Ischaemic Heart Disease

Dr Thabo Makgabo

Definition of IHD

- Condition in which there is inadequate supply of blood and oxygen to a portion of the myocardium.
- Imbalance between myocardial oxygen supply and demand.

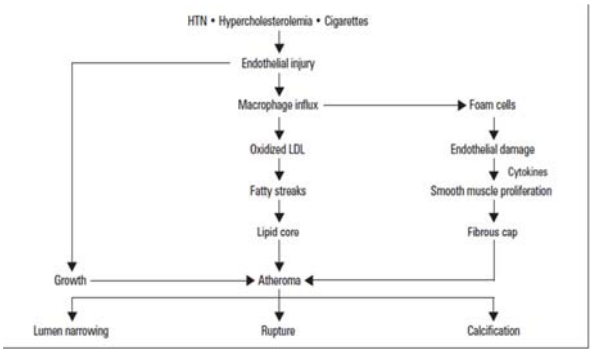
Causes of coronary artery disease

Type	Comment
Atherosclerosis	Most common cause. Risk factors include hypertension, hypercholesterolemia, diabetes mellitus, smoking, and a family history of atherosclerosis.
Spasm	Coronary artery vasospasm. Vasoconstriction appears to be mediated by histamine, serotonin, catecholamines, and endothelium-derived factors. Because spasm can occur at any time, the chest pain is often not exertion-related.
Emboli	Rare cause of coronary artery disease. Can occur from vegetations in patients with endocarditis
Congenital	Congenital coronary artery abnormalities are present in 1–2% of the population. However, only a small fraction of these abnormalities cause symptomatic ischemia

Atherosclerosis risk factors

- **SHIFT MAID**:
  Smoking
  Hypertension
  (N)**I**DDM
  Family history
  Triglycerdides & fats
  Male
  Age
  Inactivity
  Diet / **D**rink

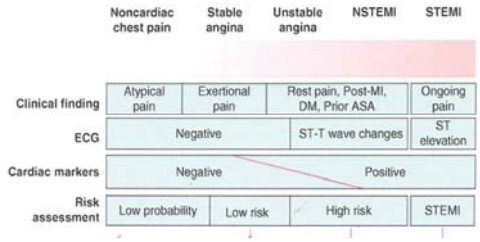
Pathophysiology of Atherosclerosis

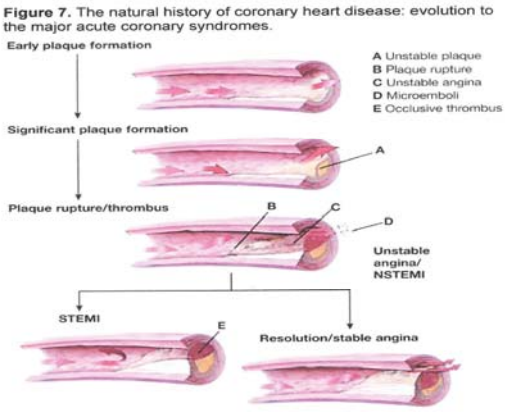


- **Angina Pectoris (Stable angina)**
  - A transient discomfort caused by an inadequate blood flow and oxygen delivery to the heart muscle
  - Most often due to a fixed stenosis caused by an atheroma.
  - Commonly lasts for < 20 minutes, brought on by factors increasing heart rate and relieved by rest or nitrates
- **VARIANT ANGINA (Prinzmetal's Angina)**
  - Myocardial ischaemia secondary to coronary artery vasospasm, with or without atherosclerosis
  - Uncommonly associated with infarction or LV dysfunction
  - Typically occurs between midnight and 8 AM, unrelated to exercise, relieved by nitrates

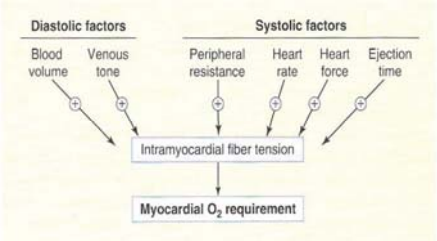
Acute Coronary Syndromes (ACS)

- Usually caused by coronary atherosclerosis with superimposed thrombus on ruptured plaque
- Spectrum of ACS
  - Unstable angina (UA)/non-ST elevation myocardial infarction (NSTEMI)
  - ST elevation myocardial infarction (STEMI)

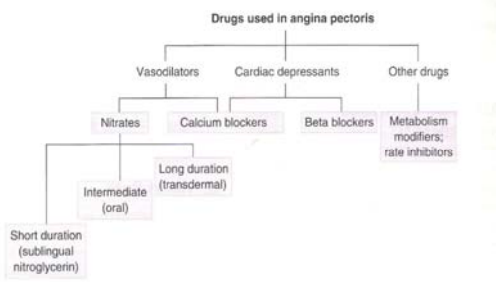




Pathophysiology of IHD



Antianginal drugs



Nitrates

- **Subclass**
  - Short Acting
    - Nitroglycerin sublingual (1 – 15 min)
    - Isosorbide dinitrate sublingual (20-30 min)
- **Mechanism of Action**
  - Releases nitric oxide (NO), increases cGMP (cyclic guanosine monophosphate), and relaxes smooth muscle, especially vascular
- **Clinical Applications**
  - Acute angina pectoris; acute coronary syndrome
- **Pharmacokinetics**
  - Rapid onset (1 min); short duration (15 min)
- **Toxicities, Interactions**
  - Tachycardia, orthostatic hypotension, headache

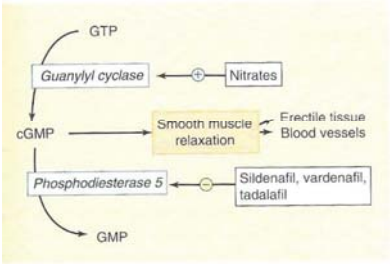
Nitrates

- **Subclass**
  - Intermediate-acting nitrate
    - Nitroglycerin, oral
    - Isosorbide dinitrate
    - Isosorbide mononitrate
- **Mechanism of Action**
  - Releases nitric oxide (NO), increases cGMP (cyclic guanosine monophosphate), and relaxes smooth muscle, especially vascular
  - Active metabolite dinitroglycerin
- **Clinical Applications**
  - Prophylaxis of angina
- **Pharmacokinetics**
  - Slow onset
  - Duration: 2–4 h
- **Toxicities, Interactions**
  - Tachycardia, orthostatic hypotension, headache

Nitrates

- **Subclass**
  - Long-acting nitrate
    - Transdermal nitroglycerin patch
- **Mechanism of Action**
  - Releases nitric oxide (NO), increases cGMP (cyclic guanosine monophosphate), and relaxes smooth muscle, especially vascular
- **Clinical Applications**
  - Prophylaxis of angina
- **Pharmacokinetics**
  - Slow onset
  - Duration of plasma levels: 24 h; duration of effect: 10 h (tachyphylaxis- development of tolerance)
- **Toxicities, Interactions**
  - Tachycardia, orthostatic hypotension, headache
  - Loss of response is common after 10–12 h exposure to drug

Nitrates- Interactions



Calcium Channel Blockers

- **Subclass**
  - Non-Dihydropyridine Ca2+ channel blocker
    - Verapamil
    - Diltiazem
- **Mechanism of Action**
  - Block L-type Ca2+ channels in smooth muscle and heart→ decreased intracellular Ca2+
  - Cardiac > vascular effect (significant dose-dependent slowing of AV nodal conduction velocity)
- **Clinical Applications**
  - Angina (both atherosclerotic and vasospastic)
- **Pharmacokinetics**
  - Oral, parenteral
  - Duration: 6–8 h
- **Toxicities, Interactions**
  - Constipation, pretibial edema, flushing, dizziness
  - Higher doses: cardiac depression, hypotension

Calcium Channel Blockers

- **Subclass**
  - Dihydropyridine Ca2+ channel blocker
    - Nifedipine
    - Amlodipine
- **Mechanism of Action**
  - Block L-type Ca2+ channels in smooth muscle and heart→ decreased intracellular Ca2+
  - Vascular > cardiac effect
- **Clinical Applications**
  - Angina
- **Pharmacokinetics**
  - Oral; slow-release form
  - Duration: 6–8 h
- **Toxicities, Interactions**
  - Pretibial edema, flushing, dizziness
  - Less constipation, cardiac effect

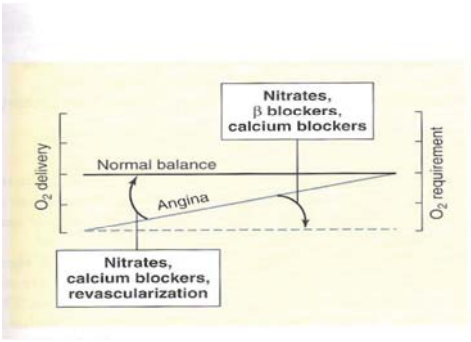
Beta Blockers

- **Examples**
  - Propranolol
  - Atenolol
- **Mechanism of Action**
  - Blocks sympathetic effects on heart and blood pressure → Decrease in myocardial oxygen demand
  - Reduces renin release
- **Clinical Applications**
  - Angina, ACS
- **Pharmacokinetics**
  - Oral
  - Duration: 6 h
- **Toxicities, Interactions**
  - bronchospasm (can be fatal in asthmatics),
  - atrioventricular block,
  - heart failure
  - CNS sedation,
  - Lethargy
  - sleep disturbances

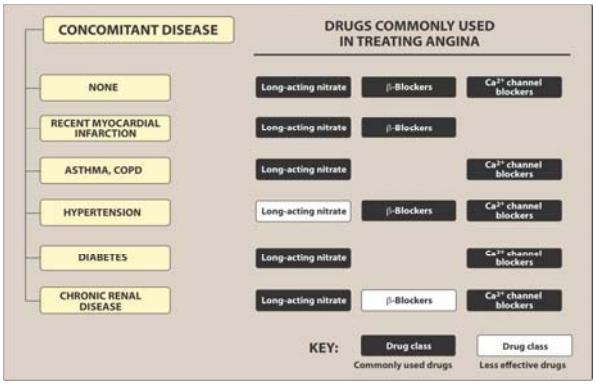
Combined effect of Antianginals

	Nitrates Alone	Beta Blockers or Calcium Channel Blockers Alone	Combined Nitrate and Beta Blocke or Calcium Channel Blocker
Heart rate	*Reflex increase*	**Decrease**	**Decrease**
Arterial pressure	Decrease	**Decrease**	**Decrease**
End-diastolic pressure	**Decrease**	*Increase*	**Decrease**
Contractility	*Reflex increase*	**Decrease**	No effect or decrease
Ejection time	Reflex decrease	*Increase*	No effect
Net myocardial oxygen requirement	**Decrease**	**Decrease**	**Decrease**

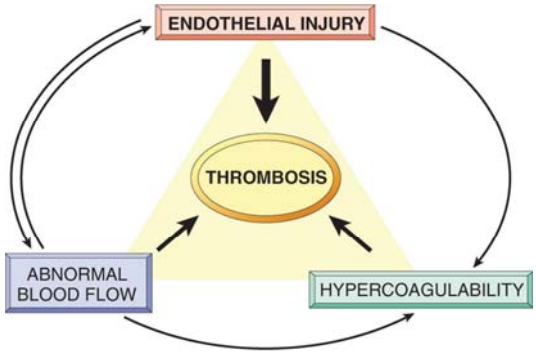
Antianginal drugs



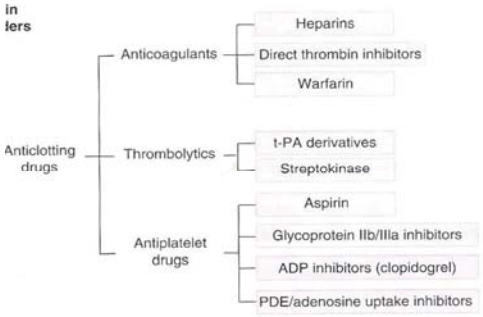
In Summary



Pathophysiology of IHD



Anticoagulants



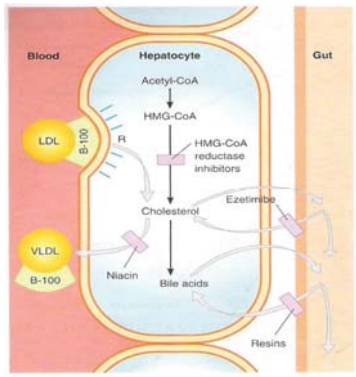
Management of US/NSTEMI

1. Aspirin – early use reduces mortality significantly
2. Clopidogrel (if allergic to aspirin)
3. Anticoagulant – (Unfractionated heparin or low molecular weight heparin)- in US decreases AMI by 8 – 15%
4. Beta blocker- in US reduces acute myocardial infarction by 13%
5. Statin e.g. Atorvastatin, simvastatin
6. Glycoprotein IIb / IIIa platelet receptor inhibitor
7. Nitrates- immediate effect but no longterm effects to reduce the risk of sudden death from another MI
8. Calcium channel blocker ONLY for coronary spasms
9. Morphine

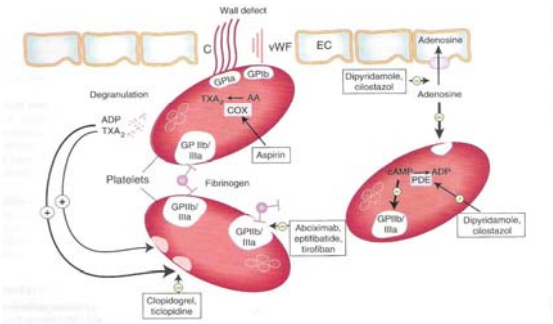
Management of STEMI

1. ***Measure to limit myocardial infarct size and decrease mortality***
   a. Aspirin
   b. Clopidogrel
   c. Statins e.g. Atorvastatin, simvastatin
   d. Beta Blockers
   e. ACE inhibitors
2. ***Measure to control cardiac pain***
   a. Nitrates
   b. Morphine
3. ***Reperfusion Measures***
   a. Fibrinolytic Therapy (e.g. Alteplase = promotes conversion of plasminogen to plasmin)
   b. Primary percutaneous coronary intervention

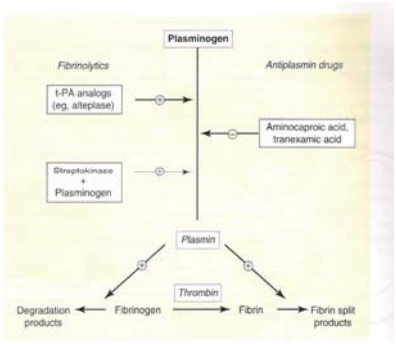
Statins (example -Atorvastatin)



Antiplatelet Agents



Fibrinolytics



Management of IHD in a nutshell

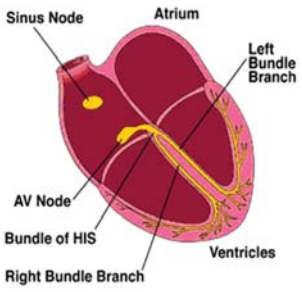
- Lifestyle changes and medications.
- Easy as **ABCDE**
  - **A**nti-platelets, anticoagulants, ACE inhibitors, and analgesics
  - **B**lood pressure and beta-blockers
  - **C**holesterol-lowering drugs (typically statins) and cigarettes (stopping)
  - **D**iet and diabetes control
  - **E**xercise and education

Anti-arrhythmic Drugs

Dr Thabo Makgabo

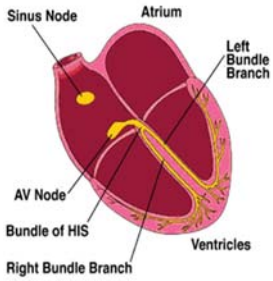
Normal Sinus Rhythm

- Heart rhythm is determined by SA node = Cardiac Pacemaker
- Called sinus rhythm
- Specialised pacemaker cells spontaneously generate APs
- APs spread through the conducting pathways
- Normal sinus rate 60-100 beats/min



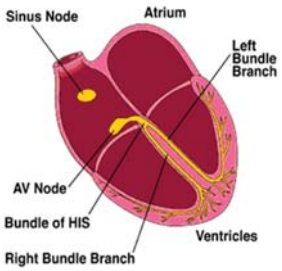
Conducting System

- SAN AP triggers atrial depolarisation
- AVN - Only pathway for AP to enter ventricles
- Conducts slowly: Complete atrial systole before ventricular systole
- Conducts rapidly through His Bundles & Purkinje – Ventricular depolarization & contraction



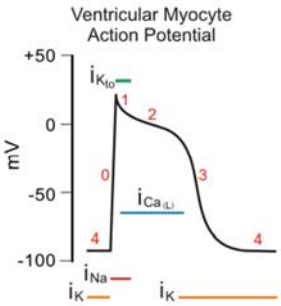
Conducting System

- Permits rapid organized depolarization of ventricular myocytes
- Necessary for the efficient generation of pressure during systole
- Atrial activation complete 0.09s after SAN firing
- Delay at AVN
- Septum activated 0.16s
- Whole ventricle activated by 0.23s



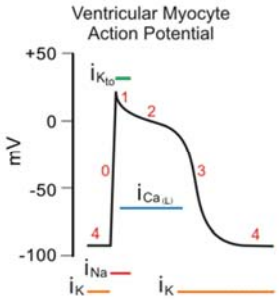
Cardiac Action Potential

- Phase 4: RMP
  - AP depolarizes cells to threshold -70mV
- Phase 0: Rapid depolarization
  - Caused by a transient opening of fast Na channels
  - Increases inward directed depolarizing Na+ currents



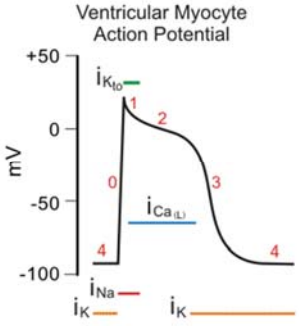
Cardiac Action Potential

- Phase 1: Initial repolarization
  - Open K channel: transient outward hyperpolarizing K+ current
  - Large increase in slow inward Ca++ occurs at the same time
  - L-type CaCh open -40mV
  - Repolarization delayed
- Phase 2: Plateau phase
  - Plateau phase prolongs AP duration vs APs in nerves and skeletal muscle



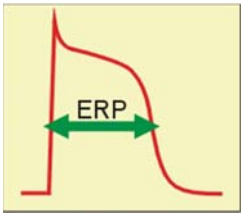
Cardiac Action Potential

- Phase 3: Repolarization
  - K channels open
  - Inactivation of Ca++ channels
  - Action potential in non-pacemaker cells is primarily determined by relative changes in fast Na+, slow Ca++ and K+ conductances and currents

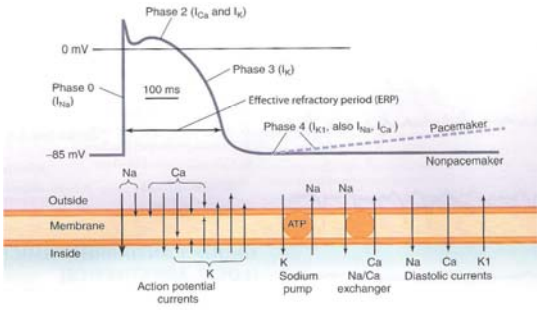


Refractory Periods

- Once an AP is initiated, there is a period (phase 0,1,2, part 3) that a new AP cannot be initiated.
- Effective or Absolute refractory period (ERP or ARP)
- Stimulation of cell by adjacent cell depolarizing does not produce new propagated APs
- Prevents compounded APs from occurring & limits frequency of depolarization and HR

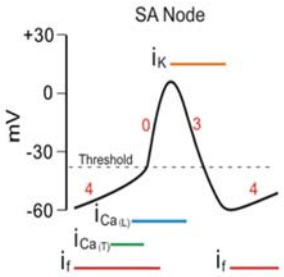


Cardiac Action Potential



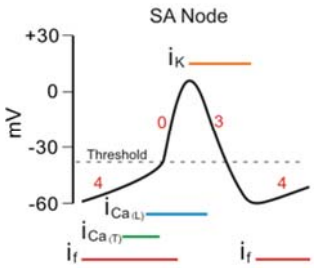
SAN Pacemaker Potential

- Fully repolarized -60mv
- No stable RMP
- Phase 4: Spontaneous depolarization or pacemaker potential
- Slow, inward Na+ channels open - "funny" currents
- Cause the membrane potential to begin to spontaneously depolarize
- During Ph4 there is also a slow decline in the outward movement of K+



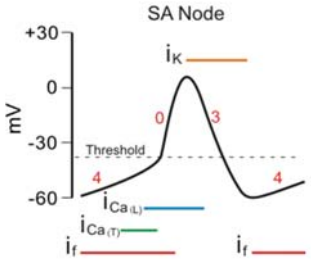
SAN Pacemaker Potential

- -50mV T-type CaCh open
- Ca in: further depolarizes
- -40 mV L-type CaCh open
- More Ca in: further depol
- AP threshold -35mV
- Phase 0: Depolarization
- Primarily caused by Ca++ conductance through the L-type Ca++ channels
- Movement of Ca++ through these is slow so the rate of depolarization (Phase 0 slope) is slower than in other cardiac cells

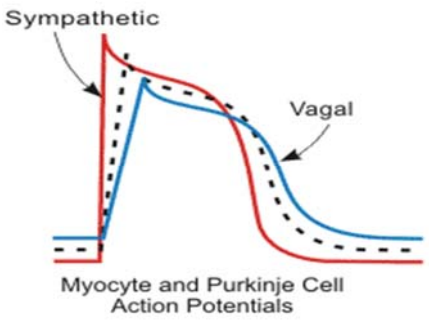


SAN Pacemaker Potential

- Phase 3: Repolarization
- K+ channels open
- Increase the outward hyperpolarizing K+ currents
- At the same time the L-type Ca++ channels close
- Ca++ decreases
- Inward depolarizing Ca++ currents diminish
- Repolarization



Autonomic Effects on AP



What is an Arrhythmia ?

- Heart condition where disturbances in
  - Pacemaker impulse formation
    - Abnormal rate
    - Irregular rate
  - Contraction impulse conduction
  - Combination of the above
- Results in rate and/or timing of contraction of heart muscle that is insufficient to maintain normal cardiac output (CO)

Causes of arrhythmias

- Cardiac ischemia
- Excessive discharge or sensitivity to autonomic transmitters
- Exposure to toxic substances
- Unknown aetiology

Mechanisms of Cardiac Arrhythmias

- Result from
  - Disorders of impulse formation (↑ automaticity)
  - Disorders of impulse conduction
  - Both

Alterations in Impulse Formation

A. Abnormal Automaticity

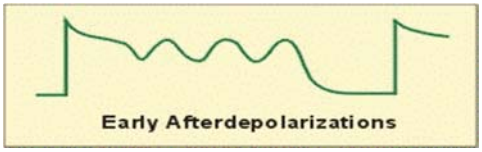
- Automaticity of pacemakers can either become abnormally increased or decreased
- Cells in the myocardium outside the conduction system in disease, inappropriately acquire the property of automaticity and contribute to abnormal depolarization

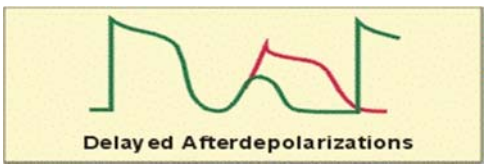
B. Triggered Activity due to Afterdepolarizations

There are two types of triggered activity:

- Early Afterdepolarizations
  - action potential prolongation
  - membrane potential becoming more positive during repolarization
  - result in self-maintaining depolarizing oscillations of action potential, generating a tachyarrhythmia
  - basis for the degeneration of QT prolongation, either congenital or acquired, into Torsades de Pointes
- Delayed Afterdepolarizations
  - occur after the action potential has fully repolarized, but before the next usual action potential, thus called a delayed afterdepolarization
  - commonly occurs in situations of high intracellular calcium (digitalis intoxication, ischemia) or during enhanced catecholamine stimulation

Afterdepolarizations



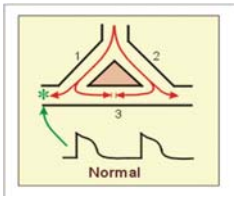


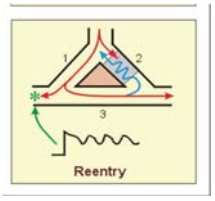
Disorders of impulse conduction

- **Re-Entry Circuits**
  - the presence of self-sustaining re-entry circuit causes rapid repeated depolarizations in a region of myocardium
- **Conduction Block**
  - ischaemia, fibrosis, trauma and drugs can cause transient, permanent, unidirectional or bidirectional block
  - most common cause of block is due to refractory myocardium
  - if block occurs along the specialized conduction system, distal zones of the conduction system can assume pacemaking control
  - conduction block can not only lead to bradycardia, but also tachycardia when impaired conduction leads to re-entry phenomenon
- **Bypass Tracts**
  - normally the only conducting tract from the atria to the ventricles is the AVN
  - congenital development of additional, or accessory conducting tracts bypass the AVN and facilitate premature ventricular activation before normal AVN conduction

Re-Entry Mechanism

- Both unidirectional block and slowed retrograde conduction necessary
- When an action potential reaches a division in the conduction path , the impulse proceeds around and stimulates distal myocardium.
- If the action potential propagates through a block (refractory tissue) in the retrograde direction but not in the forward direction, unidirectional block is present .
- This can occur as a result of cellular dysfunction with changes in cellular refractoriness.
- Slowed retrograde conduction of the action potential through (2) encounters excitable tissue in A because these myocytes have had sufficient time to repolarise by this time point, and now the impulse is free to excite A again thus generating a reentry circuit.





Therapeutic overview

- Na+ channel blockade
- β-adrenergic receptor blockade
- Prolong repolarization
- Ca2+ channel blockade

- Adenosine
- Digitalis glycosides

Vaughan-Williams Classification

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

Class I A Agents

- **Example**
  - Procainamide
  - Disopyramide
  - Quinidine
- **Mechanism of Action**
  - Use- and state-dependent block of I_{Na} channels; some block of I_K channels.
  - (Quinidine)Slows spontaneous SA nodal depolarization as its predominant effect.
  - prolonged action potential duration and refractory period
- **Clinical Applications**
  - Atrial and ventricular arrhythmias, especially after myocardial infarction
- **Pharmacokinetics**
  - Oral and parenteral; oral slow-release forms available
  - Duration: 2–3 h
- **Toxicities, Interactions**
  - Increased arrhythmias, hypotension, lupus-like syndrome
  - Disopyramide- antimuscarinic effects and heart failure
  - Quinidine-cinchonism (tinnitus, headache, gastrointestinal disturbance) and thrombocytopenia

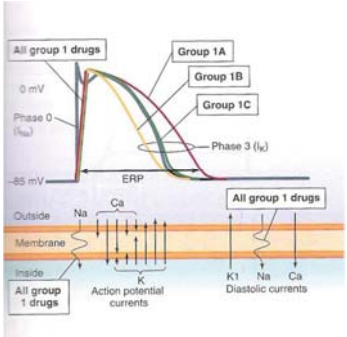
Class I B Agents

- **Example**
  - Lidocaine
  - Mexiletine
- **Mechanism of Action**
  - Highly selective use and state-dependent I_{Na} block; minimal effect in normal tissue; no effect on I_K
- **Clinical Applications**
  - Ventricular arrhythmias post-myocardial infarction and digoxin-induced arrhythmias
- **Pharmacokinetics**
  - IV and IM
  - Duration: 1–2 h
- **Toxicities, Interactions**
  - Central nervous system (CNS) sedation or excitation

Class I C Agents

- **Example**
  - Flecainide
- **Mechanism of Action**
  - Selective use and state-dependent block of I_{Na}; slowed conduction velocity and pacemaker activity
- **Clinical Applications**
  - Refractory arrhythmias
- **Pharmacokinetics**
  - Oral
  - Duration: 20 h
- **Toxicities, Interactions**
  - Significant pro-arrhythmic effect (induction of lethal arrhythmias), CNS excitation

Class I Agents



Class II Agents

- **Beta Blockers**
- **Mechanism of Action**
  - Blocks β receptors → slowed pacemaker activity
- **Clinical Applications**
  - Postmyocardial infarction as prophylaxis against sudden death ventricular fibrillation
- **Pharmacokinetics**
  - Oral, parenteral
  - Duration: 4–6 h
- **Toxicities, Interactions**
  - bronchospasm (can be fatal in asthmatics),
  - atrioventricular block,
  - heart failure
  - CNS sedation,
  - Lethargy
  - sleep disturbances

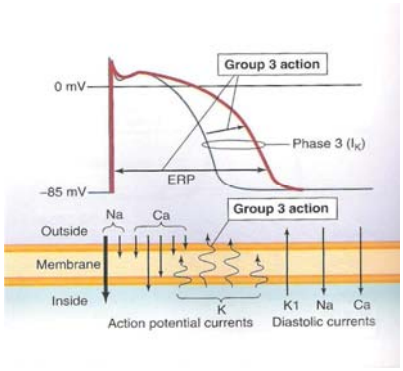
Class III Agents

- **Example**
  - Amiodarone
- **Mechanism of Action**
  - Strong I_K block produces marked prolongation of action potential and refractory period therefore it interferes with outward potassium current.
  - Group 1 activity slows conduction velocity; groups 2 and 4 activity confer additional antiarrhythmic activity
- **Clinical Applications**
  - Life threatening arrhythmias for immediate control ; used off-label in many arrhythmias (broad spectrum of therapeutic action)
- **Pharmacokinetics**
  - Oral, parenteral
  - Half-life and duration of action: 1–10 wk
- **Toxicities, Interactions**
  - Thyroid abnormalities, deposits in skin and cornea, pulmonary fibrosis, optic neuritis (Pulmonary function and thyroid hormone status should be checked!!!)

Class III Agents

- **Example**
  - Sotalol
- **Mechanism of Action**
  - Strong I_K block produces marked prolongation of action potential and refractory period.
  - Beta blocker
- **Clinical Applications**
  - Ventricular arrhythmias and atrial fibrillation
- **Pharmacokinetics**
  - Oral
  - Duration: 7 h
- **Toxicities, Interactions**
  - Dose-related torsade de pointes; cardiac depression

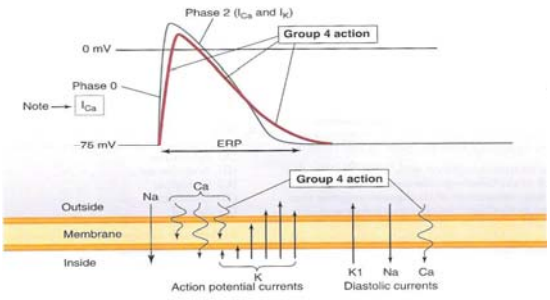
Class III Agents



Class IV Agents

- **Calcium Channel Blockers**
  - **Example**
    - Verapamil
    - Diltiazem
  - **Mechanism of Action**
    - State and use-dependent I_{Ca} block slows conduction in AV node and pacemaker activity; PR interval prolongation
  - **Clinical Applications**
    - AV nodal arrhythmias, especially in prophylaxis
    - Rate control in atrial fibrillation
  - **Pharmacokinetics**
    - Oral, parenteral
    - Duration: 6- 7 h
  - **Toxicities, Interactions**
    - Cardiac depression; constipation, hypotension

Class IV Agents



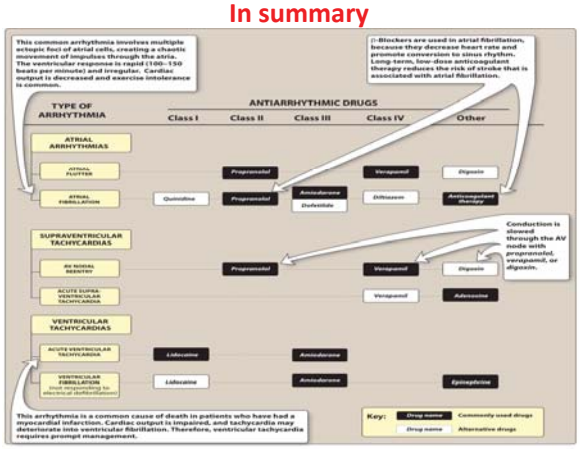
What about Adenosine?

- **Mechanism of Action**
  - Increase in diastolic I_K of AV node that causes marked hyperpolarization and conduction block; reduced I_{Ca}
- **Clinical Applications**
  - Acute nodal tachycardias
- **Pharmacokinetics**
  - IV only
  - Duration: 10–15 s
- **Toxicities, Interactions**
  - Flushing, bronchospasm, chest pain, headache

What does Digoxin Do?

- Cardiac glycoside
- Blocks Na/K ATPase pump in heart
- **It increases vagal activity and decreases sympathetic tone**
- Increased IC Ca
- Inotropic: Increases force of contraction
- AVN increased refractoriness
- Decreases conduction through AVN and SAN
- Negative chronotrope: Slows HR

In summary



Take-Home Message

- Anti-arrhythmics are also pro-arrhythmics
- Dangerous side effects
- If patient is unstable rather cardiovert
- Enlist expert help
- Stick to drugs you know

thank you !!!