml.
Therefore, the prescription will be as follows:
Valoron drops: 4 drops in 10 ml of paracetamol syrup per os about 30 min preoperatively.

Intraoperative fluid therapy (see Chapter 18)

Intraoperative monitoring
Monitoring (invasive and non-invasive) required in the children is similar to that of adults but with minor adjustments. First the *alarm limits* should be adjusted for each age group. *Appropriately sized accessories* should be available, e.g. blood *pressure cuffs* and *pulse oximetry sensor*. Apart from monitoring ventilation and cardiac output, and correct placement of the ET tube or LM, *end-tidal PCO$_2$* (PETCO$_2$) also gives an early warning of malignant hyperthermia.

The small tidal volumes and rapid breathing rates in infants present difficulties in some of the capnograph models. Mainstream analyser is less accurate in children weighing less than 10 kg. With side-stream analysers, the inspired PCO$_2$ can appear falsely high and the PETCO$_2$ falsely low. The degree of error can be minimized by using a shorter sampling line, lower gas sampling flows (100 ml min^{-1} instead of 200 ml min^{-1}), and placing the sampling site as close to the endotracheal tube as possible (usually attached to the filter).

Perioperative ventilatory and metabolic monitoring is essential in infants and children (see above under control of breathing and metabolic differences).

Analgesia (see also Chapter 10)
Children as well as infants experience pain. Considerable maturation of pain pathways has occurred by 26 weeks of gestation. Therefore, *neonates do experience pain* and respond to pain or injury with specific behaviour and with autonomic, hormonal, and metabolic stress responses. Extreme pain

experienced during the neonatal period may have long-lasting adverse effects. Direct injections are painful and must be avoided in children. The oral, intravenous, or rectal routs may be used. All children must be *admitted to an appropriate postoperative unit to monitor the side-effects* of analgesics, e.g. ventilatory suppression, sedation, nausea, and vomiting. Pain should be managed by employing a *multimodal approach* by using drugs of different classes as well as local anaesthesia.

Paracetamol remains the most important analgesic in neonates and children and can be administered orally, rectally or intravenously. *Opioids* can be used in the peri-operative period. The opioid used depends on the type of the surgery. Shorter acting opioids such as alfentanil, fentanyl, and sufentanil are used intraoperatively and in the recovery room. However, the most useful opioid analgesics are morphine injections and tilidine drops. The dose of tilidine is 0.7 mg kg^{-1} to 1.0 mg kg^{-1} at 6-hourly intervals. The intravenous dose of morphine in children older than 6 months is 50 µg kg^{-1} to 100 µg kg^{-1} every 4 hours to 6 hours, and in babies younger than 6 months, 25 µg kg^{-1} to 50 µg kg^{-1} every 4 hours to 6 hours. Patients with renal failure should not receive morphine since the active metabolites have very long (up to 30 hours) $t_{1/2}$s and accumulate.

Ibuprofen and diclofenak are popular *NSAID*. NSAIDS should only be administered once haemostasis has been accomplished and if the surgeon agrees with the use of these drugs, e.g. after orthopaedic surgery. Gastro-intestinal side effects are uncommon.

The most common *regional technique* employed in children is a *caudal block*. This block can provide both intra-operative and post-operative pain relief for various abdominal, pelvic and bilateral lower limb procedures. Bupivacaine is the drug commonly used. The maximum dose is 2 mg kg^{-1}. The solution containing 5 mg ml^{-1} is used. This is diluted to the volume required as follows: 0.5 ml kg^{-1} for pelvic procedures, 1 ml kg^{-1} for procedures up to the umbilicus and 1,5ml/kg for procedures above the umbilicus. Caudal block is normally done with the patient in the lateral position and the landmark used is the sacral hiatus. A "pop" can be felt when the sacrococcygeal membrane is penetrated either by a 22G-needle or a paediatric epidural needle. The pain relief provided by caudal anaesthesia will last for 4 hours to 6 hours. Allowing the parents to soothe the child in the post-operative period may assist with pain relief.

CHAPTER 23

ANAESTHETIC MANAGEMENT OF THE TRAUMA PATIENT
(See also Chapters 18 and 27)

Key points
- Pre-assessment of trauma patient
- Initial basic monitoring
- Resuscitation according to ABCD
- Management of hypoxia
- Intra-operative ventilation
- Circulation with haemorrhage control
- Guidelines to estimate blood loss
- Types of fluid to be given to hypovolaemic patient
- Disability
- Neurological fall out assessment e.g. Glasgow Coma Scale
- Exposure & environmental control
- Hypothermia
- Acidosis. Acidosis – shifts oxygen saturation curve to the right – unloads O_2 easier, therefore do not hyperventilate patient and make them alkalotic

In this chapter, the focus is on the anaesthetic management of the patient who has sustained trauma. The trauma may vary from minor with little systemic effects to major trauma with significant systemic effects. Bear in mind that the outcome of a patient with limited vital organ reserve sustaining minor trauma, may be similar to that of a patient with good vital organ reserve sustaining major trauma.

The management of patients presenting for emergency procedures is at higher risk for medico-legal consequences. The anaesthetists may be implicated in neurological injury during the resuscitation process. Good clinical notes during the whole process will avert medico-legal actions.

In this discussion the emphasis will be on the worst case scenario, but the student must be able to apply the principles in all situations.

The anaesthetist should ideally be involved in the emergency department (ED) with the resuscitation of the trauma victim. Presently, most trauma patients are only seen by the anaesthetist on the operating table for the first time.

Pre-operative assessment
- **History**

  If the patient is conscious and has the ability to communicate, the anaesthetist must obtain a history. Otherwise, a history is obtained from relatives, the surgeon and ED officer. The history involves the condition of the patient before injury, during injury (what happened), and after injury (**CAMELCS**):

  o *Chronic illnesses*

  The presence of *major organ disorders* increase morbidity and mortality after trauma. These include cardiovascular (including cerebrovascular disease), liver, renal, and pulmonary diseases. These patients mostly need *increased perioperative monitoring and care*.

  o *Allergies and addictions*

  Conscious patients may be able to give a history of allergies, or such information may be indicated on a Medic Alert bracelet. Patients may disclose addition or the use of recreational drugs (present or past), but signs of the use of addiction may only be suggested by body habitus, skin lesions, breath odour, etc. Recreational drug use may have serious implications, i.e. the ability to launch a stress response and interactions with anaesthetic agents.

  o *Medication*

  The anaesthetist must be aware of chronic medication, which the patient takes. These agents may compromise resuscitation and interact with anaesthetics. They include angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers, β blockers, psychotropic agents, etc. The anaesthetist must also enquire about interventions since admission, including cardiovascular drugs, antibiotics, sedatives, fluid (what, how much, and effect), and angiographic procedures involving radiocontrast (remember the nephrotoxicity of these

substances).

- o *Events or environment related to injury*
  These include the mechanism of injury, including sharp or blunt, penetrating of superficial, accelerating or decelerating, crush injury, burns, inhalation injury, electrocution, environmental temperature, etc.
- o *Last meal*
  In principle, *all trauma victims are at risk aspiration*. Most trauma victims had eaten or took recreational substances (alcohol, amphetamine analogues, cocaine, etc.) less than six hours previously. Moreover, the stress response to injury *slows gastric emptying*; it does not matter how long they are nil per os, stomach emptying decreases from the moment of injury. Therefore, it is unnecessary (and dangerous) to postpone procedures to get patients nil per os (more than six hours).
- o The history is followed by the **C**linical examination and **S**pecial investigations

- **Clinical examination**
  Special investigations *do not replace the clinical examination*, namely neurological state, the airway (remember airway implications of head injury, facial injury, and neck injury), cardiac, vascular, respiratory (upper airway, lower airway, lungs; see Chapter 3), abdomen (remember abdominal compartment syndrome), limbs (remember vascular occlusion, crush injury). Take note of *tubes* (airway, intravenous, intra-arterial, central venous, intercostal, gastric, urinary), whether they are patent, what fluids are administered into them, or what fluids are draining from them.

  Regarding the neurological state, the degree of disability must be documented and the patient treated accordingly. This is particularly important regarding transport, movement, and positioning of the patient, as well as airway management (see Chapter 3). A quick neurological examination to document the level of consciousness includes the response to different stimuli (AVPU):
  Alert, **V**ocal stimuli response, **P**ainful stimuli response, and **U**nresponsive.

  A more thorough neurological examination, including the Glasgow Coma Scale should be done after the patient has been stabilized. Although this is primarily performed by the ED physicians, the anaesthetist must take note of it and document it. *A decreased level of consciousness and decreased movement must not be ascribed to the effects of hypoxia, drugs, or metabolic derangements, before head trauma and spinal cord injury have been excluded.*

- **Special investigations**
  Certain *baseline special investigations* are routinely performed, including haematological (haematocrit), blood biochemistry (urea, creatinine, electrolytes, acid-base state, glucose), and radiological as indicated by the type of injury. Regarding radiological investigations, the anaesthetist must specifically look at the ***reported investigations of the spine*** and involvement of the airway. Regarding the *chest radiograph*: look for surgical emphysema, diaphragmatic hernia with intestines in the thorax, rib fractures, pneumothorax, tension pneumothorax, haemothorax (can contain a large volume of blood), pulmonary contusion, foreign objects (knife blades, bullets, aspirated objects), mediastinal shift, pericardial effusion. On the *abdominal radiograph*: look for gas under the diaphragm, distended bowel, pelvis fractures, and foreign bodies.

  Never evaluate injuries in isolation of each other; there is generally *anatomical and physiological crosstalk between injuries*, e.g. pneumothorax → tension pneumothorax, neck injury → airway involvement, long bone fractures → fat embolism syndrome, crush injury → renal failure, vascular injury → angiography → renal injury, abdominal distension → renal failure, pink urine → renal failure.

  Patients presenting for *life-saving procedures* are often anaesthetised without knowledge of the above-mentioned information. Therefore, the anaesthetist must be *vigilant in identifying co-morbidities and exposure to xenobiotics intraoperatively*.

The anaesthetist *must document his pre-, intra-, and postoperative findings* and management as soon as possible. It does not only contribute to improved care, but may become evidence in future litigation – which is not uncommon in trauma-related procedures.

Lastly, the trauma team must be on the lookout for *living will* instructions on bracelets, e.g. do not intubate, do not resuscitate, organ donor, etc.

Principles in anaesthetising the trauma patient

As has been illustrated in previous chapters, the anaesthetist must adhere to the following principles:

- *Anatomical considerations*
  What is injured from the head to the toe? What has been damaged from the skin to the bone (see Chapter 26), brain, spinal cord, bone marrow, blood vessels, and blood? What has been damaged from the mouth/nose to the pleura (including the airway)? What has been damaged from the mouth to the anus and urethra?

- *Physiological considerations*
  In what way do the anatomical defects impact on vital organs? The functions of the vital organs are to keep the organism alive during the acute phase after anatomical injury. Therefore, primary anatomical injury to the vital organs has a very high morbidity and mortality.

  The vital organs are the brain, heart and blood vessels (including the endothelium), airways (upper and lower) and lungs, liver and gastrointestinal tract (see Chapter 16), kidneys (see Chapter 16), endocrine organs (remember, all vital organs have endocrine functions involved in survival of the organism; see Chapter 17), haemopoietic system (blood-forming tissue, blood cells, haemostatic system, cellular and humoral immune systems).

  Delayed or inadequate resuscitation, as well as the inability of vital organs to compensate for anatomical injury (too large an insult or limited premorbid vital organ reserve), leads to tissue loss (e.g. loss of a limb) and in severe cases, loss of vital organ function. Vital organ damage include brain injury, cardiac failure, vascular failure (hypovolaemia, endothelial dysfunction, vasoplegia), lung injury, liver and gastrointestinal failure, kidney failure, haemopoietic failure (anaemia, coagulopathy, uncontrolled inflammation).

  A localized anatomical injury may have distant effects on vital organs, e.g. tibial fracture → compartment syndrome → kidney failure; long bone fracture → fat embolism syndrome → respiratory failure; abdominal trauma → abdominal compartment syndrome → renal failure, etc.

  The complication of physiological injury (end organ failure) is homeostatic (enzyme) failure, including hypoxia, acidosis, and electrolyte disturbances.

- *Pharmacological (xenobiotic) considerations*
  The trauma victim may have been exposed to xenobiotics that lead to injury, e.g. recreational substances (acute or chronic addition), or toxins (smoke inhalations, irradiation, organophosphates, medicine overdose). The type of injury determines the choice of resuscitation agents (fluid, drugs) and anaesthetic drug, but keep in mind that end organ dysfunction invariably has pharmacokinetic and pharmacodynamic implications.

  Blood loss decreases blood volume (central volume of distribution), dilution of plasma protein concentrations, and blood cells. Dehydration (long periods nil per os, gastrointestinal losses, exposure to the elements) causes haemoconcentration but a decrease in in central volume of distribution. Vasoplegia, e.g. after spinal injury, is treated with plasma expanders and vasoconstrictors, and is accompanied by haemodilution (increased free drug concentrations) and an increased central volume of distribution.

These changes usually increase the effects of drugs, including anaesthetic drugs; both regarding pharmacokinetics (effect size) and pharmacokinetics (duration of effect). These changes are mostly due to an increased free drug concentrations and a smaller is volume of distribution. Free drug concentration refers to the fraction of total blood drug concentration that is not bound to plasma proteins or blood cells, interacts with receptors, and is (more readily) cleared from the plasma by the liver and kidneys.

- *Monitoring considerations*
  Monitoring refers to the detection of what happened (radiological, chemical, haematological), end organ function (cerebral, cardiac, vascular, renal, etc.), and the effect of resuscitation and anaesthesia on end organ function. Minimum intraoperative monitoring for major trauma is:
  o Non-invasive blood pressure
  o ECG
  o Pulse oximetry
  o Capnography
  o Core temperature
  o Urinary catheter
  o Metabolic and haematological monitoring using blood from an central venous and/or arterial cannula

Therefore, trauma should always be regarded as a systemic disease with anatomical and physiological, pharmacological, and monitoring components. The anaesthetists should come in the habit early in their career to focus on both the primary anatomical defect, but more importantly have a multi-system approach.

Anaesthetic technique in the trauma patient
Hypoxia (lack of oxygen at tissue level) is very common in trauma victims. Al the aspects of hypoxia, namely oxygen supply and consumption must be addressed intraoperatively (see Chapter 12, 14, and 15). The anaesthetic technique involves the following steps or aspects: Preoperative assessment and consideration (see above), resuscitation, induction of anaesthesia and airway management, maintenance of anaesthesia, emergence and extubation, and postoperative care:

- *Preoperative assessment (see above)*
- *Resuscitation*
  Do not resuscitate patients who has sustained major trauma on your own; *get assistance*. Resuscitation consists of steps to maintain tissue oxygenation (see Chapter 14) and protection of vital organ function, i.e. maintenance of homeostasis. This includes **A**irway management (see Chapter 3), ventilation or **B**reathing (see Chapters 4 and 13), and **C**ardiovascular support, including fluid management (see Chapters 12 and 18). Also give attention to **D**isability (neurological injury – peripheral and central, i.e. brain and spinal cord) and problems arising from **E**xposure to the elements.

  O *Airway managements and breathing* (also see Chapters 3, 4, and 13)
    The chest should be exposed and auscultated bilaterally for breath sounds. If the patient has already been intubated, the anaesthetist must ensure that the endotracheal tube (ETT) is indeed in the trachea. The size and depth of the EET must be recorded. The nature or surgery may require reintubation, e.g. from orotracheally to nasotracheally or via a tracheostomy. Reintubation is much more difficult than primary intubation since swelling of the airway compromises laryngoscopy.

    If the patient has *burns (thermal or chemical) of the face or upper airway* and has not been intubated, intubation must be done as soon as possible since swelling will soon make laryngoscopy very difficult. For *airway management in the patient with a cervical spine injury*, see Chapters 4 and 20.

When the ETT is correctly placed, the trachea must be suctioned to remove secretions and foreign matter. A *bronchoscopy* may be done at this stage. An *intercostal drain* must be inserted in the presence of haemo- and pneumothoraxes.

The *mode of ventilation* is determined by the condition of the lungs. In principle, lung-protective ventilation is applied (see Chapters 4 and 13). Trauma-related pathology influences the mode of ventilation. These conditions include haemothorax, pneumothorax, mediastinal shift, surgical emphysema (bronchial rupture), and pulmonary contusion.

- o *Circulation and coagulation* (see Chapters 12, 18, 19, and 20)
  The endpoint of resuscitation is adequate tissue perfusion ensuring aerobic metabolism and haemostasis. Therefore, resuscitation consists of three inseparable simultaneous activities: surgical resuscitation (anatomical), haemodynamic resuscitation with fluid, blood, vasotropes and inotropes (physiological, pharmacological) and haemostatic resuscitation with clotting factors, platelets, and antifibrinolytics (physiological, pharmacological). *Survival with initial aggressive fluid resuscitation is better than with pharmacological (vasotropes and inotropes) resuscitation.*[44]

On-going blood loss must be stopped and hypovolaemic shock should be appropriately treated. Blood loss can be estimated according to clinical signs (Table 1). The *awake shock index (ASI)* can be calculated. It is an entity, which signifies a low cardiac output – due to hypovolaemia or cardiac failure. The ASI = pulse rate/systolic blood pressure, e.g. (60 beats per minute/120 mm Hg) = 0.5. The normal ASI varies from 0.4 to 0.7. A high or an increasing ASI is a sign of compromised cardiac output. The ASI come in very useful since both the heart rate and blood pressure may still be within normal limits, while the ASI is on the increase. An ASI of > 0.8 to 1.0 indicates a blood loss of about 10% of the blood volume, 1.0 to 1.5 of 20% to 33%, > 1.5 to 2.0 of 33% to 50%, and > 2.0 of > 50%. Please note that these percentages refer to blood volume loss, which may be *due to dehydration or to haemorrhage*.

Venous access is achieved by placing the largest *peripheral venous cannulas possible (e.g. two 14 G or 16 G cannulas)*. On insertion, collect blood samples for haematocrit and cross matching. Administer resuscitation drugs through peripheral venous lines as needed.

Do *not waste time* on the insertion of central venous and arterial catheters. Insertion of these catheters is often be problematic in hypovolaemic patients. Once the patient is more stable other monitoring catheters can be inserted. A central venous pulmonary artery *sheath (8.5 F) can then be inserted*. A *multilumen central venous catheter* (7 F) can be placed next to or through the sheath. Large bore multilumen catheters are available. They can be used for fluid administration, drug therapy, as well as monitoring; *do not waste time to gain central venous access in the acute phase*.

The *mainstay of management of hypovolaemia is warm crystalloid balanced resuscitation* fluids such as Ringer lactate and Balsol. Thereafter, synthetic colloids (controversial), and blood products are used as indicated. For a discussion on fluid resuscitation, see Chapter 18).

Twenty five per cent of patients with major trauma will present with a coagulopathy at the time of admission and have a poor outcome. Tissue trauma and systemic hypoperfusion are the primary triggers for the development of an acute ***trauma-induced coagulopathy***. It is caused by the following factors – often in conjunction with each other:
- *Dilution* of clotting factors erythrocytes, and platelets by resuscitation fluids (bank blood, crystalloids, and colloids)
- C*onsumption* of clotting factors and platelets
- *Activation of the fibrinolytic system* or hyperfibrinolysis
- *Hypothermia (< 33˚C)*
- *Acidosis* and metabolic changes associated with it

All of the above factors directly affect *fibrinogen polymerization* (formation of fibrin) and metabolism early after massive trauma.[45] [46] Therefore, acute coagulopathy of trauma is characterised by an early hyperfibrinolysis-associated coagulopathy. Other bleeding-related deficiencies usually develop later.

Major trauma causes excessive activation of the protein C pathway, which inhibits factors V and VIII, as well as the inhibitors of fibrinolysis (plasminogen activator inhibitor 1 and thrombin-activatable fibrinolysis inhibitor). This coagulopathy can then be exacerbated by subsequent physiologic and physical derangements such as consumption of coagulation factors, haemodilution, hypothermia, acidosis and inflammation, all factors being associated with on-going haemorrhage and inadequate resuscitation or transfusion therapies.

The normal fibrinogen level is 2.0 g L^{-1} to 4.0 g L^{-1}. Bleeding increases at fibrinogen levels below 1.5 to 2.0 g L^{-1}. The critical level of fibrinogen is below 0.5 g L^{-1} to 1.0 g L^{-1}. Fibrinogen decreases to a critically low level sooner than other pro-coagulants and platelets after major blood loss. It is therefore recommended to correct impaired fibrin polymerization by the early administration of fibrinogen concentrate or cryoprecipitate. One unit of cryoprecipitate contains about 300 mg of fibrinogen. Therefore, one unit of fibrinogen increases the fibrinogen level in the average adult with about 50 mg L^{-1}. If it is assumed that the fibrinogen level has decreases to less than the critical level of, say, 500 mg L^{-1}, the patient will need about 10 units.

Table 1 Clinical signs of hypovolaemia in adults

Class	BL	HR	BP	PP	RR	UO ml h^{-1}	MS
1	<15%	<100	Normal	Normal	<20min^{-1}	>30	Slightly anxious
2	15% to 30%	>100	Normal	Decreased	20 to 30 min^{-1}	20-30	Anxious
3	30% to 40%	>120	Decreased	Decreased	30 to 40 min^{-1}	5-15	Anxious and confused
4	> 40%	>140	Decreased	Decreased	> 40 min^{-1}	Negligible	Confused and lethargic

BL blood loss; HR heart rate; BP blood pressure; PP pulse pressure; RR respiratory rate; UO urinary output; MS mental status

What is the acceptable blood pressure in the trauma victim? The concept of permissive hypotension has been propagated. This was based on the premises of preventing further bleeding by dislodging clots and diluting clots and red blood cells. Several systolic blood pressures have been suggested, e.g. SBP < 90 mm Hg. However, there is little evidence in humans that support this value. It has however been shown that the neurological outcome of brain injury victims is much worse if SBP is allowed to decrease to < 110 mm Hg. ***Therefore, the haemodynamic target in the adult trauma victim should probably be a SBP > 110 mm Hg.*[47]**

In the case of penetrating vascular injury or vasculopathic vascular lesions such as a dissecting or ruptured aorta, permissive hypotension may be indicated, say, a SBP of about 90 mm Hg. However, remember, major vascular injury often affect brain perfusion – directly or indirectly.

o *Disability*
The doctors attending to the trauma victim must, as have been pointed out earlier, attend to injuries, which may contribute to future disability. These include neurological injury (peripheral and central, i.e. brain and spinal cord), vascular injury (limb ischaemia), and eyes.

o *Exposure and environmental control*
The patient might have been exposed to physical, biological, or chemical factors. These should be addressed – not only regarding the patient, but also the care givers:
- *Physical*: Extreme temperatures (cold or hot environments, including fires), radioactive irradiation (acute radiation illness), blast injury
- *Chemical*: external or internal (inhalation, swallowing) exposure to toxic (e.g. CO, pesticides, smoke), caustic chemicals (acids, alkalis), or drowning
- *Biological*: Insects, animals, or microbacterial pollution

Hypothermia increases oxygen consumption, impairs coagulation, increases sensitivity to drugs, prolongs drug action, causes vasoconstriction and dysrhythmias, etc. Hypothermia is caused by exposure to a cold environment at the accident scene, during transport, in the radiology suite, and the operating room. The transfusion of cold fluids contributes to hypothermia. These factors can be prevented by covering the patient with reflective (space blanket) and convective blankets (e.g. Bair hugger). The hospital environment must be warm; if not, e.g. in radiology suites, the trauma victim must be covered. All intravenous fluids must be warmed.

Although hypothermia is generally regarded as being detrimental, *permissive or even induced hypothermia* may be beneficial in patients with brain or spinal cord injuries. In these patients core temperature is allowed to decrease to about 35˚C in an attempt to improve neurological outcome.

Hyperthermia may also occur in the trauma patient. Hyperthermia is characterized by a *normal temperature setting of the thermoregulatory centre* with an uncontrolled increase in body temperature that exceeds the ability to loose heat. It may be endogenous (e.g. exercise in hot humid environments, malignant hyperthermia) or exogenous exposure to heat. Hyperthermia may be seen in patients with a head injury (pontine lesion), status epilepticus, after exposure to warm environments, e.g. dry warm natural environment (non-exertional heat stroke), patients who were exposed to warm humid environments (exertional heat stroke), and ingestion of drugs (anticholinergics, alcohol, amphetaminoids, cocaine. Fever can be treated with antipyretics, but hyperthermia needs active cooling. These patients are warm, dehydrated and confused (exclude a head injury).

Hyperthermic patients may develop *heat stroke* when *thermoregulation fails*. This is complicated by rhabdomyolysis, haemolyse, electrolyte disturbances (hyperkalaemia, hyperphosphataemia), renal failure, coagulopathy, etc.

The endpoints of fluid resuscitation are:
- Improvement in blood pressure (< 20% below the patients premorbid blood pressure),
- Heart rate (< 20% higher than the premorbid heart rate),
- Pulse pressure variation,
- Awake shock index (< 1.0),
- CVP (titrated to effect)
- Pulse pressure variation (< 12% in the absence of cardiac failure)
- Haematocrit (> about 24%),
- Adequate haemostasis
- Blood gasses (normocapnia and SaO_2 between 88% and 92%; higher is unnecessary) , Arterial-end tidal CO_2 difference (< 10 mm Hg),
- Acid-base state (standard base deficit < about 5 mM),
- Normal electrolytes and glucose (< 10 mM)
- Urinary output (no pigment, may be > 0.5 ml kg^{-1} h^{-1})
- Core temperature > 36°C (except in patients with a brain injury)

(See also Chapters 12, 13, 14, 18, and 20)

- *Induction of anaesthesia and airway management*
  Intraoperatively, resuscitation takes preference above anaesthesia; in the critically ill patient, anaesthesia often consists of oxygen and muscle relaxants only. When the patient's condition allows it, hypnotics and analgesic are added. Therefore, the prevalence of intraoperative awareness is higher in this population of patients. In this regard, conscious monitoring is useful, e.g. spectral entropy and bispectral index (BIS) of the EEG.

  Induction of anaesthesia in the hypovolaemic patient may lead to cardiovascular collapse. However, induction must not be postponed to resuscitate the patient if the definitive procedure halt massive blood loss, e.g. large vascular injury. In such cases, hypotension is tolerated and preferred

until control of haemorrhage is secured (*permissive hypotension*).

All patients presenting for emergency surgery must be regarded an aspiration risk. If the patient receives a general anaesthetic, a *rapid sequence induction and intubation* is indicated (see Chapter 3). If *airway injury* precludes the administration of an intravenous induction, alternative methods must be applied to secure the airway (see Chapter 3).

The *choice and dose of induction agent* is determined by pharmacodynamic and –kinetic considerations (see above). If the patient has been intubated or is unconscious, induction is unnecessary; he/she is relaxed and maintenance of anaesthesia is stared. Many patients have received analgesics and/or sedative during the preoperative period. This decreases the dose of induction agents.

Ketamine is the induction agent of choice in the trauma scenario:
1. It is the only induction agent with *sympathomimetic* properties.
2. It is profoundly *analgesia*, even at 10% of the induction dose of 1 mg kg^{-1} to 2 mg kg^{-1}.
3. It causes *amnesia*.
4. It is far *less protein bound* (about 30%) than the other induction agents. Therefore, the free (active) drug concentration is less influenced by haemodilution.
5. The notion that "the negative inotropic effect of ketamine manifests in the sympathetically depleted patient – particularly patients with septic shock" is probably over-emphasised and has not been proven in humans. In such cases, tiny doses of any induction agent are indicated anyway.
6. The use of ketamine (and suxamethonium) in the patient with increased *intracranial or intraocular pressure* is controversial; remember that ketamine, like all other sedatives and hypnotics (intravenous and inhalational), depresses ventilation and can therefore increase intracranial and intraocular pressure. However, all the other induction agents (to a lesser extent etomidate) cause dose-dependent cardiovascular depression (hypotension), which decreases cerebral perfusion. But simultaneously, induction agents (including ketamine to some extent) decrease the oxygen consumption and vasoconstriction of non-injured brain. Therefore, any other induction agents (thiopental, propofol, etomidate, midazolam, or an opioid) may be used if the dose is limited to, say, *25% to 30% of the dose* in normovolaemic patients with normal cardiovascular function and normal plasma protein and blood cell concentrations.

Etomidate is a drug with little cardiovascular effects and is safe in the patient with cardiovascular disease, including hypovolaemia. *However*, even an induction dose may depress the production of cortisol for several hours, which can attenuate the (necessary) stress response to injury.

Suxamethonium is still, despite several contraindication (see Chapter 8), the muscle relaxant of choice for a rapid sequence induction; it causes rapid, profound, reliable, and short-lived relaxation (if the patient has enough pseudocholine esterase). These properties allow rapid intubation, which limits the period of apnoea and hypercapnia. *Suxamethonium can cause life-threatening hyperkalaemia and is therefore contraindicated* in the following trauma-related conditions: spinal cord injury after 24 hours, burns after 24 hours, hyperkalaemia following massive muscle trauma, e.g. after crush injury, electrocution, and burns, and in patients with renal failure. *Alternatives* are rocuronium and atracurium (see Chapter 8).

- *Maintenance of anaesthesia*
  All inhalational agents cause a degree of myocardial depression and vasodilatation, and are seldom well tolerated well in by cardiovascularly compromised patients. In such cases, anaesthesia can be maintained by an infusion of ketamine (1 mg kg^{-1} h^{-1} to 3mg kg^{-1} h^{-1}) or an opioid, e.g. sufentanil 3 μg kg^{-1} h^{-1}, fentanyl 20 μg kg^{-1} h^{-1}, or remifentanil 20 μg kg^{-1} h^{-1}.

A vapour may be added as the cardiovascular status allows. *Nitrous oxide should be avoided in trauma patients*, especially when gas is trapped in spaces, e.g. intracranial air, intraocular air, blast

injury with systemic gas emboli (alveolo-venous fistulae), pneumothorax, and bowel obstruction. Cardiac output and liver perfusion is better maintained with isoflurane, sevoflurane, and desflurane than with halothane.

The muscle relaxants of choice after intubation are atracurium and cisatracurium since they are independent of liver and kidney function for their clearance. If postoperative ventilation is planned, other long-acting relaxants may be used.

Intraoperative analgesics decrease the need for hypnotics. The following may be used:
- Morphine titrated to effect with boluses of 20 µg kg^{-1} h^{-1}(50 µg kg^{-1} h^{-1}to 300 µg kg^{-1} h^{-1}). Remember that morphine has active metabolites, which are very long acting in patients with renal failure.
- Sufentanil boluses of 0.05 µg kg^{-1} h^{-1} to 0.1µg kg^{-1} h^{-1}
- Fentanyl boluses of 0.5 µg kg^{-1} h^{-1} to 1.0 µg kg^{-1} h^{-1}
- Ketamine boluses of 0.1 mg kg^{-1} h^{-1} to 0.2 mg kg^{-1} h^{-1}
- Paracetamol IVI 15 mg kg^{-1} every 6 hours for the first 24 hours (if liver function is adequate)

Avoid NSAIDS since they decrease kidney perfusion and compromise the healing of fractures.

- *Emergence and extubation in the operating theatre (See also Chapter 3)*
  The general principle in this regard is that if ventilatory function is inadequate at the end of surgery, the patient must not be woken up (see Chapters 3, 12, and 19).The *indications for intubation and ventilation must have abated*. The patient can be extubated if the following conditions are met with:
  o The patient must be *awake*.
  o The patient must be able to *maintain and protect the upper and lower airway* after removal of the ETT. This includes *muscle tone and airway reflexes* to maintain and protect the airway. *Remember, a difficult intubation is a difficult extubation*.
  o The patient must have regained the *control of breathing*, i.e. central (effect of opioids) and peripheral (effect of hypnotics).
  o The *perfusion (cardiovascular function), ventilatory, and diffusion (lung parenchyma)* of the lungs must be able to sustain adequate ventilation (removal of CO_2) and oxygenation.
  o The patient must be able to perform the *work of breathing*, i.e. elastic and non-elastic and have the cardiac output to perfuse the muscles of breathing. Whenever *the burden to ventilate and oxygenate* becomes larger than the ability of the muscles of breathing to comply with the requirement of work of breathing, the patient must not be extubated. These include intraabdominal hypertension (splinting of the diaphragm), circulatory failure of any cause, severe anaemia, and toxic hypoxia, e.g. CO toxicity.
- *Postoperative care*
  Postoperative care depends on the ability of vital organ function to sustain homeostasis, i.e. airway, ventilation, oxygenation (perfusion, oxygen content of arterial blood), haemostasis, and excretory function (gastrointestinal, liver, kidney). Therefore, if you cannot stop any vital organ support at the end of surgery, the patient must be admitted to an intensive or high care facility. *The completion of surgery does not signify resuscitation to be complete.*

Specific trauma-related entities
- *Hypothermia and hyperthermia (see above)*
- *Fibrinolysis of trauma (see above)*
- *Head injury (see your neurosurgery notes)*
- *Spinal injury, including cervical spine injury (*Chapters 3 and 26)
- *Fat embolism syndrome and compartment syndrome* (see Chapter 12 and your Orthopaedics notes)
- *Myoglobinuria* (Chapter 16)
- *Abdominal compartment syndrome* (Chapter 16)
- *Oliguria* (Chapter 16)
- *Damage control surgery*[48]

- *Head injury (see your neurosurgery notes)*
  The aim in the management of patients who have sustained a traumatic brain injury is to *prevent secondary brain injury*, i.e. *prevent further injury* and protect the undamaged areas. Remember that a patient which suffered a *cardiac arrest* must strictly speaking be regarded as having an injured brain and managed as such.

  Head injuries may be are *cranial and extracranial*. Extracranial injuries include scalp injuries (a small seemingly trivial wound may be the only indication of penetrating brain injury), neck injuries, facial injuries (including the facial skeleton and airway), and base of the skull. Skull base fractures may be complicated by cerebrospinal fluid (CSF) leak, which contraindicates nasotracheal intubation and insertion of a nasogastric tube since these tubes may cause meningitis and they can be passed into the cranium. The *triad of head, facial, and neck injuries* must always be excluded; they often coexist and the one may complicate the other (can you tell why?).

  The main concern is brain perfusion. Brian perfusion is impeded by *increased intracranial pressure (ICP)*. The cranium is a limited space, which is filled by brain, blood, and cerebrospinal fluid. If the volume of the one increases, the other(s) must give way. When brain volume increases due to brain oedema or blood volume increases due to intracranial haemorrhage (intra- or extracerebral), CSF may be displaced into the spinal subarachnoid space. However, the component that is generally decreased is brain perfusion. Remember that decreased brain perfusion aggravates cerebral oedema.

  To maintain brain perfusion, the objective is to ensure adequate cerebral perfusion pressure (CPP:

  $$CPP = (Mean\ arterial\ pressure - ICP).$$

  CPP can be improved by:
  o *Increasing mean arterial pressure and decreasing venous pressure.*
  o *Decrease brain volume by preventing cerebral or treating oedema.*
  o *Decrease CSF volume by inserting a ventricular drain.*
  o *Decrease the oxygen consumption of the brain and detrimental cerebral cascades.*
  o *Maintenance of systemic homeostasis.*

  The intraoperative monitoring of the brain-injured patient usually include:
  o *Decreasing intracranial venous pressure and increasing mean arterial pressure*
    Decrease intracranial venous blood by elevating the trunk about 15°, and avoid hyperextension and rotation of the head. Please note, *NOT the anti-Trendelenburg position*, since this aggravates hypotension by causing venous pooling in the legs. Elevating the trunk also decreases intrathoracic pressure, which improves venous drainage and pulmonary ventilation.

    Blood pressure is maintained by cardiovascular support described above. These include *isotonic* intravenous fluids, a cardiovascular stimulant (adrenaline 100 ng kg^{-1} min^{-1} to 150 ng kg^{-1} min^{-1}) or an inotrope (dobutamine 5 µg kg^{-1} min^{-1} to µg kg^{-1} min^{-1}), or a vasoconstrictor (phenylephrine 0.5 µg kg^{-1} min^{-1} to 1.0 µg kg^{-1} min^{-1}). (The use of phenylephrine may decrease cerebral perfusion, even though blood pressure increases, since it causes cerebral vasoconstriction via stimulation of the superior (cervical) sympathetic ganglia.)

    What should the mean arterial pressure be? Patients with increased ICP often have a deceivingly normal or high blood pressure due to the cerebral ischaemic reflex (increased sympathetic tone). These patients are normo- or hypertensive with a normal heart rate, i.e. a normal or decreased ASI. Terminally, they develop a Cushing reflex with severe hypertension and bradycardia, followed by hypotension due to brain stem failure.

    An increased blood pressure is necessary to perfuse the brain in the presence of increased ICP.

However, increasing the blood pressure may aggravate cerebral oedema. In normal brain (where autoregulation is intact) oedema ensues when the blood pressure increases above the autoregulatory limit (normally a mean arterial pressure of about 150 mm Hg). In the injured brain, increased blood pressure increases blood flow where blood vessels are already dilated due to ischaemia and injury. Here, autoregulation is not intact anymore and any overzealous elevation of blood pressure will worsen cerebral oedema far easier than in normal brain. (For a discussion on autoregulation, see Chapters 12 and 25)

It is recommended that the *cerebral perfusion pressure* (please note, *not* mean arterial pressure) in previously normotensive patients be *maintained between 60 mm Hg and 70 mm Hg*. How does one do that? Remember to measure arterial pressure at the base of the skull (the ear) using an *intra-arterial cannula*. If one assumes that the ICP is high, say > 20 mm Hg (normally < 10 mm Hg), the mean arterial pressure is calculated as follows:
Remember,

$$CPP = (Mean\ arterial\ pressure - ICP)$$

Therefore, *mean arterial pressure* = (CPP + ICP) = (70 + 20 mm Hg) = 90 mm Hg *at the ear*.

The calculated osmolality of Ringer lactate is about 270 mOsm L^{-1}. However, the osmolality as determined by the freezing point method is much lower (about 250 mOsm L^{-1}), which makes Ringer lactate effectively hypotonic. Therefore, resuscitation with Ringer lactate may (theoretically) aggravate cerebral oedema. In our hospital, we *make Ringer lactate isotonic* by adding hypertonic saline. The recipe is as follows:
Take 20 ml of a 5% sodium chloride solution and add it **<u>STERILELY</u>** to 1 L of Ringer lactate. The osmolality of 5% NaCl solution is about 1700mOsmol L^{-1}. Therefore 20 ml contains 20 ml/1000 ml ×1700 mOsm = 34 mOsm. The new solution will therefore be isotonic.

Intracerebral blood volume can be decreased by decreasing the $PaCO_2$. But remember, hypocapnia causes vasoconstriction in the non-injured brain, resulting in hypoperfusion and hypoxia of normal brain and displacement of blood to injured brain where it can exacerbate brain oedema. On the other hand, *hypoventilation increases $PaCO_2$*, which causes vasodilatation in normal brain areas, resulting in stealing of blood from injured brain where blood vessels are already dilated, and worsens hypoxia in this area (*cerebral steal*). *Therefore, patients are ventilated to normocapnia*, i.e. to a $PaCO_2$ of about 35 mm Hg (4.7 kPa) at our altitude of 1400 m.

<u>Since CO_2 plays a major role in cerebral perfusion, airway management (to create and open airway and to protect the airway) is probably the number one priority in the management of the brain-injured patient.</u>

o *Decrease brain volume by prevention and/or treatment of brain oedema.*
Prevent brain swelling by early intubation, adequate ventilation, and optimal brain perfusion (see above). *The use of mannitol* is based on the premises that increased plasma osmolality draws water from oedematous brain tissue. This may be true for parts of the brain where the blood-brain barrier (BBB) is still intact. However, it may cross to brain tissue in parts where the BBB has been disrupted, worsening oedema and increase the ICP further. It has therefore been recommended that *mannitol is given once the dura has been open. The literature does not support the routine use of mannitol*. If the surgeon insists on mannitol, the dose is about 0.25 g kg^{-1}lean body mass (more does not work better). Mannitol solutions usually contain 25% mannitol, i.e. 25 g in 100 ml. A patient with a *lean* body mass of, say, 80 kg will need:
0.25 g kg^{-1}× 80 kg = 20 g = about 100 ml of a 25% solution.
o *Decrease CSF volume by inserting a ventricular drain*
If the drainage and reabsorption of CSF is blocked, the surgeon may decide to insert a drain into a lateral ventricle.
o *Decrease the oxygen consumption of the brain and detrimental cerebral cascades*
Brain injury is followed by *several interacting cascades*, including inflammation and apoptosis

(programmed cell death). The only intervention that may attenuate these processes is *permissive or induced hypothermia* (see above). *Sedation* with GABA$_A$ agonists, typically barbiturates (sodium thiopental) has been used for decades. These drugs do not only cause a so-called barbiturate coma, but is also anticonvulsive. *Anticonvulsives*, e.g. phenytoin are also used. *Corticosteroids have no place* in the management of traumatic brain injury.

o *Maintenance of systemic homeostasis.*
These include maintenance of ventilation, electrolytes, haematocrit, and normoglycaemia. Cerebral injury is often complicated by several systemic manifestations. These include:
- *Diabetes insipidus* (hypothalamic injury) causes a diuresis, hypernatraemia, and a low urine osmolality
- *Cerebral salt wasting* (rare following trauma, more often after subarachnoid haemorrhage) results in diuresis, hyponatraemia, and a high urine Na and osmolality.
- Coagulation disturbances, including hyperfibrinolysis
- Temperature disturbances, e.g. hyperthermia after pontine injury
- Cardiac manifestations of brain injury, including ECG abnormalities resembling ischaemia

o *Intraoperative monitoring of the brain-injured patient usually include:*
- Cerebral perfusion pressure and function (including the EEG)
- Core temperature
- ECG, pulse oximetry, capnography, and anaesthetic agents (autoregulation in normal brain is maintained by isoflurane and sevoflurane up to a MAC ≤ 1.0)
- Intra-arterial blood pressure and central venous pressure monitoring.
- Urinary output, electrolytes, and osmolality
- Metabolic monitoring, including acid-base state, blood gasses, electrolytes, blood glucose, and haematocrit. The arterial cannula also allows the collection of arterial blood samples for blood gas measurements.

- *Damage control surgery[48]*
In the past all injuries was attended to during the first theatre session. However, this approach gave rise to excessive operation times. In the multiple trauma patient it has been shown that outcome improves if only the most life- and limb-threatening injuries should managed as soon as possible. The patient should then be transferred to the intensive care unit for further stabilized (haemodynamic, temperature, metabolic). This concept is known as *damage control surgery DCS). DCS should be performed* when the following triad is identified:
o Hypothermia (cooler than 35°C)
o Acidosis (pH < 7.2)
o Clinical coagulopathy (The surgeon notices wide-spread oozing).

The decision to do DCS should be *based on the initial physiological state* of the patient and injuries. Do not allow metabolic failure to set in. This early decision is imperative to the patient's survival. The surgeon must make the decision to do damage control surgery only within 15 minute of starting surgery. At that stage, wounds are pack but not sutured. The patient is taken to the intensive care unit for further resuscitation and returned to theatre at a later stage for definitive surgery.

Occupational health and hazards
The last, but not the least entity associated with trauma surgery, are health care workers. During these procedures, they are more often exposed to *blood and other body fluids* than during elective procedures. There is also an increased risk of *needle stick injury*. These factors increase the risk of *transmission of infections* such as HIV and hepatitis. Therefore, precautionary measures should be taken such as gloves, protective eyewear, and gowns. The *psychological impact* of their exposure to the trauma environment should not be under-estimated and attended to.

CHAPTER 24

ANAESTHESIA FOR BURN PATIENTS
(For the pre- and postoperative management of burns, please see your surgery notes)

Key points

- Physiological consequences of burns injury
- Anatomical complications of burns, including the airway (face and inhalation burns)
- Fluid therapy
- Temperature management
- Pain management
- Change in pharmacodynamics and -kinetics: analgesics, muscle relaxants
- Monitoring

Burns usually refer to loss of the skin, which may vary from the epidermis to the muscle. Burns may be caused by exposure of the person to direct heat (wet or dry), chemical substances, or electrical current. Burn injuries *often involve other structures*, including muscle, airway, and lungs.

In this chapter, emphasis is placed on intraoperative management of the patient who has sustained burns. The anaesthetist is involved in the resuscitation in the acute phase (within the first 24 hours) when other injuries are attended to, as well as during subsequent procedures, such as escharotomies and skin grafts.

Although burn injuries are *graded according to their depth* (Grades I to IV) and the percentage of the *body surface area (BSA) affected*, attention must be given to *deep injuries. Deep injuries* include thermal injury to muscle, extensive injury to tissue between the entrance and exit of electrical current (voltage > 1000 V often involve muscle, heart, blood vessels and blood), and inhalation of smoke (chemical injury) or hot gas (thermal injury). Therefore, burn injuries must always be regarded as *superficial as well as internal*.

Of all injuries, major burn injury causes the most extensive activation of the stress response, fluid and electrolyte shifts, catabolism, pain, and disfigurement. A burn is classified as a major burn if:

- Greater than 10% BSA of third degree burns
- Greater than 20% to 25% BSA of second degree burns
- Greater than 15% to 20% BSA of second degree burns in extremes of age (neonates, infants, and > 60 years)
- Burn injuries involving the face, hands, feet, or perineum
- Inhalational burn injuries
- Chemical or electrical burns
- Burns with associated trauma
- Circumferential burns, especially of the chest
- Patients with concomitant disease

Burns patients present initially shortly after injury for resuscitation, attendance to other injuries, and airway management. Thereafter, they return to the operating room frequently for debridement of wounds, wound dressings, and covering of wounds.

Regarding the evaluation of burn injury, the attending doctors must be on the look-out for *intoxication* (CO, inhalational, recreational) *other injuries in burn and non-burn areas,* e.g. airway injury, head injury, spinal injury, *fractures, and vascular compromise* of the limbs due to vascular injury or circumferential eschar. Attention must also be paid to characteristics of wounds that point to the *possibility of abuse* – especially in children and the elderly.

Baseline laboratory investigation must be done on admission and to monitor resuscitation. These are urea, creatinine, electrolytes, acid-base and blood gas analysis, haematocrit, and haem pigments.

Physiology of burn injury[49]

Burn injuries are renowned for their impact on *homeostasis*. It is an injury with *multisystem* complications (Table 1).

Table 1 Systemic complications of burns[50]

System	Early	Late
Cardiovascular system	↓Cardiac output ↑ Systemic vascular resistance Hypovolaemia	↑Cardiac output Tachycardia Systemic hypertension
Airway and lungs	Airway obstruction, oedema CO, cyanide toxicity Pulmonary oedema	Chest wall restriction Tracheal stenosis Infection
Kidney	↓ Glomerular filtration rate, myoglobinuria	↑ Glomerular filtration rate ↑Tubular dysfunction
Endocrine, metabolic	Severe stress response	↑ Metabolic rate lasting 9 -12 months ↑ Core body temperature ↑ Muscle catabolism ↑ Lipolysis ↑ Glycolysis ↑ Insulin resistance ↓ Thyroid hormones ↓Vitamin D ↓ Parathyroid hormone
Liver	↓ Perfusion, apoptosis → ↑ AST, ALT, bilirubin, ↑ Intrahepatic fat and oedema	↑ Perfusion ↑ Metabolism
Haematological	Haemoconcentration, haemolysis, thrombocytopenia, hypercoagulability	Anaemia
Gastrointestinal	↓ Perfusion → mucosal damage Endotoxaemia	Stress ulcers, adynamic ileus, acalculous cholecystitis
Neurological	Cerebral oedema, ↑ Intracranial pressure Hypertensive encephalopathy → seizures	Hallucination, personality change, delirium, seizure, coma

Burns cause coagulation of tissue and the surrounding microcirculation, which results in injury of the surrounding tissue – both in area and in depth. The systemic response is caused by loss of the barrier function of the skin regarding vascular integrity (oedema), barrier against invasion by micro-organisms (local and systemic sepsis), and conservation of heat (hypothermia). Injured tissue releases inflammatory substances that cause systemic vasodilatation (hyperdynamic circulation) and hypercoagulability (thrombosis).

Burns exceeding about 20% of the BSA, hypoproteinaemia as well as inflammatory mediators released from the burnt tissue cause interstitial oedema in distant organs and soft tissue. The metabolic rate, and consequently oxygen consumption, may double after burn injury. This causes an increase in cardiac output and ventilation to supply the increased oxygen demands. During the early stages cardiovascular changes include hypovolaemia, hypotension, and tachycardia. This is followed by cardiovascular stimulation causing hypertension, and tachycardia. The hypermetabolic state is often complicated by hyperglycaemia (increased gluconeogenesis, insulin resistance) and hypoproteinaemia (increased protein catabolism). The physiological changes are probably due to the stress response (stimulation of the hypothalamic and pituitary gland, increased glucagon, cortisol, vasopressin, and adrenaline).

Reduced splanchnic perfusion and dysfunction of the gastrointestinal barriers give rise to fluid loss (ileus, oedema, and ascites), bacterial overgrowth, endotoxin translocation, and *gastroduodenal ulceration* (patients receive prophylactic antiulcer therapy, e.g. H_2-receptor blockers). Gastrointestinal oedema, ascites, and circumferential eschar of the torso increase intraabdominal pressure, which may cause intraabdominal hypertension and even *abdominal compartment syndrome* (see Chapter 16). This may necessitate escharotomy and abdominal decompression. *Acute gastric dilatation* needs nasogastric decompression. *Acalculous cholecystitis* may need surgery.

The pathophysiological complications of burns are managed by the following modalities:
- supply of additional substrate (nutritional support)
- insulin resistance (strict glucose control)
- anabolic support (anabolic steroids promote protein synthesis, attenuate muscle wasting, and promote wound healing)
- suppression of the adrenergic response with β blockade decreases heart rate, and supraphysiological thermogenesis
- analgesia, including opioids and ketamine.

In this Chapter emphasis will be placed on early resuscitation and anaesthetising the burns victim.

Initial resuscitation

Burns cause the breakdown of external and internal borders between body compartments, i.e. environment-skin and intracellular-interstitial, and interstitial-intravascular (capillary leak) extracellular. These give rise to fluid shifts from the body to the environment (loss of fluid and body heat), and internal fluid shifts with the formation of oedema. *These fluid shifts are always complicated by intravascular fluid depletion (hypovolaemia)*. These changes are aggravated by vasodilatation.

The oedema is caused by the injury itself (thermal, chemical, electrical) as well as the systemic inflammatory response. Depending on the cause of injury, oedema involves the superficial structures (the skin, subcutaneous tissue, and muscle), as well as the gastrointestinal tract, airway, and lungs. Severe burns injury may be complicated by wide-spread oedema, multiorgan failure and septic shock.

The more extensive the injury, the more *homeostasis is disrupted*. These include hypothermia, electrolyte abnormalities (hyperkalaemia, hyponatraemia, acidosis or alkalosis), anaemia, and hypoalbuminaemia. Extensive burns, especially electrical injury, cause internal injury, including rhabdomyolysis, haemolysis, cardiac injury, nerve injury, and brain injury. These injuries often cause myoglobinaemia, haemoglobinaemia, hyperkalaemia, and hyperphosphataemia.

Intraoperatively the emphasis is on cardiovascular function, ventilation, airway management, maintenance of homeostasis, and anaesthesia.

- *Cardiovascular considerations*
  The hallmark of burn injury, especially in the presence of other injuries, e.g. fractures, is the complexity of fluid therapy. Fluid therapy is a very controversial topic in healthy patients; in trauma and more so, in burns victims, controversy abounds – perhaps due to the gravity and complexity of the pathophysiology.

  Regarding fluid therapy of the burns victim, there is agreement that:
  o Burn victims are very *prone to hypovolaemia* – ***but***
  o Over-resuscitation leads to *fluid creep*: increased burn and non-burn oedema, pulmonary oedema, prolonged mechanical ventilation, abdominal compartment syndrome, and fasciotomies on unburned limbs.
  o The *Consensus formula* provides for hypovolemic resuscitation (see below).
  o Patients with *inhalation injury require more fluid* than that prescribed by the Consensus formula.
  Regarding fluid therapy of the burns victim, there are uncertainties regarding:[51]
  o *Resuscitation endpoints* regarding cardiovascular function and urine output is not reliable enough and the value of newer measurements of cardiovascular function has been questioned.
  o The *pathophysiology of burn oedema and fluid creep* in burns is unresolved. Is it iatrogenic? What initiates it? Are there changes that affect the entire cardiovascular system?
  o The role of *oral resuscitation strategies* should be investigated.
  o The value of *pharmacological agents* that will reduce the capillary leak (e.g. high doses of vitamin C) must be clarified.

  *The Consensus Resuscitation Formula for fluid requirements in burn victims*49
  First 24 hours
    Adults and children >20 kg
    Ringers lactate: 2 ml kg^{-1} %$^{-1}$ to 4 ml kg^{-1} %$^{-1}$ of which 50% is given during the first 8 hours (counting from the time of injury)
    Colloid: none
    Children <20 kg
    Ringers lactate: 2 ml kg^{-1} %$^{-1}$ to 3 ml kg^{-1} %$^{-1}$ of which 50% is given during the first 8 hours (counting from the time of injury)
    Ringers lactate with 5% dextrose: maintenance (rate according to the 4-2-1 rule – see Chapter 18)
    Colloid: none
  Second 24 hours

All patients

Crystalloid: to maintain urine output; if silver nitrate is used, sodium leeching will mandate continued isotonic crystalloid; if other topical burns treatment is used, free water requirement is significant; serum sodium should be monitored closely.

Colloid (5% albumin in Ringers lactate):

0% to 30% burn: none

30% to 50% burn: 0.3 ml kg^{-1} $\%^{-1}$ day^{-1}

50% to 70% burn: 0.4 ml kg^{-1} $\%^{-1}$ day^{-1}

70% to 100% burn: 0.5 ml kg^{-1} $\%^{-1}$ day^{-1}

Nutritional support should begin, ideally by the enteral route.

The Consensus formula is similar to the Parkland formula, which is still widely used:

o Ringer lactate 4 ml per kg body mass per % BSA burnt, e.g. a patient with a body mass of 80 kg, who has sustained burns to 25% BSA will require a *total volume* of

$$4 \text{ ml } kg^{-1} \%^{-1} \times 80 \text{ kg} \times 25\% = 8000 \text{ ml}$$

o 50% is given during the first 8 hours (from the initial injury)

o 50% is given over the next 16 hours

o On the second day after injury, fluid requirement is decreased since capillary leak decreases. *Colloid fluids* (e.g. albumin) are then administered. The original recommendation was plasma 0.4 ml kg^{-1} $\%^{-1}$. There is a resurge in the use of colloid after 24 hours.

o The endpoint of fluid therapy is hemodynamic stability, homeostatic normalisation, and urine output at a rate of 1ml kg^{-1} h^{-1}.

What are the endpoints of resuscitation of the burns victim? What is enough?

Since end points have not yet been demonstrated that reflect tissue perfusion reliably, monitoring during early resuscitation remains controversial. Vital signs (blood pressure, heart rate, ventilation) and urine output in burn patients do not reflect tissue perfusion. It is difficult to set endpoints if endpoints cannot be defined. This often leads to over-hydration (fluid creep).

The following endpoints of resuscitation have been suggested:[49]

o *Sensorium*: rousable and comfortable

o *Digital temperature*: warm peripherally

o *Systolic blood pressure*: for infants, 60 mm Hg systolic; for older children, 70 mm Hg to 90 mm Hg plus (2 × age in years) mm Hg; for adults, mean arterial pressure > 60 mm Hg

o *Pulse rate* : 80 min^{-1} to 180 min^{-1} (depending on age)

o *Urine output*: 0.5 ml kg^{-1} h^{-1} to 1 ml kg^{-1} h^{-1} (glucose negative)

o *Standard base deficit*: < 2 mM (that is the same as > -2 mM)

Fluid creep[52]

It has been known for many years that burns lead to a life-threatening "shocklike" syndrome that should be treated with infusions of crystalloid – initially believed to be normal saline. Refinements in resuscitation (formulae mostly based on body mass and size of the burn) have led to successful resuscitation of most patients and complications such as renal failure are only rarely seen.

The most widely accepted formula is the Parkland formula, described by Baxter and Shires in 1968. However, several reviews have reported patients with major burns, which required resuscitation volumes significantly larger than the Parkland recommendations. These cases were complicated by oedema, and abdominal compartment syndrome (ACS) in the absence of intraabdominal pathology. It appeared as though hypertonic crystalloid and colloid-based resuscitation reduce the development of ACS. This over-hydrated state was called "fluid creep", which resulted in a trend to resuscitate with smaller volumes of fluid.

Was fluid creep a new phenomenon, what was it associated with, was it harmful, and preventable? *Inhalation injuries* have been identified as a factor associated with increase in fluid requirements, from 35% to 65% more than in patients without inhalation injury. Fluid creep is also associated with major burn injuries, electrical burns, multiple trauma, delayed onset of resuscitation, and alcohol or drug addiction. There may be errors in burn estimation (under-or over-estimation), overzealous or careless treatment, especially failure to decrease infusion rates after 8 hours, and accepting or chasing higher urinary outputs. Excessive fluid administration is also complicated by pleural and pericardial effusions, compartmental compression in unburned extremities, elevated intraocular pressures, and prolonged intubation in the absence of inhalation injuries or airway burns.

What are the causes of fluid creep?

o The *Parkland Formula underestimates fluid requirements in patients with very large burns*. If these patients receive larger fluid volumes, survival increases. This finding might have influenced doctors to extrapolate these increased

requirements to patients with less extensive burns.
- o Opioid dosage correlates with fluid requirements (*opioid creep*). Opiates have significant cardiovascular effects, including vasodilatation. This is an unlikely cause since high doses of opioids are tolerated well in other scenarios.
- o *Goal-directed resuscitation* in burn and non-burn patients has become fashionable in recent years. Resuscitation was performed until several endpoints have been achieved. These includes *normalisation* of base deficit (BD) and lactate and *supra-normalisation* of cardiac index (CI), oxygen delivery (DO$_2$) and oxygen consumption (VO$_2$). Goal-directed therapy (pushing variables to goals) is associated with the administration of larger fluid volumes and an increased prevalence of ACS. Neither meta-analyses nor controlled trials have demonstrated goal-directed therapy to be superior to treatment based on standard *vital signs and adequate urine output*. In burns, it appears that *only normalisation* of CI, DO$_2$, VO$_2$, BD, and lactate predicts survival, does not turn non-responders into responders, and that it takes up to 48 hours to occur – irrespective of the resuscitation regimen applied. (___I think that fluid creep does not only occur in the burn injury scenario, but also in other fluid therapy situations, e.g. intraoperative, trauma, etc___.)

  Potential management of fluid creep
- o Restrict Early Fluid Resuscitation
  Excessive initial resuscitation may contribute to fluid creep, which becomes visible later. Fluid requirements must be less than the Parkland predictions for the first few hours. Doctors receiving a burn victim at a burn unit must enquire from the referring centre about the amount of fluid the patient has received. This will prevent over-resuscitation. Hypertonic saline does not improve outcome.
- o Consider Routine Colloid, or "Colloid Rescue"
  Crystalloid resuscitation if is often successful. However, oedema formation correlates with total volume of fluid administered. Patients that receive both crystalloids and colloids require lower fluid volumes, which is associated with a lower prevalence of ACS. It has therefore been suggested that crystalloids be given during the first 24 hours (as has been suggested by both the Parkland and the Consensus Formulae) but to administer a colloid bolus after 24 hours or when fluid requirements is increasing during resuscitation to escape from fluid creep ("colloid rescue"). Chung et al during Operation Iraqi Freedom, administer albumin 5% in Ringer lactate if the *projected* 24 hour fluid requirements are > 6 ml kg^{-1} %$^{-1}$.[53] This protocol has eliminated ACS. (For calculation of the projected 24 hours fluid requirements, see the Appendix.)
- o It is clear that resuscitation protocols may be confusing. Therefore, the University of Utah has developed a protocol, which includes colloid rescue (See appendix).[52]

- *Monitor resuscitation and complications*
  All the factors alluded to above emphasise the importance of monitoring. Invasive monitoring may be indicated in some patients. The pulmonary artery catheter may be useful in patients with cardiac failure, ventilatory failure, or in patients who do not respond to standard resuscitation, but has not been shown to improve outcome.

  ACS causes oliguria (*urinary output*), compromises circulation (*blood pressure, heart rate*) and ventilation (*signs of ventilatory compromise*), and is associated with a poor outcome. Early decompressive laparotomy improves survival significantly. Therefore intraabdominal pressure *(bladder pressure)* must be monitored in patients with major burns and those with an estimated fluid requirement of $\geq$ 6 ml kg^{-1} %$^{-1}$ for the first 24 hours, or $\geq$ 250 ml kg^{-1} or $\geq$ 500 ml h^{-1} or $\geq$ 20 L total. Rising intraabdominal pressure must be managed early with escharotomy, fluid drainage, fluid restriction, and colloid rescue (see Appendix).

- *Airway management*
  Indications of inhalational injury include:
  - o History of impaired mentation and/or confined burn area
  - o Explosion injury
  - o Facial burns and scorched eyebrows and nasal hairs
  - o Hoarse voice
  - o Productive cough and carbonaceous sputum
  - o Carbon deposits or acute inflammatory changes in the oropharynx

  Although the patient may maintain his airway initially, oedema may cause airway obstruction; this may happen rapidly. ___Therefore, these findings mandate early endotracheal intubation – before airway obstruction ensues.___ Be prepared to establish a surgical airway should oedema prevents endotracheal intubation (Figure 1).

- *Ventilation*

  Burns that involve skin only usually do not compromise ventilation. However, major burns complicated by airway and lung involvement may necessitate ventilatory support. Remember, burns patients are in a catabolic state with a very high metabolic rate, increased oxygen consumption, and consequently an increased CO_2 production. Therefore, a higher minute ventilation is often required. Burns involving the chest may *restrict ventilation*, especially in the presence of thick *eschar* or *scarring* (restrictive lung function). This may be aggravated by circular chest *bandages*.

Figure 1 Airway oedema in a burns victim49

- **Preoperative assessment and management**

  The preoperative assessment of a burn patient includes:
  o *Type and severity* of burn injury
  o *Associated injuries*
  o *Fluid status*
  o *Systemic physiologic changes*, including haemodynamics, pulmonary compliance, volume status (including oedema), and urine output.
  o *Current therapy*: cardiovascular, ventilation and ventilator setting, antibiotics
  o Significant co-existing medical illness.
  o Since distortion of the structures surrounding the airway can compromise the airway, a *thorough airway evaluation is essential*.
  o *Laboratory studies* including blood count, electrolytes, urea and creatinine, blood gasses and acid-base state, coagulation studies.
  o *Nutrition* should be continued as long as possible. In unintubated patients, enteral nutrition must be stopped since patients can develop gastric stasis which increases the aspiration risk. Nasojejunal nutrition and parenteral nutrition can be continued.
  o Burns patients are exposed to procedures repeatedly and often experience pain, fear, and anxiety. *Appropriate premedication* including sedation and analgesia should be given before transport to the operating theatre.

- **Anaesthesia**

  Patients may present during the acute phase, skin grafts, wound dressings, and reconstruction procedures.
  o *Adequate intravenous access* is essential. This is usually inserted during the initial resuscitation, but may become problematic if the patient is brought to theatre repeatedly. If central venous cannulas are used, strict infection control must be adhered to (as is the case in all patients).
  o Ketamine is the *induction agent* of choice.
  o Depending on the airway, a rapid sequence induction should be performed in the acute phase. Beware of airway oedema in patients with burns that involve the airway (see above).
  o Burns are complicated by an *increase in the number of extrajunctional muscular nicotinic acetylcholine receptors (nAChR)* and a *decreased affinity of the junctional receptors for agonists and antagonists*. This is called *up-regulation.* When this large number of receptors in

the muscle membranes outside the neuromuscular junction depolarises under the influence of suxamethonium (an agonist), the inward flux of Na^+ ions is followed by a massive efflux of K^+ ions. The potassium efflux caused by *suxamethonium* causes a *surge in plasma potassium.* Therefore, it is contra-indicated from about 24 hours after the burn injury until the burns have completely healed. From what percentage BSA burns should suxamethonium be avoided? Burns involving $\geq 20\%$ of the BSA, deep electrical burns, in the presence of other injuries that contraindicate suxamethonium (e.g. crush injury). For how long? Until the burns have healed.

o *Rocuronium* is the muscle relaxant of choice after 24 hours for intubation. It must be kept in mind that these patients may be resistant to the effects of non-depolarizing muscle relaxants and may need 2 times to 5 times the normal dose.

o Burn surgery is usually very painful. Intravenous paracetamol is useful and should be given intraoperatively. Opiates such as morphine should be titrated to effect. Patients receive large quantities of morphine during their hospital stay and develop tolerance to opioids. Ketamine is a useful adjuvant analgesic but tolerance is also common.

o *Maintenance of homeostasis* may be difficult. The patient may present during the initial admission to hospital to attend to other injuries and require initial resuscitation for the burns as well as for associated injuries. These changes have been discussed. *Particular attention should be given to maintenance of body temperature and blood loss.*

o *The operating theatre should be warm* (about 25°C), the patient must be covered with convection *heating blankets* (Bair Hugger). Intravenous *fluids* and cleaning solutions should also be warmed.

o *Blood loss can be substantial.* Blood loss is calculated according to the area of burns debrided as well as the skin donor areas. The anaesthetist should know the Hct of the patient beforehand and blood should be available in theatre if a large area is going to be grafted. *Blood loss is about 2 ml kg^{-1} $\%^{-1}$ bleeding area* and should be *replaced with packed red blood cells and plasma.* If possible, only 10% of the burn area should be grafted at a time.

o *Routine monitoring is used.* *Additional monitoring* is dictated by the nature of injuries. *ECG electrodes* can be placed on any unburnt areas. *Blood pressure* cuffs must be applied over unburnt areas if possible. Although arterial cannulas are convenient to measure blood pressure in these patients, repeated cannulation of arteries must be avoided if possible. Blood sampling may be done from central venous lines if necessary. *Temperature monitoring* is essential. *Metabolic and haematological monitoring* depends on the injury, surgery, blood loss, and systemic complications. These include blood gas and acid-base analysis, electrolytes, haematocrit, and urinary output.

- **Changing of wound dressings**
  o Intramuscular or subcutaneous ketamine 5 mg kg^{-1} to 10 mg kg^{-1} is used. Tolerance often sets in resulting in increased dose requirements.
  o Nitrous oxide 70% can be used.
  o Breathing is monitored continuously by taping the Capnograph sample line next to the mouth
  o ECG, blood pressure, pulse oximetry, and breathing should bemonitored.
  O Wound dressing must be done in a warm environment.

APPENDIX

PROJECTED 24 HOURS FLUID REQUIREMENTS

Example: Body mass: 60 kg; BSA burns: 40%; Since burn injury: 10 hours
Fluid requirements to maintain blood pressure and heart rate ate acceptable level: 8 L
Calculation of fluid requirements up to now (10 hours):
Per hour up to now = 8 000 ml/10 h = 800 ml h^{-1}
Per kg per hour up to now = 800 ml h^{-1}/60 kg = 13.3 ml kg^{-1} h^{-1}
Per kg per hour per % burns up to now = 13.3 ml kg^{-1} h^{-1}/40% = 0.33 ml kg^{-1} h^{-1} $\%^{-1}$
Projected 24 hour requirements: 0.33 ml kg^{-1} h^{-1} $\%^{-1}$ × 24 h = 8 ml kg^{-1} $\%^{-1}$, which is > 6 ml kg^{-1} $\%^{-1}$

Protocol for Fluid Resuscitation of the Adult Burn Patient:

Begin LR using burn center fluid resuscitation calculations

STEP ONE

Infuse at calculated rate as ordered by MD. Measure Urine Output after one hour

Vitals Unstable:
HR > 140, < 60
BP < 90/60
SaO2 < 90

CALL PHYSICIAN

Vitals Signs Stable: HR < 140, BP > 90/60, SaO$_2$ > 90

Urine Output < 15 mL	Urine Output 15-30 mL	Urine Output 30-50 mL	Urine Output 50-200 mL	Urine Output > 200 mL
Increase IV rate by 20% or 200mL/hr (whichever is more)	Increase IV rate by 10% or 100mL/hr (whichever is more)	Leave IV as is	Decrease IV rate by 10% or 100mL/hr (whichever is more)	Decrease IV rate every 1/2 hour by 10% or 100mL/hr, whichever is more. Measure blood sugar, lactate, hemoglobin. Call physician with questions.

REPEAT STEP ONE EVERY HOUR UNTIL:

Urine Output < 15 ml/hr for two or more hours despite increasing fluid rate

Calculated maintenance rate is reached and held for two hours AND patient is at least 24 hours post-burn

Patient requires increasing fluids or more than twice current calculated rate for two or more hours.

CALL PHYSICIAN: Check urinary catheter, assess breath sounds, vital signs, bladder pressure. Consider albumin protocol.

Fluid resuscitation is complete: switch patient to maintenance IV of D5/0.45 NaCl + 20 mEq KCl/liter at calculated maintenance rate

Patient may need colloid resuscitation: **CALL PHYSICIAN** to discuss. Check foley catheter, vital signs, bladder pressure

If patient again develops oliguria or hemodynamic instability, **CALL PHYSICIAN**. Restart patient on LR at current rate and return to **STEP ONE**.

Albumin protocol: begin a combination of 5% albumin at 1/3 of current IV rate, plus LR at 2/3 current rate. Repeat **STEP ONE**. Decrease IV as tolerated, maintaining the ratio of 1/3 albumin: 2/3 LR until maintenance rate is maintained for two hours.

Switch IV fluid to plain LR and repeat **STEP ONE**

CHAPTER 25

HEAD INJURIES AND RAISED INTRACRANIAL PRESSURE
(See also Chapter 23)

In this chapter, only management of the patient with increased intracranial pressure will be discussed. For more detail, please see your trauma, neurosurgery, and neurology lectures.

Main points
- Clinical diagnosis of raised intracranial pressure
- Measures to lower intracranial pressure
- Anaesthetic management of the head-injured patient
- Patients with polytrauma and a head injury are often hypovolaemic and therefore hypotensive.
- To maintain cerebral perfusion pressure in these patients it is essential to maintain their blood pressure.

A patient presenting with *depressed consciousness* may suffer from *metabolic* (hypoxia, hypoglycaemia, hyperglycaemia, uraemia, liver failure, electrolyte disturbances), *toxic* (ethanol, recreational drugs), or *organic brain pathology*. Organic brain pathology are due to trauma, primary intracranial pathology (e.g. brain tumours, epilepsy, cerebral aneurism, and infarction), or secondary (e.g. hypertensive bleed, infection).

Remember, *resuscitation* of the patient who has sustained trauma that includes a head injury does not differ from resuscitation in the absence of head trauma. In the head-injured patient, additional attention is merely given to factors that affect *cerebral perfusion pressure* (CCP).

REMEMBER, THE FIRST AND MOST IMPORTANT LAW IN PATIENTS WITH A HEAD INJURY IS THE AIRWAY, THE AIRWAY, AND THE AIRWAY SINCE IT PREVENTS INCREASED INTRACRANIAL PRESSURE:
- Endotracheal intubation prevents pulmonary *aspiration.*
- Endotracheal intubation prevents *airway obstruction* and therefore *hypoventilation.*
- Endotracheal intubation allows ventilation and thereby prevents *hypercapnia*
- Endotracheal intubation allows ventilation and thereby prevents *hypoxaemia*

Before intubating a head-injured patient, trauma to the cervical spine and facial bones must be excluded (see Chapters 3 and 23).

The general practitioner working at the periphery may be called upon to manage and anaesthetise a patient for life-saving surgery, e.g. drainage of an extradural haematoma via a burr hole.

Signs and symptoms of raised intracranial pressure
Early: Headache, nausea, vomiting, papilloedema, seizures.
Late: Increased intracranial pressure causes cerebral ischaemia (see below). Cerebral ischaemia evokes the cerebral ischaemic reflex, which consists of increased activity of the sympathetic nervous system. This gives rise to hypertension and tachycardia, which is followed by severe hypertension and a reflex bradycardia, known as the Cushing reflex. This is a preterminal sign consisting of hypertension, bradycardia, respiratory abnormalities, coma, and ipsilateral neurological deficit. This is followed by bilateral papillary dilatation, decorticate posturing, and lastly decerebrate posturing.

Beware of a normal to high blood pressure and a normal heart rate in the trauma patient; hypovolaemic shock may be masked by cerebral ischaemia.

Measures to lower intra cranial pressure
The intracranial content consists of brain, cerebrospinal fluid (CSF), and blood (arterial and venous). Since the intracranial volume cannot change (after the cranial sutural lines have closed), an increase in any one of the components will elevate intracranial pressure (ICP) if the volume of the others do not decrease.

In the presence of brain masses (oedema, haematoma, tumour, abscess), blood vessels will be compressed and CSF may be displaced to the spinal cord. When these compensating mechanisms have been exhausted (intracranial compliance decreases), ICP *increases rapidly with a concomitant decrease in CPP* (Figure 1).
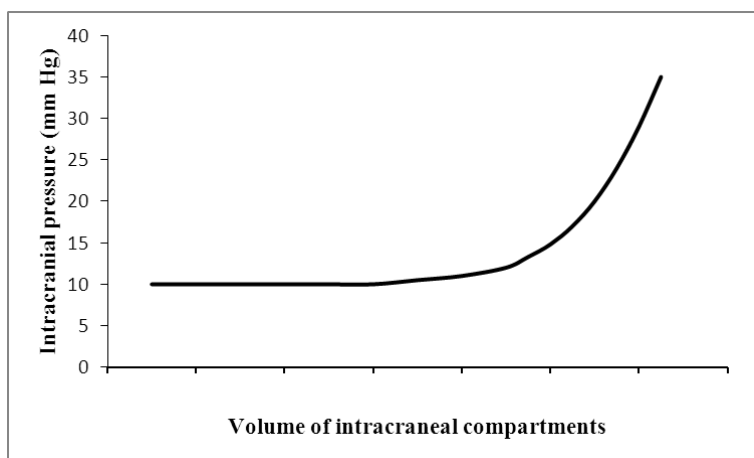

Figure 1 Intracranial compliance curve

Therefore, the treatment of increased intracranial pressure consists of the following principles:
- *Remove space-occupying lesions.*
- *Drain CSF*
- *Decrease intracranial blood volume.*
  - Decrease arterial blood volume by *preventing arterial vasodilatation* caused by hypercapnia, hypoxaemia and high concentration of anaesthetic vapour (isoflurane > 1.0 MAPP and sevoflurane > 1.2 MAPP).
  - *Ventilation* influences intracranial blood volume. Cerebral blood flow increases linearly with increasing $PaCO_2$ and a $PaO_2 > 50$ mm Hg. Hypocapnia causes vasoconstriction in normal brain, which may shift blood to injured brain where oedema is aggravated. Avoid hypoventilation since hypercapnia causes vasodilatation in normal brain tissue. This steals blood from injured brain where ischaemia is exacerbated. Therefore, neurosurgical patients are ventilated to (low) normocapnia, namely a PaCO2 of between 31 mm Hg and 35 mmHg.

    Coughing and high ventilator pressure must be avoided. Although positive end-expiratory pressure (PEEP) increases intrathoracic pressure and thereby decreases venous drainage from the brain, improved oxygenation takes preference since poor oxygenation is more detrimental to brain than increased intracranial pressure.

    Ventilate with pressure controlled ventilation since this mode of ventilation delivers larger tidal volumes at lower peak pressures than volume controlled modes.
  - Increase tone in arteries of *intact brain* where autoregulation is still functional (see Chapter 12) by *decreasing oxygen consumption* with propofol, barbiturates, or anaesthetic vapours (< 1.0 MAC), anticonvulsants (phenytoin 15 mg kg^{-1} over 15 min), and hypothermia (controversial, but 34°C may be adequate).
  - Prevent *venous congestion* by preventing high intrathoracic pressure (coughing, increased intraabdominal pressure). *Positioning* is important. Elevate the upper body 20° to 30°, and keep the head in the neutral position (no rotation, flexion, extension). Do not put the bed in anti-Trendelenburg position; this causes hypotension due to pooling of blood in the lower extremities. Avoid the Trendelenburg position since it decreases venous drainage from the brain.

- *Prevent brain oedema*
Maintain adequate *cerebral perfusion pressure* (CPP) without aggravating oedema formation with too high blood pressure (intubation, pain). Remember, in normal brain autoregulation maintains blood flow at the same level by vasoconstriction when blood pressure increases within the autoregulatory limits (50 mm Hg to 150 mm Hg in normotensive patients). However, in the hypoxic and injured brain, autoregulation is blunted and blood flow changes linearly with blood pressure. Therefore, high blood pressure may aggravate oedema formation in injured brain (Figure 2).

What is CPP and how much is enough?
CPP is the difference between mean arterial pressure (MAP) *at the level of the base of the skull* (ear) and intracranial pressure (ICP) or venous pressure (VP), whichever is higher, at the base of the skull:

$$CPP = MAP - ICP$$

The aim of resuscitation is tissue perfusion, and therefore tissue oxygenation. Therefore, the endpoint of resuscitation in the presence of increased intracranial pressure is a *CPP of between 60 mm Hg and 70 mm Hg*. This is a compromise between ischaemia and increased oedema formation (Figure 2).

The normal ICP is up to about 10 mm Hg. If a pressure screw has been inserted and ICP is known, CPP is easy to calculate. If ICP is not available, it is safe to assume that ICP is elevated to at least, say 20 mm Hg. In previously normotensive patients, MAP at the level of the ear must be calculated:

$$CPP = MAP - ICP$$
$$70 \text{ mm Hg} = MAP - 20 \text{ mm Hg}$$
$$\text{Therefore, } MAP = 70 \text{ mm Hg} + 20 \text{ mm Hg} = 90 \text{ mm Hg.}$$

How does one know that the CCP is between 60 mm Hg and 70 mm Hg?
If you do not have the facilities to measure arterial pressure with an intra-arterial cannula, you must remember to subtract pressure from the MAP measure with a blood pressure cuff at the level of the heart if the head is at a higher level than the heart. How much? Remember, there is a column of blood from the aortic root (midaxillary line at the level of the heart) to the brain. Therefore, MAP at the ear is higher than at the aortic root if the head is lower, but lower if ear is higher than the aortic arch.

If the *vertical difference* between the aorta root (lower) and the ear is, say 30 cm, the pressure difference is about 30 cm H_2O (or blood). How much is this pressure difference in mm Hg at the level of the ear? What is the difference in MAP?
The density of blood is about the same as that of water (1 g cm^{-3} = 1 g ml^{-1}), while the density of mercury is 13.6 g ml^{-1}.

Therefore, a mercury column of 1 cm (10 mm) high, will have a mass of a water column that is 13.6×10 mm high = 136 mm = 13.6 cm.
Or, a column of blood (water) that is 30 cm high has a pressure of 30 cm (300 mm) H_2O at its base. This is 300/13.6 mm Hg ≈ 22 mm Hg*.
For each 10 cm vertical elevation of the head (ear) above the heart (middle of upper arm), the cerebral perfusion pressure decreases by about 7 mm Hg

Example: If the cuff MAP at the level of the heart (middle of upper arm) is, say 90 mm Hg, the MAP at a vertical level 30 cm higher is
$$90 \text{ mm Hg} - 22 \text{ mm Hg} = 68 \text{ mm Hg.}$$
If the intracranial pressure is high, say 20** mm Hg, the
$$CPP = 68 \text{ mm Hg} - 20 \text{ mm Hg} = 48 \text{ mm Hg, and this is too low.}$$
Therefore, you must increase the blood pressure urgently; if the patient is hypovolaemic, *give fluid*; or you must administer as *vasoconstrictor* to elevate the MAP.

How high should the minimum MAP target at the level of the heart in this example be (at least)?

$$CPP^{\#} = MAP - ICP$$

Therefore, MAP at the level of the heart = CPP + ICP + 22* mm Hg

$= 65^{\#}$ mm Hg + 20** mm Hg + 22* mm Hg = 107 mm Hg (at least)
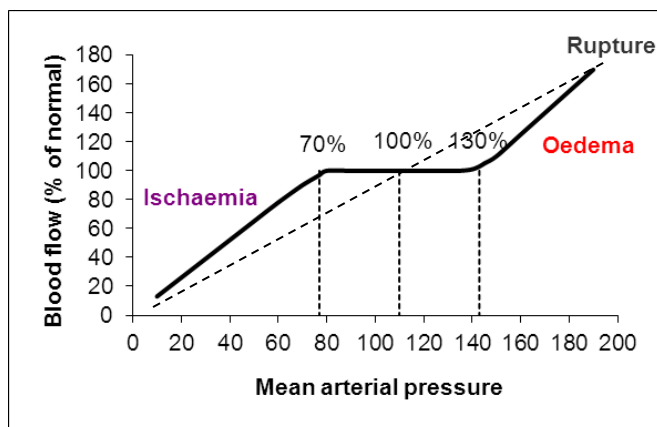

Figure 2 The arterial autoregulation curve
___ normal; ---- blunted

- o *Fluid therapy in patients with increased intracranial pressure*
  The endpoints of fluid therapy in the patient with a head injury is to ensure tissue oxygenation (including the brain) by correcting plasma volume, electrolyte disturbances, osmolality, and oxygen-carrying capacity (haematocrit, haemoglobin concentration).

  Since the brain is more dependent on crystalloid osmotic pressure than colloid osmotic pressure to regulate interstitial fluid, hypotonic fluid must be avoided. Therefore, give Ringer lactate of which the osmolality has been increased from 270 mOsm to about 300 mOsm by adding about 20 ml of sodium chloride 5% solution (or alternate Ringer lactate and 0.9% sodium chloride).
  - o Ensure *normal to high plasma osmolality* since the brain interstitial fluid is influenced more by crystalloid than colloid osmotic pressure.
  - o Do not use glucose containing fluid for resuscitation and treat *hyperglycaemia* since hyperglycaemia worsens ischaemic brain injury.
  - o Maintain *brain oxygenation* with adequate cardiac output and blood oxygen content (haematocrit > 30%, haemoglobin concentration > 100 g L^{-1})
- *Treat brain oedema*
  - o High doses of *glucocorticosteroids*, e.g. dexamethasone 0.1 mg kg^{-1} twice daily intravenously may help for oedema around *infection and tumours* but not for brain injury.
  - o Dehydrate the normal brain (intact blood-brain barrier, BBB) with the *osmotic agent mannitol* – only after the dura has been opened since mannitol may leak into areas where the BBB is interrupted and thereby aggravate oedema and increase ICP. The dose is 0.25 g kg^{-1} to 0.5 g kg^{-1} over 30 minutes. Mannitol is marketed as a 20% solution (20 g of mannitol per 100 ml, or 0.2 g per ml). Therefore, you can give about 1.5 ml kg^{-1} = 0.375 mg kg^{-1}. Remember, mannitol has side-effects: it can cause an acute hyperkalaemia, hypervolaemia if fluid extracted from the interstitium is not excreted, and hypovolaemia if the diuresis is not replaced. The use of mannitol is controversial.

Anaesthetic management of the patient with a head injury
- Be aware of and attend to *other injuries* associated with head injuries (airway, spine) and other causes of altered consciousness.
- If the patient has not been intubated, do a *rapid sequence induction*.
- The *induction agent* depends on the condition of the patient. Although ketamine may increase intracranial pressure by increasing blood flow to certain brain areas, it maintains blood pressure

better, especially in the hypovolaemic patient. This effect is minimal if ventilation is maintained.

- *If the patient arrives in theatre intubated*, the correct position of the tube is confirmed, he/she is relaxed, and connected to the ventilator immediately. The induction agent may be omitted and the maintenance agent started.
- The *muscle relaxant* of choice is suxamethonium since it facilitates rapid intubation and minimizes the period of apnoea. The fasciculations do not increase intracranial pressure since the induction agents decrease cerebral blood flow. Rocuronium may be used but hypoventilation and straining during intubation may occur.
- The *intubation response* can be attenuated by an *opioid* such as alfentanil about 15 μg kg $^{-1}$, and *lignocaine* 1.5 mg kg^{-1} before the induction agent.
- Ventilate the patient to low-normocapnia using pressure-controlled ventilation (see above).
- *Position the patient* as required by the procedure, but try to keep the head above the level of the heart.
- The surgeon may decide to stabilise the head in a *Mayfield head clamp*. The clamp consists of three pins that are pressed into the skull to keep the head in a fixed position. The placement of the clamp is probably the most stimulating and painful incident known in anaesthesia, and causes a *powerful sympathetic nervous system response*. The abrupt severe hypertension may increase intracranial pressure and cause intracranial haemorrhage. The only way to eliminate this response is to mark the spots where the pins will penetrate the scalp and *infiltrate the area from the skin to the periosteum with about 3 ml of lignocaine 2% and wait for about 5 minutes*. Thereafter, the clamp can be applied safely – if the surgeon sticks to the marked areas!
- Surgery involving the intracranial venous sinuses may be complicated by *massive air embolism*, particularly if the head is positioned higher than the heart. Should this happen, cardiovascular collapse may occur. The surgeon must immediately cover the source of embolism with a wet swab, while the anaesthetist gives 100% oxygen, is administers adrenaline and fluid in an attempt to force the air from the right heart. The head must be lowered to prevent further embolism. If a central venous cannula is *in situ*, the anaesthetist may try to remove some air from the heart.
- *Maintain CPP* (see above). Beware of a *decrease in blood pressure when ICP decreases* after removal of the space occupying lesion.
- *Maintain anaesthesia* with a vapour (< 1.0 MAC) and avoid nitrous oxide since intracranial air may expand. The use of an opioid will allow you to decrease the vapour concentration.
- Maintain adequate *muscle relaxation* with a nondepolarising agent.
- Administer *fluid as necessary for resuscitation*. *Maintenance fluid* consists of Ringer lactate with added sodium chloride.
- *Monitor* the ECG (may display neurogenic changes, especially of the ST segment and T wave), blood pressure (CPP), central venous pressure (if indicated by the type of injuries), pulse oximetry (SpO$_2$), capnography, temperature (maintain mild hypothermia), muscle relaxation (neuromuscular transmission), blood gases, acid-base state, electrolytes, glucose, and urinary output.
- Head injuries may be *complicated by hyponatraemia* due to an increase in secretion of vasopressin (ADH) or cerebral salt wasting (rarely with trauma, more often with subarachnoid haemorrhage) due to release of brain natriuretic polypeptide. The former causes hyponatraemia and oliguria, while the latter causes hyponatraemia and diuresis.
- The end-points of resuscitation of the head-injured patient are:
  o CPP of 60 mm Hg to 70 mm Hg, assuming an intracranial pressure of at least 20 mm Hg
  o SaO$_2$ (or SpO$_2$) > 90%
  o PaCO$_2$ in the low-normal range (31 mm Hg to 35 mm Hg in Pretoria; 35 mm Hg to 38 mm Hg at sea level)
  o Haemoglobin about 100 g L^{-1}
  o Mild hypothermia (about 35°C)
- *Extubation should be considered*, other injuries permitting, if the patient was not intubated preoperatively, and if surgery was uneventful.

The management of the head-injured patient are summarised in Table 1

Table 1 Management of the head-injured patient

ABC of resuscitation	Manage cerebral perfusion pressure and metabolic rate	End-points
Other injuries Cervical spine Airway Rapid sequence induction Haemodynamic resuscitation	Positioning Blood pressure Drugs: • Anaesthetic agents beneficial (lower ICP) • Mannitol (? in presence of interrupted BBB) • Steroids (? value in trauma) Permissive hypothermia	$CPP > 60$ mm Hg $SaO_2 > 90\%$ $PaCO_2$ normal Glucose normal Mild hypothermia $Hct > 100$ g L^{-1}

CHAPTER 26

ORTHOPAEDIC ANAESTHESIA

Main points
- An approach to the orthopaedic patient with regards pre- . intra- and post-operative management.
- The use of tourniquets in orthopaedic surgery.
- The management of patients with a cervical spine injury presenting for surgery and anaesthesia.
- Anaesthetic management of patient with spinal cord lesions. Only use the technique that you are most familiar with to perform endotracheal intubation in a patient with an unstable cervical spine.
- Anaesthetic management of patients with limb fractures.
- Fat embolism: How fat embolism is related to anaesthesia, how it presents and management of the patient with suspected fat embolism.
- The risk factors, clinical presentation and management of a patient with cement implantation syndrome.

*The most important approach to patients presenting with skeletal trauma is to prevent local and systemic complications by **early***:
- Resuscitation,
- Wound care,
- Reduction and fixation of fractures, and
- Mobilization of the patient.

The same approach applies to patients who undergo elective major skeletal surgery.

Perioperative approach to the orthopaedic patient

Pre-operative
- The orthopaedic patient population is highly variable. Patients vary from very young to very old and from healthy to frail and sick.
- Injury and co-morbid conditions (e.g. arthritis) may make functional assessment difficult and predispose to problems with the anaesthetic (e.g. atlanto-axial instability with rheumatoid arthritis)
- When planning a regional technique for the patient, take special note of the use and timing of anti-coagulant medication. Orthopaedic surgery is associated with a high risk of deep venous thrombosis and pulmonary embolism so many orthopaedic patients will either be on some form of anti-coagulation, or will receive it in due course.
- Emergency patients are often polytrauma patients. Therefore, all the considerations applicable to the severely injured need to be taken into account.
- Groups of patients deserving special attention are patients with autoimmune disease such as rheumatoid arthritis, patients with bone tumours, and patients with bone sepsis.

Intra-operative
- All patients need intravenous *antibiotic prophylaxis* prior to surgery. A single dose will suffice. If the procedure lasts longer than 4 hours, a second dose of antibiotics is required.
- Unusual *positioning* is often necessary for orthopaedic procedures. Take care to protect the patient's eyes, pressure points, and vulnerable nerves.
- *Blood loss* may be significant. Plan and ensure adequate IV access before starting surgery.
- A *tourniquet* is often applied.
- Insert a *urinary catheter* for long procedures or if an epidural or spinal anaesthetic is being used.
- Consider additional *monitoring* (e.g. central venous pressure, intra-arterial pressure line) according to the extent of surgery and patient co-morbidity (e.g. Cardiovascular disease); neuromonitoring (evoked potentials, wake-up test)

Post-operative
- Adequate *analgesia* is essential, as most orthopaedic patients need early mobilisation post-operatively.
- Many patients will receive *anti-coagulation* post-operatively. Take this into account when using neuraxial techniques.

Tourniquets

General principles

- Tourniquets are commonly used in orthopaedic surgery to provide a *bloodless surgical field*.
- *Pneumatic* tourniquets are preferable to mechanical tourniquets.
- The use of an Esmarch bandage is contra-indicated where there is *infection or malignancy* (due to the risk of dissemination).
- Adequate *exsanguinations* can be achieved by elevating the affected limb for 5 minutes before the application of the tourniquet.
- Exsanguination of the lower limbs leads to an increase in *central blood volume*. This may lead to acute decompensation in patients with *cardiovascular disease*.
- Peripheral vascular disease is a relative contra-indication to the use of a tourniquet.
- Avoid use of a tourniquet in patients suffering from *crush injuries*.
- The use of a tourniquet in patients with *sickle-cell disease* is controversial.

Technique

- Put cotton wool under the tourniquet cuff.
- Inflation pressure for the tourniquet cuff is based on the patient's pre-operative blood pressure:
  - For upper limb surgery use systolic BP + 50 mmHg
  - For lower limb surgery use systolic BP x 2
- Tourniquet *application time*s:
  - Inform the surgeon after *1 hour* has elapsed.
  - *1 hour 30 minutes* tourniquet time should be regarded as *a safe maximum*; 2 hours tourniquet time can be used, but may not be safe for all patients.
- *Following tourniquet release*, expect an increase in the end-tidal CO_2 and look out for signs of pulmonary emboli, decreased blood pressure and a decrease in the central venous pressure.
- *Tourniquet pain* (associated with prolong tourniquet inflation times) is accompanied by signs of sympathetic stimulation (tachycardia, hypertension) and usually does not resolve despite deepening the anaesthesia or providing additional analgesia. It usually develops 30 minutes to 60 minutes after tourniquet inflation and only resolves once the tourniquet has been deflated.

The double tourniquet technique and the intravenous block

This technique is used when an intravenous block (Bier block) is used. A Bier block is a form of regional anaesthesia for minor surgery on typically the hand, wrist, or foot.

Prepare a solution of 0.5% lignocaine sterilely. Please note: the lignocaine must not contain adrenaline or preservatives; *use the intravenous form* that is packed in an ampoule – not the multidose preparation that is packed in a vial and used for local infiltration. Ten ml of a 2% lignocaine solution is 200 mg. For a patient with an *ideal body mass* of 70 kg,[xxviii] this is about 3 mg kg^{-1} (remember, the toxic dose of lignocaine without adrenaline is 4 mg kg^{-1}). This is diluted with 30 ml of Ringer lactate to make 40 ml of a 0.5% (2% × 10 ml/40 ml) solution.

The skin proximal to the site of surgery is disinfected and an intravenous cannula is inserted into a vein proximal to the site of surgery. The cap at the back of the stylet of the cannula is used to occlude the cannula. *Two tourniquets* are put on the upper arm (or lower leg). The limb is exsanguinated by elevation of the limb and by applying a crepe bandage around the limb distal to the tourniquets. In an attempt to attenuate tourniquet pain in the awake patient, the *proximal* tourniquet is inflated to the required pressure, while the distal tourniquet next to it is left uninflated. The lignocaine solution is injected through the intravenous cannula. Replace the cap on the cannula. The solution fills the vascular bed distal to the inflated proximal tourniquet. The distal one next to it is left uninflated for about 5 minutes. This allows the lignocaine solution to reach and numb the tissue beneath the distal tourniquet. Thereafter, the distal tourniquet is inflated to the required pressure. When you are sure that

---

[xxviii] Doses of local anaesthetics are calculated according to ideal body mass or at the most according to the *obese dose-determining mass* (ODDM). ODDM = Ideal body mass + 0.4(total body mass – ideal body mass)

the distal tourniquet is adequately inflated, the proximal one is deflated. The intravenous cannula is left in situ and covered with a sterile dressing.

The distal tourniquet must remain inflated for *at least 30 minutes* to allow the lignocaine to bind to the tissue. Thereafter, is may be deflated slowly over about 5 minutes to avoid a surge of lignocaine to reach the systemic circulation. You must always have an anticonvulsant (e.g. midazolam) ready should the patient develop lignocaine toxicity. If the procedure lasts longer than about 45 minutes, the anaesthetist can hand the surgeon some more lignocaine solution to inject through the cannula – keeping the toxic dose in mind.

Due to its cardiotoxicity, ***bupivacaine or ropivacaine should not be used in a Bier block***.

Patients with cervical spine injuries
Many polytrauma patients have cervical spine injuries. Factors in the history and examination that increase the chance of cervical spine injury include:
- Intoxication
- Other distracting injuries
- Posterior midline tenderness of the neck
- Loss of consciousness
- Neurological fallout

Keep in mind that *three injuries are often associated*, namely head (brain) injury, facial fractures, and cervical spine injury. Injury of all three these zones dictate careful *airway management*. Moreover, inadequate initial management of these injuries has grave complications.

It is vital to assess the cervical spine in all trauma patients before administering anaesthesia. Cervical spine X-rays **<u>MUST be adequate and reported by a radiologist</u>**. The surgeon must have performed a thorough *neurological examination* prior to anaesthesia to assess the level and extent of injury. The *neurological status* must have been *documented* before you anaesthetise the patient. This is often difficult or impossible to assess in the polytrauma patient.

Immobilisation of a suspected cervical spine injury is vital so as to avoid further injury. Both the vertebral injury and the method to restrain neck movement, can compromise airway management. In the former case, manipulation of the airway during intubation is usually accompanied by neck movement, which can aggravate injury. Regarding neck immobilization: soft collars and head traction devices complicate airway management since they hamper mouth opening.

Airway management in the patient with a neck injury or suspected neck injury
Airway involvement must be assessed on the radiological investigations; particularly the presence of a *prevertebral (retropharyngeal) haematoma*. A haematoma in this space can compromise the airway and can be an *immediate life-threatening emergency*. Difficulty breathing and stridor are worrying signs and may signify impending airway obstruction. The patient may have dysphonia, dysphagia, and be unable to swallow (drooling). Unless unconscious, patients assume the position that provides maximum airway patency; they often prefer sitting up and lean forward. The patient must be left in the preferred position. All medical staff involved in these cases should be aware of this condition (Figure 1). Passage of an endotracheal tube may be impossible, while a tracheostomy may be very difficult as the patient can or should not extend the neck.

The best method to secure the airway in the patient with a potential cervical spine injury is controversial. ***During airway management, it is the task of the surgeon to maintain the head and neck in a position that he/she regards safe***. This is done with manual in-line immobilization (MILI). MILI can be done from above or from below. If it is performed from the head, the surgeon rests his elbows next to the patients head while supporting the side of the occiput, neck, and jaw from both sides. When performed from below, the surgeon stands next to the patient. He supports himself on his

elbows and stabilizes the jaw, neck, and head from below (Figure 2). Whichever method is used to secure the airway, it must always include MILI.

Figure 1 Prevertebral haematoma in an elderly patient after a fall. Note the narrowed airway.

Figure 2 Manual in-line immobilization

Conventional laryngoscopy causes minimal movement in the cervical spine below T3; the movement occurs mainly at the occipito-atlanto-axis levels.

Apart from *the surgeon*, you must have *an assistant conversant* in airway management. Ensure that *routine equipment* for airway management is on the anaesthetic machine. These include suction, laryngoscope with a choice of blades, stylet, and Magill forceps. There must be supraglottic airways, including a Guedel airway, nasopharyngeal airway, laryngeal mask airway (LMA), and FastTrach LMA. There must be a choice of endotracheal tubes, as well as infraglottic airways (crico-thyroidotomy set).

Additional devices that facilitate laryngoscopy are useful. These items are usually fibreoptic instruments and laryngoscopes with more acute curves combined with a fibreoptic component. If you have not used these instruments, or do not have access to them, or you do not feel fit to manage these airways, rather refer these patients to a specialist centre. This will prevent airway injury, further neurological fallout, and pulmonary aspiration. ***Use a method that you are comfortable with and have used before. Do not try new methods in the emergency setting.*** Whichever method is used planning is essential; the only requirement being minimal cervical spine movement while the airway is being secured.

In all these cases, *further complications must be prevented*. These complications are local (in the neck, neurological function) and systemic (other trauma, pulmonary aspiration, hypovolaemia,

anaemia, etc.).

Regarding airway management in the patient with a neck injury, the following scenarios are possible:
- The elective case with intact neurological state
- The emergency case with intact neurological state
- The expected difficult airway

The elective case with intact neurological state
The soft neck collar is preferably removed. Traction involving the mandible must be removed. If there is no airway involvement (anatomy, mobility), you may perform a conventional intravenous induction, relax the patient, and intubate. If you are unsure, you may induce the patient with a short-acting opioid such as alfentanil 15 μg kg^{-1}, followed 2 minutes later by propofol about 2 mg kg^{-1} and lignocaine 1.5 mg kg^{-1}. You can also do a vapour induction with sevoflurane and N$_2$O. When the end-expiratory sevoflurane concentration has been at least 4% for 4 minutes, inspect the airway using a conventional Macintosh or similar curved laryngoscope blade. If the vocal cords are visible with the latter two cases, the patient is relaxed, the anaesthetic deepened, and the patient is intubated. The disadvantage with a vapour induction is that the patient may move while falling asleep.

If you cannot see the vocal chords, refrain from repeated attempts since it causes neck movement and may worsen the neurological outcome. Allow the patient to wake up, and do an awake fibreoptic intubation. **Maintain MILI during all phases of airway management**, including induction and emergence from anaesthesia since patients may move while waking up.

The emergency case with intact neurological state
There are often associated injuries, hypovolaemia, anaemia, and the risk of pulmonary aspiration. The soft collar and traction is removed followed by MILI. If you do not anticipate problems with airway management, you can follow the method describe above, with the addition of a rapid sequence induction. Cricoid pressure is applied bimanually: the assistant puts the one hand beneath the cervical lordosis while applying cricoid pressure from the front with the other hand. If you are confident that you can see the vocal cords, you can give a fast-acting relaxant such as suxamethonium 1.0 mg kg^{-1} to 1.5 mg kg^{-1} or rocuronium 1.0 mg kg^{-1}.

If you cannot see the vocal cords, wake the patient up and proceed with a fibreoptic-based intubation. If airway obstruction occurs, you must insert a *supraglottic airway*, e.g. an LMA. Keep in mind that placement of an LMA requires extension of the neck, that the cuff of the LMA may cause movement of the cervical vertebra, and that cricoid pressure complicates the insertion of an LMA. *If you are confronted with a "cannot-intubate-cannot-ventilate" situation, you must embark on a surgical airway, i.e. a crico-thyroidotomy or tracheostomy*.

Management of the elective case with a known difficult airway
In this case, you can still attempt a vapour induction followed by inspection. However, an awake fibreoptic intubation (or even a tracheostomy) from the start may be the safer option.

Remember, that neck surgery can be performed *from anterior or posterior*. In both cases the airway may be compromised. With *anterior the approach*, the endotracheal tube may be compressed by retractors during surgery. With the *posterior approach*, the patient is in the prone position and tube kinking is possible. These problems are circumvented by using a *reinforced endotracheal tube*.

Anaesthesia for patients with spinal cord lesions
Spinal cord injury is complicated by somatic (motor and sensory) and autonomic fall out. Remember that lesions above C3 to C4 affect *diaphragmatic function*; these patients may either hypoventilate or may be apnoeic.

Several systemic complications commonly occur in these patients and are often fatal. These include lung infections, urinary tract infections, renal failure, anaemia, thromboembolism, osteoporosis, pathological fractures, decubitus ulcers, depression, and neuropathic pain. All of these comorbidities must be addressed during the perioperative period. Of all these neurological defects, the **autonomic neuropathy** has the greatest intraoperative implications.

The *pathophysiology of the autonomic neuropathy* of spinal cord injury consists of three phases:

- *Spinal storm* is the initial short-lived phase (hours). There is an intense neuronal discharge with a massive sympathetic response due to direct spinal cord stimulation. This may present as severe hypertension and cardiac dysrhythmias, which may lead to myocardial infarction, acute left ventricular failure, and pulmonary oedema.

- *Spinal shock* follows the spinal storm phase and persists for up to three weeks after injury. It is a time of hyporeflexia, including loss of sympathetic tone (see Autonomic neuropathy, Chapter 12). These patients present with severe *hypotension and bradycardia,* especially due to positioning, hypovolaemia, and positive pressure ventilation. Hypovolaemia must be treated promptly with volume expanders. A vasoconstrictor such as phenylephrine 1.0 μg kg^{-1} min^{-1} may be used for positional hypotension.

  The body below the level of the spinal lesion also loses its ability to respond to changes in body temperature; it becomes poikilothermic (the same temperature as the environment). Therefore, *guard against hypothermia in the cold theatre environment*.

  Regarding blood pressure and temperature: blood pressure must be maintained at normal or above normal levels since vulnerable spinal cord is dependent on adequate perfusion, while mild hypothermia may improve the neurological outcome.

- *Return of spinal reflexes* follows the phase of spinal shock. There is a return of efferent sympathetic discharge, muscle tone, and reflexes. This phase (autonomic hyper- or dysreflexia) is characterised by a massive, disordered autonomic response to somatic (skin, muscle, bone) or visceral (bowel, genito-urinary tract) stimulation below the level of the spinal cord lesion. These stimuli include bladder distension, bladder catheterisation, urinary tract infection, labour, cervical dilation, bowel obstruction, faecal impaction, and acute abdomen.

  Autonomic hyperreflexia is associated with lesions above the level of T6 and uncommon with lesion below the T10 level. The most likely cause is a loss of descending inhibitory control on regenerating pre-synaptic fibres. Stimuli below the lesion cause severe sympathetic discharge below the level of the lesion. If the vascular bed above the lesion is large enough to accommodate the blood volume shifted from the vasoconstricted blood vessels below the lesion, the cardiovascular response is mild. However, with higher lesions (commonly above T6), the blood volume shifted from below the lesion overwhelms the smaller capacity of the vascular bed above the lesion. This is characterized by anxiety, sweating, severe hypertension with a reflex bradycardia, headache, flushing, and nausea.

  Intraoperative autonomic hyperreflexia must be prevented by blocking afferent somatic and visceral stimuli. *General anaesthesia* including volatile agents prevents this response. *Spinal (intrathecal) anaesthesia* causes a deep sensory block and is very effective. *Epidural anaesthesia* gives a less dense block and is less effective. Regardless of the anaesthetic technique, the anaesthetist must have a *vasodilator ready* if the response should occur. Since the arterial and venous vasodilator sodium nitroprusside is no longer available, we are left with the venodilators *glyceryl trinitrate*. The dose is boluses of about 1 μg kg^{-1} followed (if necessary) by an infusion of about 1 μg kg^{-1} min^{-1}. I suggest that you *prepare a solution containing about 50 μg ml^{-1}* (e.g. 50 mg in 50 ml injection added to 200 ml saline in a *glass container*$\rightarrow$ 50 mg in 250 ml = 50 000 μg in 250 ml = 200 μg ml^{-1}. Take 5ml (1000 μg) of this solution and dilute it to 20 ml = 1000 μg in 20 ml = 50 μg ml^{-1}. The surgeon must stop the stimulus if possible, while the anaesthetist is administering boluses of about 50 μg.

Somatic hyperreflexia presents with muscle spasms, which is treated with the GABA$_B$ agonist *baclofen*.

Immobilization complicates the use of muscle relaxants. The appearance of *extrajunctional nicotinic receptors* decreases the sensitivity to *non-depolarising muscle relaxants*, while the massive muscle membrane depolarisation following the administration of *suxamethonium* is complicated by a large flux of K$^+$ to the extracellular fluid. This can cause a fatal *hyperkalaemia*. Opinions vary but most sources suggest avoiding suxamethonium from say 72 hours after the injury until at least 9 months after injury. However, it has been suggested that suxamethonium must be *avoided altogether* in these patients.

General intraoperative care of these often frail osteoporotic anaemic patients (as should be in all patients) includes attention to positioning, pressure points, and temperature. Since plegic patients are often exposed to latex catheters, they may develop a *latex allergy*.

Anaesthesia for limb fractures
The patient population and procedure time are extremely variable. Procedures vary from closed reductions, to open reduction and internal fixation, or external fixation. These procedures can be done under general or regional anaesthesia, or a combination of the two. When using regional anaesthesia, consider the possibility that *the signs heralding the onset of compartment syndrome in the affected extremity may be masked*.

Patients often have other injuries and are kept fasted for extended periods while awaiting surgery. Check for signs of dehydration and adequately rehydrate patients before surgery. Take a careful history and do a thorough examination. DO NOT FORGET THE CERVICAL SPINE! Consider aspiration prophylaxis and regard the patients as having a full stomach.

With long bone fractures, *occult blood loss* may be considerable. These patients also have an increased chance of developing *deep venous thrombosis*. *Tourniquets* are routinely used. Therefore, *antibiotic prophylaxis* must be given *BEFORE tourniquet* cuff inflation.

Fat embolism syndrome
Fat embolism occurs frequently (especially with long bone and pelvic fractures) and refers to the presence of fat globules in the blood and urine. *Fat embolism syndrome (FES)* is relatively rare and the diagnosis is generally made by exclusion. Although FES is more often associated with long bone fractures, it also occurs with acute pancreatitis, cardiopulmonary bypass, and liposuction. Always consider the diagnosis in the patient with significant fractures who becomes dyspnoeic.

FES typically consists of the triad of mental confusion, hypoxaemia, and petechiae over the neck, chest, and shoulders. It develops 12 hours to 36 hours after the insult, but may be fulminating. The hypoxaemia is the result of an acute lung injury (ALI). The ALI causes tachypnoea, dyspnoea, bilateral crepitations, haemoptysis, and diffuse opacification on chest X-ray photo. A coagulopathy may develop but is more likely a complication of the associated trauma. The temperature may increase to 42°C and a tachycardia is often present. Other signs include retinal changes (fat emboli), jaundice, and renal failure.

The pathophysiology of fat entering the circulation has a *mechanical and a biochemical* component. In the former, fat from the intramedullary bone compartment enters venous sinusoids and embolises to the lungs migrates through the lungs to the systemic circulation. According to the biochemical mechanism, triglycerides from the bone are liberated into the blood where high levels of catecholamines cause lipolysis, forming free fatty acids. The free fatty acids are directly toxic to the pulmonary capillary bed and pneumocytes.

The treatment of FES is supportive, namely resuscitation, reduction and fixation of fractures, and

ventilatory support.

Cement implantation syndrome

This syndrome is commonly seen in patients who are receiving hip or knee replacements where methyl methacrylate bone cement is used. Clinically the syndrome presents with hypoxia, hypotension, and cardiovascular collapse. Suggested causes of the syndrome include fat embolism, reaction to the methyl methacrylate bone cement, and air embolism.

Prevention and treatment include venting he bone cavity while the prosthesis and cement is forced into the bone shaft; pressures as high as 600 mm Hg in bone shafts have been recorded during insertion of the prosthesis pin and cement. Ask the surgeon to suction the bone cavity so that it is completely dry before bone cement insertion. Make sure that the patient is well hydrated and intravascularly full before cement insertion. Start volume loading as soon as you smell the cement. Vasoconstrictors such as phenylephrine may be necessary to treat the hypotension.

Congenital musculoskeletal conditions

Patients with congenital musculoskeletal conditions present for corrective procedures. These include scoliosis and club foot repair. These patients, especially patients with scoliosis, often suffer from other defects or diseases, e.g. pulmonary hypertension, the cause of the scoliosis (e.g. paralytic, neurofibromatosis), etc. The possibility of *malignant hyperthermia* must always be kept in mind in children with congenital musculoskeletal defects.

Summary

Patients presenting for orthopaedic procedures vary from healthy patients, to patients who have sustained major trauma, or suffer from significant co-morbidities. The ages of the patients vary from babies to centenarians. The procedures vary from minor with little systemic complications, to major surgery necessitating special postoperative care.

CHAPTER 27

EAR, NOSE AND THROAT ANAESTHESIA

Key points
- General considerations
- 99% of children are healthy except for infected tonsils. Therefore, it is a tragedy if this child has a complication during tonsillectomy, which may result in brain damage or death.
- Tonsillectomy is a dangerous procedure since the surgeon and the anaesthetist compete for the airway and catastrophic (although rarely) bleeding may result.
- Children which have developed pulmonary hypertension due to hypoxia caused by airway obstruction from tonsils and adenoids should only anaesthetised by a specialist anaesthetist as this is a dangerous condition with a high mortality if managed incorrectly.
- Maximum allowable blood loss
- Reflexes and dysrhythmias
- Positioning
- Induction
- Muscle relaxation
- Maintenance
- Monitoring
- Extubation
- Management of posttonsillectomy bleeding

Ear, nose, and throat (ENT) surgery deal with procedures involving the ears and airway, namely nose, paranasal sinuses, mouth, pharynx, and larynx. These procedures are characterised by airway involvement and the intensity of surgical stimulation:

- *Airway involvement* may be due to the nature of pathology (infection, tumours), or the nature of the surgery (rotation of the head for ear surgery). It is essential that the anaesthetist and the surgeon have a good report intraoperatively; the surgeon operating on the airway, the anaesthetist maintaining the airway.
- ENT surgery involves *richly innervated* structures by nerves carrying *parasympathetic and sympathetic fibres*: the *trigeminal nerve* to the mouth, nose, paranasal sinuses, and mouth; the *vagal nerve* to the ear, pharynx, larynx, and carotid bifurcation. These procedures are very *painful and stimulating*. They often evoke sympathetic (tachycardia and hypertension) and parasympathetic reflexes (bradycardia, secretions).
- *Acute airway obstruction* causes life-threatening hypoxaemia. This is caused by foreign bodies or infection, e.g. laryngotracheobrongitis (LTB) and epiglottitis.
- *Chronic airway obstruction* is complicated by *pulmonary hypertension* due to chronic hypoxaemia (enlarged tonsils and adenoids).
- Patients with ear pathology may have *concomitant airway infection*, e.g. babies and toddlers presenting for myringotomy to vent otitis media.
- Some ENT structures are in *close proximity to the brain*, which may become involved by ENT pathology (infection, tumours) or the procedure (ear surgery, sinus surgery).

Laryngeal procedures are not discussed in this chapter. These procedures require anaesthetists and surgeons experienced in airway management and oxygenation when tracheal intubation is precluded by the procedure or when intubation is problematic due to the nature of the pathology.

All patients having operations involving the mouth or pharynx should be intubated. Brief examinations under anaesthesia may be done without intubating the trachea, but the anaesthetist must always be ready to manage the airway appropriately.

Anaesthesia for adenotonsillectomy
Preoperative
- This procedure is mostly done on small children; often as a *day case procedure*. The procedure should be *done in the morning* since children do not tolerate long *nil per os* (see Chapter 22) periods, and to allow patients to stay at the facility until they are home-ready.
- Premedication consists of *paracetamol* 40 mg kg^{-1} as syrup (usually containing 120 mg paracetamol in 5 ml or 24 mg ml^{-1}). The *opioid dualist tilidine* (as Valoron^R drops) is added to the paracetamol syrup. The dose is 0.8 mg kg^{-1} to 1.0 mg kg^{-1} and there is 2.5 mg tilidine per drop. This premedication is given about 60 minutes preoperatively.
  Example: Write a premedication prescription for a child aged three years and a mass of 14 kg.

Paracetamol dose = 14 kg × 40 mg kg^{-1} = 560 mg = 560 mg/24 mg ml^{-1} = 23 ml ≈ 20 ml of syrup (round off to the safe side)

Plus *tilidine* 14 kg × 1 mg kg^{-1} = 14 mg = 14 mg/2.5 mg per drop = 5.6 drops ≈ 5 drops (round off to the safe side).

Therefore, your prescription will read:

Rx: Tilidine drops: 5 (five) drops added to 20 ml of Paracetamol syrup.

Administer 60 minutes preoperatively.

Intraoperatively

- *Induction and maintenance of anaesthesia*

In small children a vapour induction is done using sevoflurane (or halothane) in oxygen and air (avoid nitrous oxide since it increases postoperative nausea and vomiting). Do not forget to decrease the sevoflurane concentration to about 2.5% and halothane to about 0.8% (end-tidal concentration) once the child is anaesthetised. Thereafter, an ***intravenous cannula must be inserted. This is compulsory. No compromise. you are playing with fire!!! This drip is removed just before the patient is discharged home.***

Anaesthesia is maintained with a vapour in oxygen and air. The patient may breathe spontaneously. However, they tend do hypoventilate (increased PaCO$_2$), which may increase bleeding. Therefore, try to take over ventilation and use controlled ventilation.

- *Airway management*

The patient ***MUST BE INTUBATED***. Intubation is facilitated by administering alfentanil (potent quick-acting, short-acting opioid) and propofol. The doses are: *alfentanil,* about 15 μg kg^{-1} 90 seconds before laryngoscopy and *propofol*, about 1 mg kg^{-1} (not 2 mg kg^{-1} since the patient is already receiving sevoflurane) about 20 seconds before laryngoscopy. You may use suxamethonium (with 0.02 mg kg^{-1} atropine intravenously to prevent bradycardia) or a nondepolarising muscle relaxant before intubation. However, the duration of the procedure is 30 minutes or less, which is shorter than the duration of action of most nondepolarising relaxants.

The *route of intubation* (orally or nasally) is determined by surgeon preference. At Steve Biko Academic Hospital, patients are intubated through the mouth with an oral RAE tube (see Chapter 3). This tube is preferred since it fits snugly into the *Doughty blade of the Boyle-Davis mouth gag* used by the surgeons. This gag opens the mouth adequately, but does not cause compression of the endotracheal tube. The tube is also firmly gripped by the mouth gag and so will not be displaced. A device is placed externally on the chest to stabilise the mouth gag and this may limit ventilation.

Bradycardia can occur when the Boyle-Davis mouth gag is opened. It will subside if the gag is released and re-opened slowly. If it does not subside, atropine 0.02 mg/kg is given intravenously. Since the *gag may compress the ET tube*, the anaesthetist must constantly watch the capnogram and airway pressures. When the surgeon removes the gag, he/she must be careful not to extubate the patient.

The surgeon often places a *throat pack* into the hypopharynx. The assisting sister must record the throat packs. ***ENSURE THAT THE THROAT PACK IS REMOVED BY THE SURGEON AT THE END OF SURGERY!***

After removal of the gag, the anaesthetist must *inspect the tonsillar beds and pharynx* for bleeding. It is a good idea to insert a feeding tube to *empty the stomach* at this stage. The patient is *extubated when awake and in control of his/her airway*. Remember, the *posttonsillectomy airway is very irritable*. Laryngospasm (see Chapter 3) often occurs if these patients are extubated before they are fully awake. If laryngospasm occurs, it *may be necessary to re-intubate*. By that time, the patient is hypoxic, hypercapnic, hypertensive – all promoting bleeding. *Therefore, be patient and wait for the child to wake up before you extubate him/her.* If the patient would cough against the tube and

bleeding occurs, haemostasis was probably not adequate and then, the patient is at the right spot to manage a posttonsillectomy bleed. *Therefore, deep extubation is not advised.*

- *Intraoperative tonsillectomy blood loss*
  The blood supply of the tonsil is mainly from the external branch of the maxillary artery. Blood loss during a tonsillectomy is between 2 ml kg^{-1} and 4 ml kg^{-1} (this is body mass, not tonsillar mass!). Therefore, blood loss should be carefully monitored. Therefore, a child weighing, say 14 kg, may bleed about 50 ml. That is about 6% of his blood volume. You must calculate the allowable blood loss – especially in patients who are anaemic before surgery (see Chapter 18). A minimum target haematocrit has to be decided on prior to the procedure.
- *Intraoperative positioning*
  The patient is usually placed in a 15º head up position to reduce venous congestion. A strut placed on both sides of the head for stabilisation, is unfortunately not available at all hospitals.
- *Monitoring*
  The minimum monitoring includes an EKG, oximeter, capnography, blood pressure, and temperature. The latter is important since tonsillectomy is often the child's first anaesthetic and malignant hyperthermia may be evoked.
- *Extubation*
  VERIFY THAT THE THROAT PACK HAS BEEN REMOVED. These patients should be extubated when they are awake and able to maintain and protect the airways. The oropharynx, hypopharynx and nasopharynx should be suctioned carefully to remove blood, mucous or debris before extubation. Any secretion or object that touches the vocal cords can cause laryngospasm. Be careful not to suction the tonsillar bed since a clot may be dislodged and bleeding caused. After extubation a patient is turned onto the left slightly head-down position.
- *Home readiness after tonsillectomy*
  Ensure that there is no bleeding and that they are pain free before they go home. The facility should not be more than about half an hour's transport from the hospital should complications arise.

Posttonsillectomy analgesia and antiemetics (see also Chapter 10)
The most important and potentially fatal complication of tonsillectomy is postoperative bleeding. The use of *non-steroidal anti-inflammatory* drugs is contentious. These drugs inhibit platelet function. Although a few studies indicated the safety of the use of ibuprofen and diclofenak, a metanalysis of randomised controlled trials[54] concluded that these drugs should be avoided before and after tonsillectomy. Therefore, it seems to be safer to use paracetamol and opioids, e.g. tilidine and tramadol. *Antiemetics are not recommended* since they may mask the nausea caused by swallowed blood of postoperative bleeding.

Posttonsillectomy haemorrhage
Post-tonsillectomy bleeding may cause significant morbidity and mortality. Two types of tonsillar bleeds occur:
- *Primary bleed*
  This bleed occurs *within 24 hours* with a peak incidence eight hours post-operatively. This bleed is due to a *haemostatic problem* and is often massive. From an anaesthetic point of view, the management of this type of bleed is complicated by *difficult laryngoscopy* due to bleeding and local tissue oedema.
- *Secondary*
  This complication occurs *more than 24 hours* post-operatively with a peak incidence *one week* post-operatively. This is usually caused by *infection* in the tonsillar bed.

Two main problems of the posttonsillectomy bleed are important:
- *Hypovolaemia*
  Blood loss can be considerable. Mostly, this is not observed as the blood is swallowed and the diagnosis may only be made when a patient *vomits up large amounts of blood*. Therefore, a child should always be watched for the early sign of *excessive swallowing* postoperatively. An

intravenous line should as far as possible be secured before the induction of anaesthesia. Prior to starting, ensure that cross matched blood has been ordered and is available.

The patient must be returned to theatre as soon as possible. In the meanwhile, the patient should be resuscitated as well as possible. (This is why the intravenous line should only be removed when the patient is discharged after tonsillectomy.) If intravenous access is impossible, an *intraosseous needle* must be used (see Chapter 22).

- *Full stomach and risk of regurgitation and aspiration of swallowed blood.*

Induction of anaesthesia and intubation
You must have an *assistant*. The surgeon must also be able to perform an emergency tracheostomy. Ideally, an infusion should be started before induction. Patients have a *full stomach* due to swallowed blood. Therefore, as with the primary surgery, the patient must be intubated. Two well-functioning *suctions* next to the patient and a table that can tilt are essential.
It is not advised to place a nasogastric tube before induction, since this may dislodge clots (especially if adenoidectomy was performed) and it is unlikely that the blood in the stomach will be removed in this way since a lot of the blood consists of clots which will not pass through a nasogastric tube.

If the patient is *not bleeding actively and not shocked*, a *vapour induction* may be performed where after an *infusion* can be put up. Whether an intravenous or vapour induction is performed, a suction catheter can be inserted through the nose to clear blood from the pharynx during laryngoscopy. *However, if an adenoidectomy had be done, clots may be dislodged, which can aggravate bleeding.* Always *intubate through the mouth*, especially when an adeno-tonsillectomy was done.

Regarding the induction of anaesthesia and intubation, several options are possible:
- o A *rapid sequence induction* with cricoid pressure is the method most commonly performed. It may however be a problematic intubation due to excessive bleeding and oedema. The induction agent and muscle relaxant of choice are *ketamine 2 mg kg^{-1} suxamethonium 1 mg kg^{-1} to 1.5 mg kg^{-1}*, respectively.
- o A *vapour induction* in the left lateral position[xxix] with the head down and with cricoid pressure is used if the patient is bleeding actively. Once the patient is asleep, he/she can be turned on the back, and a laryngoscopy performed. If the vocal cords are visible, suxamethonium is administered, followed by intubation. Although the airway can be maintained more easily with this method, the risk of vomiting and aspiration is larger. *For the inexperienced anaesthetist this is probably the safest method.*
- o An *awake intubation* if the patient is severely shocked..
- o A *tracheostomy* may rarely be indicated if airway obstruction and massive bleeding makes endotracheal intubation problematic.

Extubation after posttonsillectomy bleed
Before extubation, the stomach should be emptied with a orogastric stomach tube (not nasogastric, especially if adenoidectomy was performed) to limit post-operative vomiting. Extubation is only attempted once the patient is awake and can protect his own airway.

[xxix] Remember, the glottis is slightly to the right of the esophagus. Therefore, the left lateral Trendelenburg position decreases the flow of fluid into the trachea.

CHAPTER 28

EYE SURGERY

Key points
- The *patient profile* presenting for eye surgery includes: Neonates, children, the elderly, diabetics
- The *choice of anaesthetic technique* depends on the procedure (long or short), intra-ocular or extraocular, age of the patient, ability of the patient to lie still and to co-operate.
- *Eye blocks*: Retrobulbar, peribulbar, subtenon.
- *Requirements for eye surgery*: Akinesia of the eye, hypertension or movement of the eye must be prevented, management of the oculo-cardiac reflex.
- Control of the *intra-ocular pressure*
- Be aware of the *systemic effects of eye drops.*
- *Smooth recovery* without nausea or vomiting
- *Strabismus surgery*
- *The open eye* is an emergency procedure and any increase in intraocular pressure must be prevented.

The patient profile presenting for eye surgery includes:
- Neonates with retinopathy of prematurity presenting present for laser therapy. These babies are usually premature, and have been or are ventilator dependent due to respiratory distress.
- Children present for correction of strabismus, glaucoma, refraction, or tumours.
- The elderly often present for cataract surgery.
- Diabetes is often complicated by cataracts, which should be removed.

All these patients suffer from their *age-specific co-morbidities*, which should be considered. These include hypertension, cardiac failure, and ischaemic heart disease. Ophthalmological procedures are done under topical (only local anaesthetic drops), regional (eye blocks) or general anaesthesia. The choice of anaesthetic technique depends on:
- The procedure (long or short)
- Intra-ocular (e.g. cataract surgery is usually done under an eye block) or extraocular (e.g. laser refraction procedures are done with topical anaesthesia)
- The age of the patient
- The ability of the patient to lie still and to co-operate

General anaesthesia for ophthalmological procedures is reserved for *children, confused* adults, and patient that *cough*. *Prolonged* surgery often necessitates general anaesthesia since it is very uncomfortable to lie still for a long time. *The following eye blocks are done*:
- Retrobulbar
- Peribulbar
- Subtenon

For a description of these blocks, please consult an anaesthesia text book.

Requirements for eye surgery
- Akinesia of the eye
- Intense analgesia
- Minimal bleeding
- Severe hypertension or movement of the eye must be prevented.
- Prevention of the oculo-cardiac reflex

The oculo-cardiac reflex
The oculo-cardiac reflex is caused by pulling on eye muscles or pressure on the eye. Traction on extraocular muscles or pressure on the eye can elicit a wide variety of cardiac dysrhythmias ranging from bradycardia and ventricular ectopy to cardiac arrest or ventricular fibrillation. This reflex consists of a trigeminal afferent (V1) and a vagal efferent pathway. It occurs more commonly in paediatric patients undergoing strabismus surgery. It can also be evoked in other age groups, and

during a variety of procedures. Management of the oculocardiac reflex consists of the following:
- o Tell the surgeon and cessation of stimulation until heart rate increases.
- o Confirm that the depth of anaesthesia is adequate.
- o Administer intravenous atropine 20 μg kg^{-1} if bradycardia persists.
- o The reflex eventually fatigues itself (self-extinguishes) with repeated traction on the extra ocular muscles.

Control of the intra-ocular pressure (IOP)
- The eye is a hollow sphere with a rigid wall. If the contents of the sphere increase, the IOP must rise, and can potentially cause extrusion of ocular contents through an open surgical or traumatic wound. Intraocular bleeding will increase IOP, as will a rise in venous pressure and an increase in arterial pressure.
- Any *anaesthetic intervention* that alters these parameters can affect IOP, e.g. laryngoscopy, intubation, airway obstruction, coughing, increase in central venous pressure, increase in PaCO$_2$ (hypoventilation) or Trendelenburg position. These factors should be prevented.
- *Anaesthetic drugs affect IOP*. Inhalants, opiates and intravenous drugs decrease IOP. Nondepolarising muscle relaxants do not increase intraocular pressure. Ketamine and suxamethonium increase IOP and should be used cautiously. We do however use suxamethonium in emergency eye surgery, as it is combined with intravenous induction agents and opiates, which will decrease IOP, and because good muscle relaxing conditions during intubation is more important in preventing a rise in IOP than the potential harmful effect of transient increased IOP due to suxamethonium.

Be aware of the systemic effects of eye drops
- *Echothiopate is a pseudocholinesterase inhibitor* (organophosphate) used to decrease intra-ocular pressure and provide miosis, but it can prevent the breakdown of suxamethonium causing suxamethonium apnoea.
- Timolol is a *β-adrenergic blocking agent* used in the eye to decrease intra-ocular pressure, but can cause bradycardia and bronchospasm.
- Ophthalmologists often put *vasoconstrictor drops*, e.g. phenylephrine, into the eyes to decrease bleeding. These vasoconstrictors are absorbed into the systemic circulation where they often cause severe hypertension. This often happens in small children and babies. Therefore, the surgeon must tell you what he/she is putting into the eyes!

Smooth recovery without nausea or vomiting
Vomiting increases IOP and can cause sutures to tear. Since eye surgery predisposes to vomiting, prophylactic anti-emetics should be considered.

Strabismus surgery
The *oculo-cardiac reflex* may be marked. There is an increased incidence of *malignant hyperpyrexia* and therefore temperature should be monitored. Strabismus surgery is often complicated by postoperative nausea and vomiting.

Penetrating eye injuries (The open eye)
This is an emergency and any increase in intraocular pressure must be prevented (see above):
- Avoid drugs that increase intraocular pressure such as *ketamine*.
- A *rapid sequence induction* is done.
- Controlled ventilation is preferable to maintain normocarbia.
- The inhalational agent of choice is *sevoflurane*.
- *Intubation and extubation* must be *smooth and atraumatic* to avoid hypertension and coughing.
- There is no point delaying the operation to ensure that the stomach empties since the stress response to trauma and pain *delays gastric emptying*.

CHAPTER 29

ANAESTHESIA IN REMOTE LOCATIONS, SEDATION, ELECTRO-CONVULSIVE THERAPY, AND DENTAL PROCEDURES

Key points
Factors to consider
- Facility
- Surgeon's needs
- Patient factors

Anaesthesia
- Administration of anaesthesia outside the theatre complex is fraught with danger and should not be embarked on without much consideration and preparation.
- Make sure that you have adequate recovery facilities for these patients with:
  o oxygen that can be given under pressure
  o adequate monitoring

It often happens that the anaesthetist is required to assist several subspecialties in *diagnostic or interventional procedures*. Anxious or uncooperative adults and most children are sedated or anaesthetized for these procedures. These procedures are performed in facilities where investigations require expensive equipment, which functions at *low temperature* (radiology suites). Regarding anaesthesia, these facilities are usually *poorly equipped and anaesthetist-unfriendly*. It is the task of the anaesthetist to familiarise himself with the equipment and *ensure patient safety*.

The principle of managing patients at remote facilities is called *monitored anaesthetic care (MAC)*:[55] [56]

- *Monitored*: Monitoring anaesthetic effect and patient safety
- *Anaesthetic*: Sedation, analgesia, management of complications
- *Care*: Patient safety, comfort

Guidelines for monitored anaesthetic care are available at the South African Society of Anaesthesiologists web site.[55] [56]

These facilities (areas) are mostly patient-unfriendly:
They are dark, cold, uncomfortable, noisy, and cramped. Furthermore, several of the procedures require uncomfortable body positioning (gastroenterology, nephrostomy). Problems related specific areas are:
- *Magnetic resonance imaging (MRI)*: Small area, difficult access to patient, no ferromagnetic equipment allowed, cold, and noisy.
- *Radiotherapy*: radiation pollution, small area, far away from the patient, dark (don't see disconnections, etc.)

The procedures performed include the following:
  o Diagnostic or interventional angiography (cardiac and systemic), such as endovascular prostheses and embolization.
  o Neuro-radio-angiography, e.g. coil embolization of intracranial aneurisms and arterio-venous malformations.
  o MRI
  o Gastroenterology, e.g. gastroscopy, colonoscopy, and endoscopic retrograde cholangio-pancreatography (ERCP).
  o Radiotherapy for children.

*Requirements for safe sedation and anaesthesia (**For sedation guidelines in adults and children, see** SASA Sedation Guidelines 2010)*[55] [56]

- *Standard equipment necessary*:
  - O_2 source and reserve
  - Ambu bag
  - Suction
  - Airway management equipment: tubes, airways, laryngoscopes
  - Monitoring visible from outside (glass window or video camera): pulse oximetry, capnography, and blood pressure
  - Resuscitation equipment (drugs, defibrillator, etc.)
  - Communication method to call for help
  - Scavenger
  - Safe electricity and battery back-up
- *Needs of the surgeon*:
  - Patient needs to lie still
  - Patient sometimes prone (sedation difficult in this position due to difficult monitoring and management of apnoea)
  - Manipulation of blood pressure might be necessary (increase for increased perfusion, decrease to limit bleeding)
  - Momentarily pause in respiration and/or heart beat (to deploy stents)
- *Factors related to the patient*:
  - Some patients *do not lie still* (Parkinson's disease, orthopnoea, gastro-oesophageal reflux), anxious, or *uncooperative*. In these patients, general anaesthesia is indicated.
  - Some procedures can take *several hours*. Even worse: some *lengthy* procedures require *patient co-operation*.
  - Consider *radio contrast* related side effects (iodine allergy, renal failure)
  - Remember to decrease the dose of sedatives in the elderly patient
- *The patients exposed to these environments are often compromised*:
  - Very young: babies presenting for auditory evaluation or babies with congenital abnormalities – often with brain lesion – presenting for radiological studies.
  - Very old: vasculopaths
  - Systemic diseases: patients with atherosclerosis, diabetes, hypertension, endocrine disease, hydronephrosis, or patients from intensive care
  - Localised disease with systemic effects: cerebral aneurism, intracranial arterio-venous malformations, brain tumour, endocrine tumours, gastrointestinal disease (anaemia, jaundice), etc.
- *Anaesthesia considerations*:
  - These procedures are often done on an out-patient basis. Therefore, use short-acting drugs.
  - Although many of these procedures may seem minor, *safety should never be scaled down*. One of these safety aspects is reliable *venous access*. Only flexible intravenous cannulas should be used (e.g. Venflon, Jelco, etc.); *no metal cannulas ("butterfly)"*.
  - Check for the availability of reversal drugs for sedation agents (flumazenil, naloxone).
  - Options for sedation include short-acting benzodiazepines (midazolam), propofol, opiates, ketamine, dexmedetomidine, and chloral hydrate.
  - Options for administration include IV bolus, TIVA, and TCI (target controlled infusion).

Electroconvulsive therapy (ECT)
This treatment is indicated in psychiatric patients with major depression, mania, schizophrenia, etc. who are unresponsive to other modalities of treatment. It consists of more or less 3 treatments per week for 6 to 12 treatments. An electric shock is administered to the brain causing seizure activity and this is followed by the release of neurotransmitters, which restores the biochemical balance of neurotransmitters in the brain. The electrical activity in the brain is accompanied by a general motor convulsion resulting in severe myalgia and often accompanied by long bone fractures and/or dislocations. These patients need muscle relaxants to prevent these complications and since it would be extremely uncomfortable and distressing to a patient to receive a muscle relaxant while he/she is awake, general anaesthesia is administered for ECT. A successful treatment consists of a seizure of

more than 25 seconds.

Considerations

- ECT is often done in *remote locations* (often in the only theatre located at a psychiatric hospital) (see considerations above)
- Patients are on *psychiatric medication* which may interfere with anaesthetic drugs (*lithium* enhances the duration of non-depolarising muscle relaxants and may cause renal impairment; *pethidine* may elicit a serotonergic syndrome in patients on *mono-amine-oxidase inhibitors* (MAOIs).
- ECT causes a massive *stress response*, which often manifests as a *brief parasympathetic* response (severe bradycardia) followed by a *longer lasting sympathetic* response (hypertension and tachycardia) which may cause raised intracranial pressure, cardiac dysrhythmias and myocardial ischaemia. The anaesthetist should anticipate these side-effects and be prepared to manage them.
- Anaesthetic agents may interfere with the *adequacy of the seizure* (Table 1). Drugs decreasing the duration of the seizure activity are best avoided. Therefore preferably no premedication is given.
- ECT does *not increase a patient's risk of aspiration*.
- Since patients undergo *multiple treatments* in a short period of time, *intubation should be avoided* to prevent trauma to the airway. Normocapnia is however important and mask ventilation should therefore continue until the patient is awake.
- *Documentation* is extremely important since the patient should receive a standardised anaesthetic (the same drugs in the same dosage) with every treatment.
- The procedure *lasts only a few minutes*. Long-acting muscle relaxants are therefore avoided.

Table 1 Effect of drugs on duration of seizures

Enhancing duration	No effect	Decreasing duration
Etomidate	Methohexital	Propofol
Alfentanil	Beta-blockers	Sodium thiopental
Remifentanil	Glyceryl trinitrate	Midazolam
Caffeine		Ketamine
Theophylline		Lignocaine

An example of a generic anaesthetic for ECT

- *No premedication* is given
- *Pre-oxygenate* (an apnoeic period will follow)
- *Alfentanil* (prevents severe hypertension and tachycardia without interfering with the adequacy of seizure activity)
- *Propofol* (slight reduction in seizure time but it is still adequate and it protects against the anticipated sympathetic response).
- *Suxamethonium* (0.5 mg kg^{-1} to 1.0 mg kg^{-1}) or *mivacurium* (0.15 mg kg^{-1} 0.2 mg kg^{-1}). Suxamethonium is most commonly used. Lesser dosages of non-depolarising muscle relaxants are inadequate to prevent myalgia).
- As soon as the patient is relaxed.
- The shock is administered during the period of apnoea. Stand back while the shock is being administered. B*e sure that the muscle relaxant has taken effect before the stimulus is allowed* – the patient might bite the endotracheal tube to pieces if he/she is not relaxed and the distal part might disappear down the airway! The use of a bite block next to the tube is advocated for this reason.
- After completion of the procedure, the patient is mask ventilated and receives an inhalant or Propofol boluses until spontaneous breathing resume.
- The inhalant is switched off and the patient allowed to wake up.
- NB: *Patients at risk of aspiration* should receive a *rapid sequence induction*! (Pregnancy, patients with severe gastro-oesophageal reflux disease).

Anaesthesia for dental surgery

Anaesthesia for dental surgery is challenging since the airway again shared by the anaesthetist and surgeon. Therefore, many of the principles noted for ENT (Chapter 26) surgery apply.

General principles
- All patients having oro-pharyngeal surgery needs *endotracheal (usually nasal) intub*ation.
- Dental surgeons frequently use *lignocaine with adrenaline* (1:80 000) for nerve blockade and haemostasis before procedures. The added adrenaline potentiates the dysrhythomogenic effect of halothane, often resulting in *premature ventricular contractions* (PVC; see Chapter 12).
- The entire oro-, hypo-, and nasopharynx should be *suctioned carefully* to remove blood, mucous and debris before extubation.

Specific consideration
- Dental procedures are often done as *day case surgery*. It is therefore crucial to follow the guidelines for day case admissions to prevent unsuitable patient being admitted.
- *Pre-operative evaluation* must be focused. It helps to have the patient fill in an evaluation form in the surgeon's office, and even to evaluate the patient in the pre-anaesthetic clinic, to determine suitability for day case surgery or not. When special investigations are needed (FBC, blood biochemistry, ECG, and X-rays), it will be required to obtain these before admission to *have results available timeously*.
- The *airway is shared* with the surgeon and must be protected at all times from obstruction, aspiration of blood, mucous, debris, and water from drills and rinsing. The risk for accidental *displacement of the endotracheal tube* remains real, and requires vigilance on part of the anaesthesiologist.
- Most dental procedures require *nasal intubation* as this allows better access to the oral cavity without risk of tube displacement. A north facing (connection on the brow) *RAE tube* is most convenient for this application, as it is less likely to be displaced, have the whole surface of the forehead to affix to, and all connection points are away from the surgical field and patient (lessens the chances of pressure sore). Use *half a size smaller* than you would normally use. *Heat the tube in hot water* before insertion to make it more pliable. Have the patient indicate the *nostril they breathe through the easiest*, and intubate via this nostril. Laryngoscopy to assess the glottis opening is done prior to insertion of the tube, to prevent epistaxis complicating what may be a difficult intubation. The tip of the ET-tube is steered into the glottis opening with a *Mac Gill forceps*, and advanced until the curvature reaches the nostril. Be careful not to damage the softened cuff with the forceps. Once the position of the tube is confirmed and the cuff inflated, strap the tube down onto the forehead.
- *Prevent injuries*. It is imperative that the *eyes be lubricated and closed* with an occlusive dressing before covering the surgical site with towels. Corneal abrasion is an immensely painful post-operative complication. Ensure the curvature of the ET-tube is not pulling on the *nasal alae of the nostril* it passes through. If prolonged, it may cause *pressure necrosis* of this area – which is extremely difficult to repair, will be very obvious (in your face so to speak), and may lead to medico-legal action.
- The use of a **throat pack** is mandatory in all dental surgery; it prevents aspiration of blood, mucous, and foreign matter such as dental conservation material. The throat pack should consist of a length of ribbon gauze. Small dissection swabs (Ratex) tied together or even a cut vaginal tampon will suffice. The **time of placement** of such a pack, **and** the amount of swabs used <u>**must**</u> be noted by the sister on the counting board, on the nursing notes and on the anaesthetic record, <u>**The end of the pack (or a suture tied to it) should preferably be visible outside the mouth at all times**</u> to remind the anaesthesiologist to remove it before extubation. <u>**Failure to remove the pack before extubation will result in airway obstruction. This will have serious consequence to the patient, and definite medico-legal action against the anaesthesiologist**</u>.
- Intra-oral **local anaesthetic blocks** should still be performed, even if the patient is under anaesthesia. The endogenous release of catecholamines during painful stimuli (extractions etc.) may predispose the patient to cardiac dysrhythmias (similar to the adrenaline in the solution)

especially during halothane anaesthesia.

- Some dentists still operate in the *dental chair*. The *sitting position* is detrimental to cardiovascular homeostasis since it decreases venous return, followed by precipitous decrease in cardiac output and hypotension. Elevation of the legs may counteract this, but intravascular volume expansion with fluids is needed too.
- Patients with **congenital or valvular heart lesions** may need anaesthesia for dental surgery before cardiac surgery. As this group of patients are still considered at increased risk for infective endocarditis, they require prophylactic antibiotics (see 2008 guidelines of the *American College of Cardiology at* www.acc.org and the American Heart Association at www.americanheart.org).[57]
- To supplement local anaesthesia, **conscious sedation** is fast becoming a favoured addition to the care of the dental patient. This may comprise a spectrum of interventions as simple as administration of Entenox® (oxygen: nitrous oxide 50:50) in the chair, to intravenous sedatives (midazolam, propofol, dexmedetomidine). Guidelines regarding the safe use of these modalities are available from the South African Society of Anaesthesiologists (SASA)
- The administration of an anaesthetic in a **location other than well-equipped operating room** is strongly discouraged. Before a patient's consciousness is pharmacologically depressed to a level where the airway reflexes cannot be guaranteed, the following basic requirements must be met:
  o A suction apparatus in working order
  o A table, bed or chair that can tip head down
  o A source of oxygen
  o Apparatus to ventilate a patient with (Ambu-bag, anaesthetic circuit with bag and ventilator)
  o A laryngoscope with series of blades
  o A complete set of endotracheal tubes and connections
  o Emergency drugs such as adrenaline, atropine, lignocaine for intravenous administration.

Patients may be discharged from a day care unit when the following criteria are met (also see Chapter 30):
- The patient is completely *awake* and orientated to time place and person
- The *vital signs* are stable, and has been for 30 min
- The patient has no *respiratory discomfort*
- There is no evidence of *bleeding*
- Post-operative *pain and PONV* have been addressed
- Small amounts of *oral fluids* are tolerated
- Patient is able to *empty the bladder*
- Patient is discharged into the *care of a responsible adult*
- Patient is discharged *to a location within 30 minutes of medical care*, preferably to the unit the patient was operated on

CHAPTER 30

POSTOPERATIVE CARE

Key points
- Understand the concept of MAC (*awake*)
- Understand the concept of a fully reversed patient
- Monitoring in PACU
- Documentation in PACU
- Discharge criteria from PACU (Aldrete's score)
- Requirements for a PACU
- Complications occurring in the PACU
  - o Post-operative delirium
  - o Post-operative delayed emergence
  - o Respiratory complications
- Reversal of opioids with naloxone
- Management of laryngospasm in theatre
- Management of post-intubation croup
- Management of a neck haematoma
- Management of hypotension
- Management of hypertension
- Management of dysrhythmias
- Management of pain
- Management of nausea and vomiting
- Management of hypothermia
- Management of post-operative shivering
- The nursing staff in recovery room should have experience in care of a critically ill patient, i.e. ICU trained.
- The patient should not leave the recovery room until the following are in order:
  - o Haemodynamically stable
  - o No respiratory distress
  - o No nausea and vomiting
  - o Patient is normothermic
  - o Patient is normovolaemic
  - o Pain must be adequately treated

At the end of a procedure, the administration of anaesthetics drugs is terminated or antagonized; their effects will decrease, followed by recovery of central (brain and spinal cord) and/or peripheral (peripheral nerves) neurological, and/or neuromuscular function. During the period before the patient is allowed to return to the ward, the patient is kept in the postanaesthetic care unit (PACU, recovery room)

RECOVERY FROM ANAESTHESIA
The systemic (general anaesthetics, muscle relaxants) or regional effects (local anaesthetics) of anaesthetic drug end when their concentrations decrease to subtherapeutic levels, or when their effects are antagonized by direct (naloxone for opioids and flumazenil for benzodiazepines), or indirect antagonists (neostigmine for nondepolarising muscle relaxants).

Before removal of the airway (endotracheal tube, laryngeal ask, oral airway, etc) the indications for placement of the airway must exist anymore:
- The patient must be awake (Glasgow coma scale > 8).
- The patient must be able to maintain and protect (risk of aspiration) the airway.
- Respiratory function (oxygenation, ventilation, lung perfusion, work of breathing) must have returned to levels that will maintain normocapnia and the oxygen saturation > 90% on a FiO_2 of < 40%.
- Haemodynamic function must have returned to levels that will ensure sufficient tissue perfusion.
- Temperature > 35°C

Extubation (See also Chapter 3)
- When tracheal intubation was difficult, caution must be taken before extubating the patient. One must be sure that he/she will be able to maintain the airway since re-intubation will probably be more difficult.
- The pharynx must be suctioned under vision to remove all secretions or foreign matter.

Transport to the PACU
- The patient must be awake, extubated, and neuromuscularly intact.
- There must be no critical need of cardiovascular, airway or ventilatory support.
- If the patient had received a perispinal (spinal or epidural) regional block there must be signs that neurological function is returning.

- An oxygen cylinder must be available to give oxygen to the patient if necessary.
- You must be able to tilt the bed to the Trendelenburg position if necessary.

Arrival in the PACU
The anaesthetist must hand over the patient to a trained PACU nurse. Inform the nurse about
- the procedure that was done.
- intraoperative complications.
- co-morbid conditions, e.g. hypertension, diabetes mellitus, etc.
- any treatment the patient must receive before discharge to the ward, e.g. analgesics, intravenous fluid, etc.

Before leaving the PACU, the anaesthetist must document the patient's blood pressure, heart rate, respiration, saturation, neurological function, and pain on his anaesthetic record.

Routine monitoring in the PACU
- **Consciousness**
- **Colour** of the skin and the mucous membranes.
- **Blood pressure** and **pulse** every 15 minutes until the patient is fully awake and stable.
- **Depth and rate of respiration**
- **Oxygen saturation**; give supplemental oxygen via mask if the saturation is < 91%.
- **Ability to move limbs and muscle strength:** As soon as the patient is awake, can respond to simple commands, and is able to lift his head off the pillow and to keep it raised for 5 s, he may be discharged to the ward. When a patient has received perispinal or limb blocks, the limbs must be positioned comfortably and pressure points attended to.
- **Bleeding:** Bleeding from wound, wound drains, and intercostal drains should be checked every minute
- **Temperature:** The patient must not be hypothermic as it increases oxygen consumption, bleeding, and infection.
- **Pain:** The patient must receive analgesic if necessary and must return to the ward pain free.
- **Urinary excretion:** If the patient has been catheterized, urinary output must be monitored. If uncatheterized patients remain in the PACU due to complications, urinary output must also be monitored. Excretion of less than 1 ml/kg/hr should be brought to the attention of the anaesthetist or the surgeon. This may be an indication of poor cardiac output.

NO PATIENT THAT IS HAEMODYNAMICALLY UNSTABLE OR DOES NOT BREATHE SATISFACTORILY SHOULD BE DISCHARGED FROM THE PACU.

Discharge from the PACU
Before discharge, a patient must meet certain criteria. The ***modified Aldrete score*** (Table 1) is the sum of numerical values assigned to activity, respiration, circulation (blood pressure relative to preanaesthetic level), consciousness, and oxygen saturation; a score of ≥ 9/10 indicates readiness for discharge to the ward.

Limitations of the Aldrete score:
This score does not take into consideration conditions that merit further observation in the PACU or further attention. These conditions may be present even when a patient has a score of 10. These conditions include:
- new cardiac *dysrhythmias*, whether they affect blood pressure or not
- *bleeding* at the incision site
- uncontrollable, severe *pain*
- persistent *nausea and vomiting*
- *hypothermia*

Table 1 The modified Aldrete score

Activity	moves all extremities voluntarily or on command	2
	moves two extremities	1
	unable to move extremities	0
Respiration	breathes deeply and coughs freely	2
	dyspnoeic, shallow or limited breathing	1
	apnoea	0
BP relative to pre-anaesthetic level	$\leq$ 20% higher or lower	2
	between 20 and 50% higher or lower	1
	$\geq$ 50% higher or lower	0
Consciousness	Fully awake	2
	Rousable on calling	1
	Not responding	0
O$_2$ Saturation	SpO2 > 92% on room air	2
	Supplemental O$_2$ required for SpO2 > 90%	1
	SpO2< 92% with supplemental O2	0

PACU FACILITIES

The **South African Society of Anaesthesiologists (SASA)** prescribe minimum standards for the recovery of patients. The PACU should be in an area within the theatre complex, preferably within easy reach of all the theatres, to which a patient is brought to recover from the anaesthetic prior to discharging them to the ward. **PACU equipment** must include:

- 1.5 beds per theatre
- The PACU bed must have cot sides or restraining belt, able to tilt to Trendelenburg position, and wheels that can be halted.
- Individual suction
- Individual O$_2$ outlets with flow meter, which can deliver low-pressure O$_2$ at 10L/minute.
- One drip stand per bed
- Blood pressure measuring device with an appropriate sized cuffs
- One intermittent positive pressure ventilator per 4 beds if an alternative ICU is not available; if an ICU is available, 1 ventilator per 10 beds
- One warming blanket/2 beds
- Laryngoscopes with adult and paediatric blades
- Endotracheal tubes of all sizes and with all connections available.
- One defibrillator per unit
- Writing surface at each bed

COMPLICATIONS OCCURING IN THE RECOVERY ROOM

Complications encountered in the PACU almost always involve more than one organ system. Of greatest concern are neurological, cardiovascular, respiratory, and endocrine complications. Prior to or during surgery the anaesthetist must advise the surgeon about the condition (co-morbid and surgical) of the patient and if the patient may go home after surgery, stay in the PACU for stabilization, or be transferred directly to high-care facility.

Organ dysfunction in the PACU is often a continuation of the effects of anaesthesia and surgery that persist and deteriorate in the postoperative period and is influenced by:

- *Age*: extremes of age
- *ASA status and co-morbid conditions*: cardiac, vascular, neurological (remember autonomic neuropathy, endocrine).
- *Type of surgery*: neurosurgery, head and neck (ear, nose, mouth, and throat, thyroid) thoracic, abdominal, vascular, spinal, limb surgery, radiological diagnostic or therapeutic procedures.
- *Surgical position*: supine, prone, lateral, sitting.
- *Duration* of surgery.
- *Anaesthetic technique*: General, regional, vapour, dose of opioids, use of muscle relaxants.
- *Intraoperative complications*: Blood loss, hypothermia.

All of the above factors to some extent apply to all the complications and will not be repeated.

Restlessness and prolonged emergence

- *Restlessness*

A restless patient must never be sedated if the cause of restlessness has not been identified and attended to. *Restlessness can be caused by*:

- o Cerebral effects of hypoxia and hypercapnia
- o Pain
- o Nausea
- o Full bladder
- o Uncomfortable body position
- o Hypothermia
- o Sevoflurane (delirium)
- o Ketamine (hallucinations)

Patients that had received ketamine should not be stimulated to wake up as stimulation intensifies the hallucinogenic effect. This effect wears off in about one hour. A sticker that indicates that the patient received ketamine must be placed on the patient's forehead.

- *Prolonged emergence*

Prolonged emergence may be the result of the residual sedating effect of anaesthetics – including neuromuscular block, opioids, benzodiazepines, and a high neuraxial block. Most of the non-drug causes can be excluded with a clinical examination, blood gas analysis, urea and electrolytes, and blood glucose (Table 2)

Table 2 Approach to delayed emergence

Cause, mechanism	Investigation	Treatment
Hypothermia (< 34°C)	Measure temperature	Warm patient
Cerebral hypoxia (low PaO_2, severe anaemia, low cerebral blood flow), intracranial pathology	Clinical, BGA, EEG, radiological	Cardiovascular support, intubate, ventilate
Hypercapnia (lung disease, anaesthetic drugs)	BGA	Intubate, ventilate, reverse drug
Metabolic acidosis (ketones, lactate, ingested acids)	BGA, ketones, lactate, toxicology	Resuscitate
Hypo- or hyperglycaemia	BG	Correct blood glucose
Electrolyte disturbances ($\uparrow Na^+$, $\downarrow Na^+$ e.g. after transurethral prostatectomy)	BGA, UKE	Correct disturbance
Uraemia	UKE	Correct disturbance
Endocrine (myxoedema coma, Addison)	UKE, thyroid tests	Correct deficiency

BGA Blood gas analysis; UKE Urea, creatinine, electrolytes; BG Blood glucose

Respiratory complications (Also see Chapter 13)

General and neuraxial anaesthesia affects all aspects of respiratory function to some extent: ventilation (absorption and compression atelectasis, diaphragmatic dysfunction), perfusion, diffusion, control of breathing (central and peripheral), and the integrity of the airway [reflexes (protection), tone (patency), patency]. Diaphragmatic function is decrease for days after abdominal surgery. Vital capacity decreases and closing volumes increase. Ventilation-perfusion disturbances aggravate hypoxemia. The patient should be encouraged to breathe deeply. Secretions should be removed, and oxygen administered to maintain a $SpO_2 > 92\%$.

- *Respiratory depression*

Hypoventilation may be caused due to the residual effects of opioids, sedatives, and vapours, muscle relaxants, perispinal block (high spinal or epidural block), *and very importantly, the interaction (often synergism) of these drugs.*

The effect of opioids on ventilation

All opioids suppress the effect of CO_2 on the respiratory system causing hypoventilation or apnoea. This effect is treated with the competitive opioid antagonist *naloxone*:

- o *Small dos*es of naloxone can reverse the respiratory depression without drastically reducing the analgesic effect of the narcotic.
- o *The dose* is 5 μg/kg intravenously. One ampoule contains 0.4 mg (400 μg). Dilute 0.4 mg to 10 ml (40 μg/ml) and administer increments of 2 ml (about 1 μg/kg in a 70 kg patient) every 2 minutes until ventilation is adequate.
- o *Side effects of naloxone*:
  - The *duration of action of naloxone is shorter* than that of the opiates. If ventilation improves after administration of naloxone the patient must stay in the PACU to observe any recurrence of hypoventilation.
  - The *analgesic effect of opioids may be reversed* promptly causing severe pain
  - The latter that may be complicated by sympathetic stimulation (remember, opioids are centrally acting sympatholytics). The ensuing *hypertension and tachycardia* is detrimental, especially in patients with cardiovascular disease.
  - Naloxone may cause *pulmonary oedema* due to hypertension causing cardiac failure, or due to its effect on pulmonary vascular resistance.

The effect of sedatives on ventilation
All sedatives, except ketamine, but including residual effects of anaesthetic vapours, decrease ventilatory drive of hypoxia and hypercarbia and cause apnoea. Patients with a blunted CO_2 response depend on the hypoxic drive of ventilation. They are therefore very susceptible to the ventilatory effects of opioids. The only drug available to reverse this effect is flumazenil, which reverses the effect of benzodiazepines. This is however a mere diagnostic measure as the drug is to short-acting to ensure a sustained anti-benzodiazepine effect.

- **The effect of residual muscle relaxation on ventilation**
  Muscle contraction may be ineffective due to insufficient reversal of the non-depolarising muscle relaxant. This diagnosis must be confirmed by neuromuscular stimulation as administration of additional neostigmine in a fully reversed neuromuscular block may in itself decrease the tone of the upper airway (genioglossus relaxation).
- **Pain and ventilation**
  Pain after upper abdominal and thoracic surgery hampers effective breathing.
- **Upper airway obstruction**

The upper airway starts at the lips and nostrils and ends at the vocal cords. Airway obstruction may be caused by pathology outside the airway, in the wall, or in the lumen of the airway. Airway obstruction is characterized by stridurous breathing, rib, sternal, and suprasternal retraction. The patient will always become hypoxic.

If the aetiology airway obstruction is not readily evident and is rapidly followed by hypoxia, the protocol for management of a difficult airway must promptly be instituted (Please see Airway management Chapter 3).

Protracted airway obstruction is often complicated by pulmonary oedema. The pathophysiology of this phenomenon is unclear but may be due to negative pressure or to disruption of alveoli during inspiration against the obstruction. This complication is treated by administration of oxygen via a constant positive airway pressure (CPAP) mask or intubation and ventilation. The oedema usually subsides within 24 hours.

- o *In the lumen*
  Blood, secretions, throat packs, teeth, etc may obstruct the upper and lower airway.

- o *In the wall*
  Sedatives and residual muscle relaxation cause an increase in upper airway resistance, partially due to relaxation of the genioglossus muscle and a falling back of the tongue posteriorly into the oropharynx. To correct this, the head has to be extended and the angle of the mandible should be lifted in an anterior direction. An airway can be inserted if the patient is still deeply

sedated. Remember that the presence of an airway between the teeth makes swallowing very difficult and may promote aspiration.

Laryngospasm (see also Chapter 3)
Laryngospasm is a potentially fatal complication and is caused *spasm of the supraglottic muscles*. It is *caused* by irritation of the supraglottic mucosa by secretion, blood, suctioning, or acute hypocalcaemia following thyroidectomy.
Treatment of laryngospasm:
- *Secretions and blood* should be removed from the pharynx by suctioning.
- Try to insert an airway *ventilate with 100% of oxygen*.
- *If spasm persists*, the patient becomes hypoxic, and the anaesthetist is convinced that the obstruction is not caused by pathology that would make re-intubation difficult or impossible [(severe swelling or bleeding, which may necessitate a surgical airway (crico-thyroidotomy)] the *spasm can be aborted* by administration of *propofol* 1 mg/kg to 2 mg/kg and *lignocaine* 1 mg/kg, followed by laryngoscopy to inspect and clear the airway from foreign matter, after which the patient is *ventilated* with 100% of oxygen.
- It may be necessary to administer *suxamethonium* (0,3 mg/kg) and to *reintubate* the patient. (Remember the interaction between neostigmine and suxamethonium, namely that neostigmine administered at the end of surgery is still inhibiting PChE resulting in a prolonged effect of suxamethonium).
- If *laryngospasm recurs*, spraying of the hypopharynx with lignocaine may be useful. Remember, however, that topical anaesthesia of the pharynx removes proprioception resulting in loss of pharyngeal tone, inhibition of the cough reflex, as well as inability to swallow. All these factors may contribute to further airway compromise.

Post-extubation croup[58]
Post-extubation croup is defined as inspiratory stridor and croupy cough after extubation. In children, it occurs in about 2.5% after short-term surgery/anaesthesia-related intubations, but in about 25% in the critical care practice scenario. Postextubation oedema (croup) is associated with airway trauma during intubation, tube size, duration of intubation, and children.

The supraglottic airway is a muscular compliant tube lined by supple squamous epithelium. The subglottic airway is lined by ciliated columnar epithelium. This lining is frail, loosely bound to the submucosa, and may be infiltrated with fluid (oedema).

In children, the subglottic larynx (cricoid ring) is the narrowest part of the airway. It is rigid, and unable to expand when the mucosa swells. This may cause airway compromise.
Mechanical trauma by the endotracheal tube is an important cause of subglottic stenosis. Movement of the tube may cause mucosal erosions and inflammation oedema, while pressure on the mucosa causes ischaemic necrosis (remember, the perfusion pressure of the tracheal capillaries is only about 15 mm Hg).
Postextubation croup preventable by selecting the proper tube size, avoid over inflation of the tube cuff (an audible leak at < 25 cm H_2O), and fixation of the tube that will prevent movement of the tube in the trachea. Once the diagnosis of postextubation croup is made, the patient must receive humidified oxygen, adrenaline inhalations and intravenous methylprednisolone (about 1 mg/kg) or dexamethasone (about 0.15 mg/kg).[59] If the work of breathing is to high re-intubation may be necessary.

o *Outside the wall*
   After surgery of the neck (e.g. thyroidectomy, parathyroidectomy, and carotid endarterectomy), swelling or haematoma outside the airway may obstruct airflow. In such cases, wound sutures must be removed to relieve the tension.
   Pneumothorax may present in the PACU and is characterised by hypoxaemia, mediastinal shift, and, if under tension (tension pneumothorax), cardiovascular collapse.

Cardiovascular complications (Also see Chapter 12)
The most common cardiovascular complications observe in the PACU are hypotension, hypertension, and tachycardia.

- *Hypotension*
  All he causes of intraoperative hypotension also occur or may persist into the postoperative period. It is often essential to continue intraoperative resuscitation in the PACU (Table 3).

Table 3 Postoperative hypotension

Derangement	Aetiology	Treatment
Absolute hypovolaemia	gastrointestinal fluid losses, bleeding, etc.	Elevate the legs. Intravenous volume expander
Relative hypovolaemia	Neurogenic due to neuraxial block	Vasoconstrictors: *Phenylephrine* 0.5 μg/kg to 1 μg/kg IVI (dilute 10 mg ampoule in 200ml normal saline = 50μg/ml; the usual dose is about 1 ml) *Ephedrine* 0,1 mg/kg IVI (dilute 50 mg ampoule to 10ml with sterile water = 5 mg/ml; the usual dose is about 1 ml). *Etilephrine* (Effortil) 150 μg/kg IVI (dilute 10mg ampoule to 10 ml = 1 mg/ml = 1000 μg/ml; the usual dose is about 8 mg) In the presence of a bradycardia ephedrine or etilephrine is preferred, phenylephrine is administered in the presence of a tachycardia.
Myocardial ischaemia	Ischaemic heart disease, hypotension, hypertension, dysrhythmias, anaemia	Oxygen mask Glyceryl trinitrate sublingual tablet of spray Treat the other causes
Dysrhythmias	Often a sign of significant heart disease	Treat the underlying cause
Cardiac failure	Often present preoperatively	Adrenaline is the choice inotrope. The dose is 50 ng/kg/min to 200 ng/kg/min. Dilute 1 mg ampoule to 10 ml = 0.1 mg/ml = 100 μg/ml. Dilute 1 ml of this solution to 20 ml = 5 μg/ml = 5000 ng/ml. The usual dose/min for an adult of 70 kg is 70kg x 100 ng/kg = 7000 ng = 1.5.ml/min of the second dilution.
Tension pneumothorax	Brachial plexus block, subclavian or internal jugular central venous catheters, laparoscopic surgery	Intercostal drain

- *Hypertension*
  The most common causes of hypertension in the PACU are:
  o Pre-existing hypertension
  o Pain
  o Fluid overload
  o Full bladder
  o Hypoxaemia and hypercapnia
  o Myocardial ischaemia
  o Increased intracranial pressure
  o Hypothermia
  o Endocrine disease: diabetes, hyperthyroidism, phaeochromocytoma, Cushing syndrome

Treatment of hypertension in the PACU consists of treatment of the underlying cause. Morphine is analgesic, sedative, and sympatholytic. Boluses of about 30 μg/kg every 3 minutes is administered IVI to effect.

Protracted hypertension is treated by intravenous vasodilators, including

- o *MgSO$_4$* 30 mg kg^{-1} to 50 mg kg^{-1} IVI over 5 minutes (Remember the interaction with neuromuscular blocking agents.)
- o *Glyceryl trinitrate* 0.5 to 1 µg kg^{-1} min^{-1} IVI (Put 50 mg ampoule into 200 saline in a glass container = 250 µg ml^{-1}. Dilute 1 ml to 10 ml = 25 µg ml^{-1}. Give 2 ml prn)
- o *Labetalol* 30 µg kg^{-1} min^{-1} to a total of about 2 mg/kg (100 mg in 20 ml ampoule = 5 mg ml^{-1}. The usual dose is about 2 mg min^{-1})
- o *Dihydralazine* (Nepresol) 200 µg kg^{-1} IVI over 10 min (Dilute 25 mg ampoule to 10 ml saline = 2.5 mg ml^{-1}. The usual dose is about 15 mg.)

- **Dysrhythmias** (See Chapter 12)

Dysrhythmias may be due to pain, hypoxia, hypercarbia, electrolyte imbalances, acid-base deviations and previous problems with the myocardium. Each one of these causes should be treated. The most common dysrhythmia observed in the PACU is a sinus tachycardia, is often associated with pain, and accompanied by hypertension.

Pain (see also Chapter 10)

This is one of the commonest complications seen in the PACU. Pain must have been treated adequately before sent to the ward. Several modalities can be used, including paracetamol IVI or per rectum, ketorolac IVI, diclofenac per rectum, and morphine IVI, subcutaneously, or intramuscularly.

Postoperative nausea and vomiting

Nausea and vomiting are common problems following diagnostic and therapeutic interventions. After pain, PONV accounts for the most common cause of distress to patients in the postoperative period. The aetiology is multifactorial:

The patient
- History of PONV
- Patients prone to motion sickness
- Children > adults
- Women > men
- Within about a week of menstruation
- Non-smokers > smokers

Anaesthetic techniques
- Reported at the onset of *hypotension* following spinal or epidural anaesthesia
- Inhalational anaesthetic technique causes more PONV than a non-opioid total intravenous anaesthesia (e.g. propofol). Remember that a patient with a history of severe protracted PONV might have suffered from subclinical halothane hepatitis. Therefore, a total intravenous anaesthetic (TIVA) should be considered in these patients.
- Opioid and ergometrine administration

Surgical procedures
- Strabismus surgery
- Middle-ear surgery
- Laparoscopy
- Dilatation of cervix and ovum retrieval
- Orchidopexy
- Tonsillectomy

Prevention and treatment (see Table 4)
- Allowing a clear carbohydrate-containing *oral hydration fluid* (ProvideXtra) up to 2 hours preoperatively is useful.
- *Propofol* is antiemetic. Therefore, a propofol TIVA technique is indicated in patients with a history of severe PONV.

- *Selective 5-HT$_3$ antagonists*. In our hospital, ondansetron[xxx] is used.
- The *antihistamines* cyclizine and droperidol[xxx]
- Dexamethasone
- *A combination of at least two modalities is recommended*.
- *Metoclopramide is ineffective*.

The following protocol is used in our hospital

1. Administer ondansetron 0.1 mg kg^{-1} slowly IVI intra-operatively if *ALL* the following factors are present:
   a. Patient is > 18 years old
   b. Female patient
   c. Post-operative opioids will be necessary
   d. Type of surgery involves major surgery (especially gynaecological or urological surgery), strabismus repair, breast, ear or laparoscopic surgery
2. If a patient presents with a history of PONV (male or female patients) and comes for the above-mentioned procedures:
   a. Administer ondansetron 0.1 mg kg^{-1} slowly IVI intra-operatively AND dexamethasone 0.1mg kg^{-1} IVI intra-operatively.
   b. Consider TIVA or TCI with propofol to avoid inhalational agents.
   c. Avoid the use of N$_2$O.
   d. Minimise the use of intra-operative opioids by opting for regional techniques or supplementing the anaesthesia with local anaesthesia, paracetamol and/or NSAIDs if not contra-indicated.

If a patient presents with nausea/vomiting in the recovery room – administer ondansetron 4mg slowly IVI (remember prolonged QT interval caused by ondansetron, especially in patients that may be prone to develop a long QT intervals, e.g. hypokalaemia).

Table 4 Antiemetics

Group	Example	Dose	Side effects
H$_1$antagonist	Cyclizine	0.8 mg kg^{-1} IVI/IMI 8 hourly	Drowsiness, antimuscarinic, extrapyramidal effects
Antidopaminergic	Droperidol	10 μg kg^{-1} IVI 8 hourly	Drowsiness, extrapyramidal, α$_1$ antagonist, prolonged QT interval
Antimuscarinic	Scopolamine	5μg kg^{-1} SC or IMI 6 hourly	Antimuscarinic
5HT$_3$ antagonist	Ondansetron	0.05 mg kg^{-1}0.1 mg kg^{-1}8 hourly	Antagonises effect of tramadol, prolonged QT interval
Glucocorticoid	Dexamethasone	0.1 mg kg^{-1} IVI *after* induction of anaesthesia	Severe perineal pain if injected rapidly in the awake patient.

Hypothermia and shivering

Hypothermia is a common complication of anaesthesia and surgery. Intravenous, inhalational, and epidural anaesthesia is commonly followed by shivering - more often after general (halothane shakes) than after epidural anaesthesia. Anaesthesia interferes with temperature regulation, which almost invariably, cause a decrease in core temperature intraoperatively.

Temperature control returns as soon as levels of anaesthetic drugs decrease. The physiological response to hypothermia (*rewarming*) is activated and the patient will start heat production (non-shivering and shivering thermogenesis), as well as heat conservation (vasoconstriction). Rewarming is modulated by the sympathetic nervous system and is accompanied by an increase in oxygen consumption. Rewarming is therefore accompanied by hypertension (vasoconstriction), tachycardia,

---

[xxx] Intravenous ondansetron and droperidol can prolong the QT interval and predispose patients (e.g. hypokalaemic patients) to the development of torsade de pointes.

and an increased oxygen extraction from blood. Hypothermia is poorly tolerated in the presence of impaired cardiac (cardiac failure, ischaemic heart disease) or lung reserve, or anaemia. Rewarming is followed by rewarming vasodilatation and hypotension (*rewarming shock*). Rewarming shock must be treated by cautious volume replacement.

These patients occasionally may have to be given Pethidine 25 mg intramuscularly to stop the shivering.

Treatment of postoperative shivering:
- Heat *conservation* (warm blankets)
- *Active heating* [hot air blanket (Bair Hugger), warm fluids]
- *Pharmacological*:
    - Pethidine 0.3 mg kg^{-1} IVI
    - Tramadol 1.0 mg kg^{-1} IVI
    - Ketamine 0.25 mg kg^{-1} + midazolam 0.04 mg kg^{-1} (37.5 μg kg^{-1}) IVI
    - Clonidine 2 mg kg^{-1} IVI at the end of surgery
    - Ondansetron 0.1 mg kg^{-1} before induction of anaesthesia

CONCLUSION

The patient in the PACU suffers from the consequences of some intervention. These consequences almost invariably cause derangements of all the vital organ systems: central and peripheral (including autonomic) nervous system, cardiovascular, respiratory, haemodynamic, and metabolic. Before discharge from the PACU these derangements must have disappeared to such an extent that will ensure comfort and survival on the ward. If these aims are not attainable the patient must be discharged to a high care facility.

REFERENCES

[1] Chung F, Subramanyam R, Liao P, Shapiro C, Sun Y. High SROP-Bang score indicates a high probability of obstructive apoea. Brit J Anaesth. 2012;108(5):768-775.

[2] Wilson ME, Spiegelhalter D, Robertson JA, Lesser P. Predicting difficult intubation. British Journal of Anaesthesia. 1988 Aug;61(2):211-216.

[3] Kim WH, Ahn HJ, Lee CJ, Shin BS, Ko JS, Choi SJ, Ryu SA. Neck circumference to thyromental distance ratio: a new predictor of difficult intubation in obese patients. British Journal of Anaesthesia 2011 Feb; 106(5): 743-748.

[4] Rujirojindakul P, Geater AF, McNeil EB, Vasinanukorn P, Prathep S, Asim W, Naklongdee J. Risk factors for reintubation in the post-anaesthetic care unit: a case-control study. British Journal of Anaesthesia. 2012 Jul;109(4):636-642.

[5] Anaesthesia UK. Entenox. http://www.frca.co.uk/article.aspx?articleid=100364.

[6] Lerman J. Pharmacokinetics of inhalation anesthetics. In: Foundations of Anesthesia. Ed: Hemmings HC Jr, Hopkins PM. Philadelphia: Mosby Elsevier;2006.323-335.

[7] Koblin DD. Inhaled anesthetics: Mechanism of action. In: Miller's Anesthesia, 6th edition; Philadelphia: Elsevier Churchill Livingstone;2005:105-131.

[8] Pagel PS, Kersten JR, Farber NE, Warltier DC. Inhaled anesthetics: Cardiovascular pharmacology. In: Miller's Anesthesia, 6th edition; Philadelphia: Elsevier Churchill Livingstone;2005.191-230.

[9] Farber NE, Pagel PS, Warltier DC. Inhaled anesthetics: Pulmonary pharmacology. In: Miller's Anesthesia, 6th edition; Philadelphia: Elsevier Churchill Livingstone;2005.155-190.

[10] Martin JL. Metabolism and toxicity of inhaled anaesthetics. In: Miller's Anesthesia, 6th edition; Philadelphia: Elsevier Churchill Livingstone;2005.231-272.

[11] Kopman AF, Eikermann M. Antagonism of non-depolarizing neuromuscular block: current practice. Anaesthesia 2009; 64 (Suppl. 1): 22-30.

[12] Neal JM, Bernards CM, Butterworth JF, Di Gregorio G, Drasner K, Hejtmanek MR, Mulroy MF, Rosenquist RW, Weinberg GL. ASRA Practice advisory on local anesthetic systemic toxicity. Regional Anesthesia and Pain Medicine. 2011 March-April;35(2):152-161

[13] White PF.The Changing Role of non-opioid analgesic techniques in the management of postoperative pain. Anesth Analg 2005;101:S5–S22.

[14] Narchi A, Benhamou D, Fernandez H. Intraperitoneal local anesthetic for shoulder pain after day-case laparoscopy. Lancet. 1991: 338: 1569–1570.

[15] Thiele RH, Nemergut EC, Lynch C. The physiologic implications of isolated alpha$_1$ adrenergic stimulation. Anesth Analg. 2011;113(2):284-296.

[16] Thiele RH, Nemergut EC, Lynch C. The clinical implications of isolated alpha$_1$ adrenergic stimulation. Anesth Analg. 2011;113(2):297-304.

[17] Feihl F, Broccard AF. Interactions between respiration and systemic hemodynamics. Part I: basic concepts. Intensive Care Medicine. 2009;35:45-54.

[18] Feihl F, Broccard AF. Interactions between respiration and systemic hemodynamics. Part II: basic concepts. Intensive Care Medicine. 2009;35:189-205.

[19] For an excellent review the student is referred to Wilson WC, Aronson S. A sign of renal success or impending renal failure? Anesthesiology Clinics of North America 2001; 9(4):841-883.

[20] Subramanian S, Ziedalski TM. Oliguria, volume overload, Na$^+$ balance, and diuretics. Crit Care Clin 21 2005; 291– 303

[21] Garg RK. Anesthetic considerations in patients with hepatic failure. International Anesthesiology Clinics. 2005;43(4):45-63.

[22] Malik R, Mookerjee RP, Jalan R. Infection and inflammation in liver failure: two sides of the same coin. Journal of Hepatology. 2009;51(3):426-429.

[23] British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patient (http://www.asgbi.org.uk/en/surgical_resources_and_documents/)

[24] Adapted from: Madjdpour C, Spahn R. Allogeneic red blood cell transfusions: efficacy, risks, alternatives and indications. British Journal of Anaesthesia 2005; 95(1): 33-42.

[25] O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, Williamson LM, British Committee for Standards in Haematology, Blood Transfusion Task Force. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. British Journal of Haematology. 2004 Jul;126(1):11-28.

[26] Horlocker TH, Wedel DJ, Benzon H, Brown DL, Enneking FK, Heit JA, Mulroy MF, Rosenquist RW, Rowlingson J, Tryba M, Yuan C-S.Regional anesthesia in the anticoagulated patient: Defining the risks (The Second ASRA Consensus Conference on Neuraxial Anesthesia and Anticoagulation). Regional Anesthesia and Pain Medicine 2003 May-June;28(3):172-19

[27] O'Donnell M, Kearon C. Perioperative management of oral anticoagulation. Cardiol Clin. 2008;26:299-309.

[28] Kraai EP, Lopes RD, Alexander JH, Garcia D. Perioperative management of anticoagulation: guidelines translated for the clinician. J Throm Thrombolysis. 2009;28:16-22.

[29] Messinezy M, Pearson TC. ABC of clinical haematology. Polycythaemia, primary (essential) thrombocythaemia and myelofibrosis. BMJ. 1997 Feb 22;314(7080):587-590.

[30] O'Donnell M, Kearon C. Perioperative management of oral anticoagulation. Cardiol Clin. 2008;26:299-309.

[31] Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrobotic therapy: American College of Chest Physicians Evidence-based clinical Practice Guidelines (8thed). Chest. 2008;133:299S-399S.

[32] Vandermeulen E, Singelyn F, Vercauteren M, Brichant JF, Ickx BE, Gautier P, Belgian Association for Regional Anesthesia Working Party on anticoagulants and, central nerve blocks. Belgian guidelines concerning central neural blockade in patients with drug-induced alteration of coagulation: an update. Acta Anaesthesiologica Belgica. 2005;56(2):139-146.

[33] Green L, Machin SJ. Managing anticoagulated patients during neuraxial anaesthesia. British Journal of Haematology. 2010 Apr;149(2):195-208.

[34] Breivik H, Bang U, Jalonen J, Vigfusson G, Alahuhta S, Lagerkranser M. Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine.Acta Anaesthesiologica Scandinavica. 2010 Jan;54(1):16-41.

[35] Ketchman L, Hess JR, Hiippala S. Indications for early fresh frozen plasma, cryoprecipitate and platelet transfusion in trauma. Journal of Trauma. 2006;60:S51-S58.

[36] Fiechtner BK, Nuttall GA, Johnson ME, Dong Y, Sujirattanawimol N, Oliver WC Jr, Sarpal RS, Oyen LJ, Ereth MH.Plasma tranexamic acid concentrations during cardiopulmonary bypass.Anesthesia & Analgesia. 2001 [cited 2001 May];92(5):1131-6.

[37] Heiko L, Böttiger BW, Henkelbein J, Krep H, Bernhard M. Coagulation management in multiple trauma: a systematic review. Intensive care medicine. 2011 April;37(4):572-582.

[38] Morgan JT, Clark C, Endre ZH. Accuracy or base excess – An in vitro evaluation of the Van Slyke equation. Crit Care Med. 2000;28(8):2932-2936.

[39] Kurtz I, et al. Acid-base analysis: a critique of the Stewart and bicarbonate-centred approaches. Am J Renal Physiol 2008;294:F1009-F1031.

[40] Dyer RA, Butwick AJ, Carvalho B. Oxytocin for labour and caesarean delivery: implications for the anaesthesiologist. Current Opinion in Anesthesiology. 2011;24:255-261.

[41] Holm-Knudsen RJ, Rasmussen LS. Paediatric airway management: basic aspects. Acta Anaesthesiologica Scandinavica. 2009 Jan;53(1):1-9.

[42] Vizcarra C, Clum S. Intraosseous route as alternative access for infusion therapy. Journal of Infusion Nursing. 2010 May-Jun;33(3):162-174.

[43] Tobias JD, Ross AK. Intraosseous infusions: a review for the anesthesiologist with a focus on pediatric use. Anesthesia & Analgesia. 2010 Feb 1;110(2):391-401.

[44] Sperry JL, Minei JP, Frankel HL, et al. Early use of vasopressors after injury: caution before constriction. The Journal of Trauma and Acute Care Surgery. 2008; 64: 9–14.

[45] Ganter MT, Pittet JF.New insights into acute coagulopathy in trauma patients. Best Practice and Research. Clinical Anaesthesiology. 2010 Mar;24(1):15-25.

[46] Fries D, Martini WZ. Role of fibrinogen in trauma-induced coagulopathy. British Journal of Anaesthesia. 2010 Aug;105(2):116-121.

[47] Wiles M D. Blood pressure management in trauma: from feast to famine? Anaesthesia. 2013;68:445–452.

[48] Zacharias SR, Offner P, Moore EE, Burch J. Damage control surgery.AACN Clinical Issues. 1999 Feb;10(1):95-103

[49] Sheridan RL.Burns Crit Care Med 2002;30(Suppl):S500–S514.

[50] Fuzaylov G, Fidkowski CW. Anesthetic considerations for major burn injury in pediatric patients. Pediatric Anesthesia 2009 19: 202–211

[51] Greenhalgh DG. Burn resuscitation.Journal of Burn Care and Research. 2007 Jul-Aug;28(4):555-65.

[52] Saffle JI. The phenomenon of "fluid creep" in acute burn resuscitation. Journal of Burn Care and Research. 2007 May-Jun;28(3):382-395.

[53] Chung KK, Blackbourne LH, Wolf SE, et al. Evolution of burn resuscitation in operation Iraqi freedom. J Burn Care Res 2006;27:606–611.

[54] Marret E, Flahault A, Samama CM, Bonnet F. Effects of postoperative, nonsteroidal, antiinflammatory drugs on bleeding risk after tonsillectomy: meta-analysis of randomized, controlled trials. Anesthesiology. 2003 Jun;98(6):1497-1502.

[55] www.sasaweb.com/images/Adult_Sedation_Guidelines_2010.pdf

[56] www.sasaweb.com/images/Sedation_Guidelines_Paediatrics.PDF

[57] J Am Coll Cardiol, 2008; 52:676-685

[58] Shemie S. Steroids for anything that swells: Dexamethasone and postextubation airway obstruction. Critical Care Medicine 1996; 24(10): 1613-1614

[59] Brown JC. The management of croup. British Medical Bulletin 2002; 61:189-202