Heart Failure

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Heart Failure (HF) Definition

- A complex clinical syndrome in which the heart is incapable of maintaining a cardiac output adequate to accommodate metabolic requirements and the venous return.

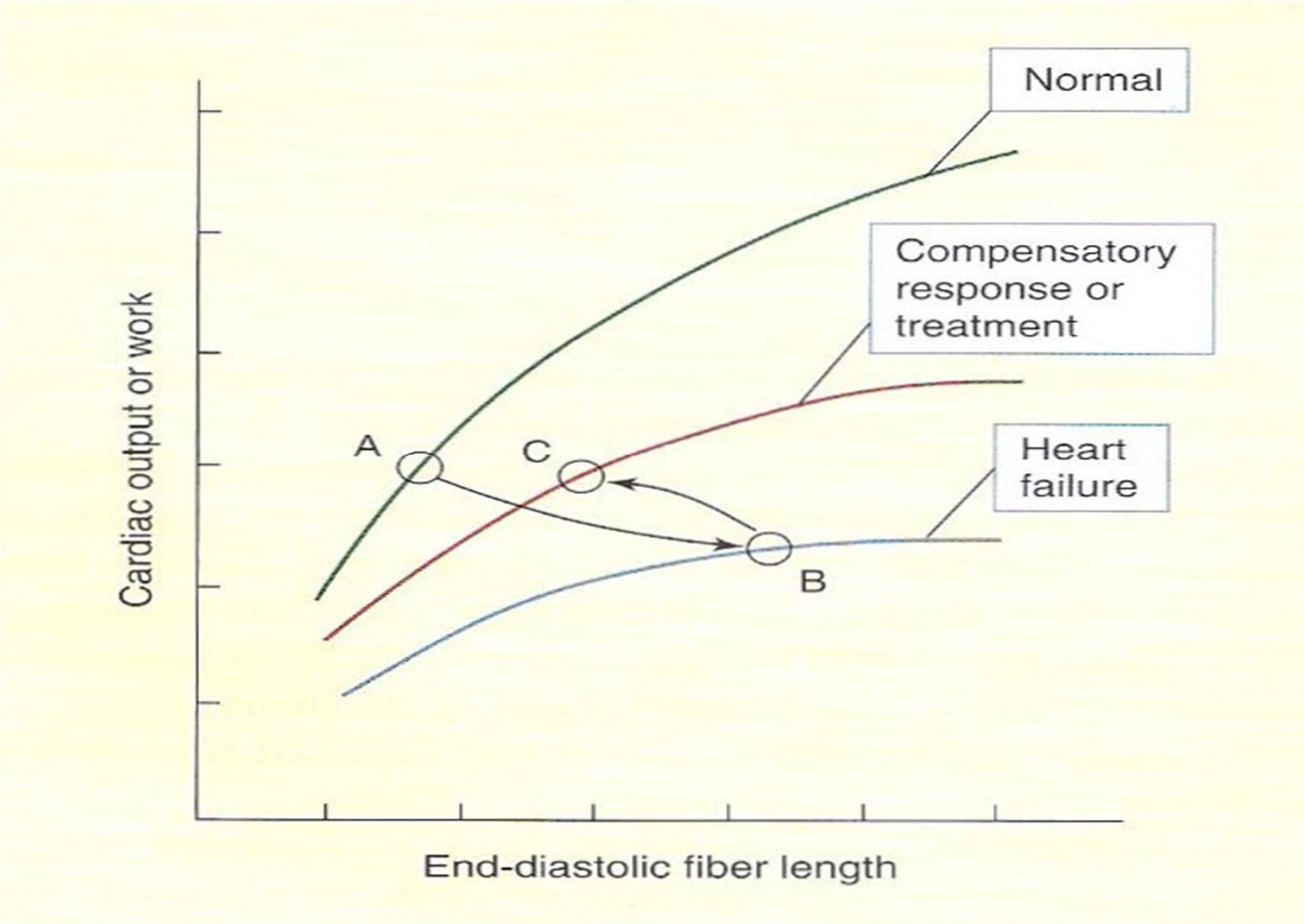
Pathophysiology

- Primary insults (myocyte loss, overload) →pump dysfunction, which leads to:
  - remodeling (dilatation, hypertrophy)
  - neurohumoral activation g necrosis and apoptosis
- Both pathways result in further damage (re-starting the cycle), oedema, tachycardia, vasoconstriction, congestion
- Compensatory response to myocardial stress (perpetuate disease process)
  - increased end-systolic ventricular pressure (pressure overload)
    - e.g. HTN, aortic stenosis g hypertrophy
  - increased end-diastolic ventricular volume (volume overload)
    - e.g. aortic regurgitation g cardiac dilatation

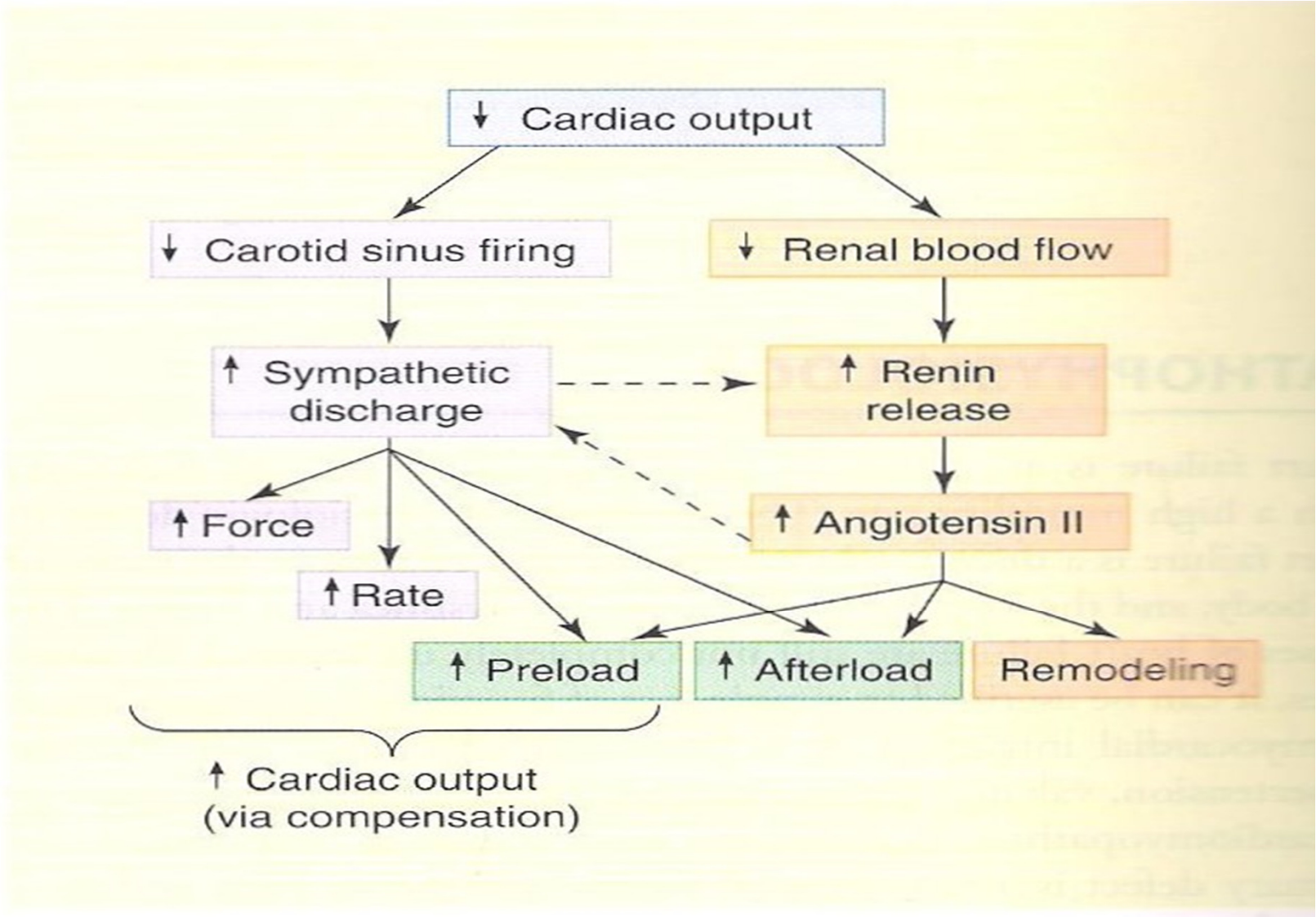
Pathophysiology Cont

- systemic response to ineffective circulating volume
  - activation of sympathetic nervous and renin-angiotensin-aldosterone systems results in:
    - salt and water retention with intravascular expansion
    - increased heart rate and myocardial contractility
    - increased afterload

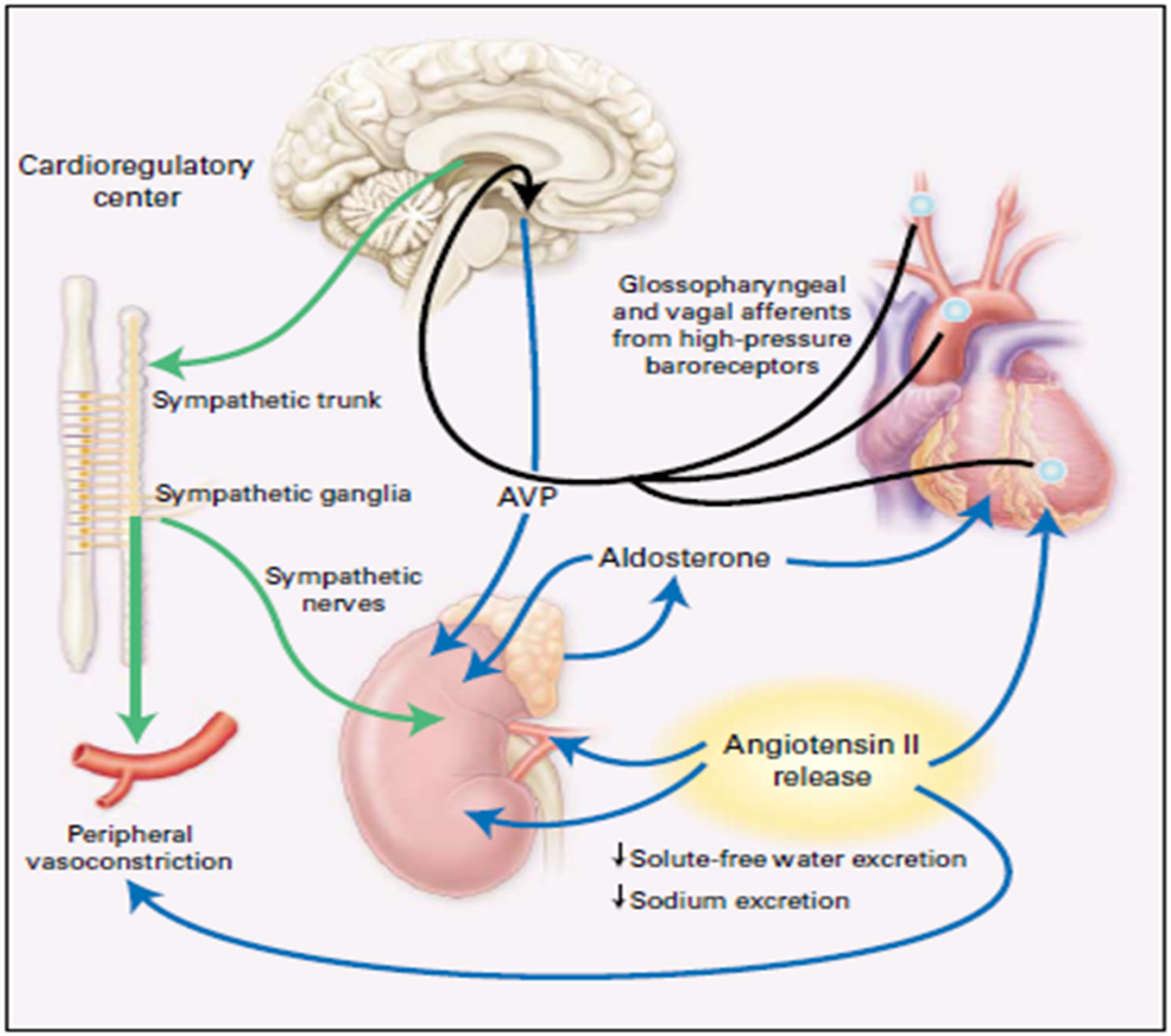
Pathophysiology of HF



Compensatory Mechanisms



Compensatory Neurohormonal Stimulation



Primary causes of heart failure

- Consider predisposing, precipitating and perpetuating factors
  - Coronary artery disease (60-70%)
  - Hypertension
  - Idiopathic (often in the form of dilated cardiomyopathy)
  - Valvular (e.g. AS, AR and MR)
  - Alcohol (may cause dilated cardiomyopathy

Precipitants of heart failure

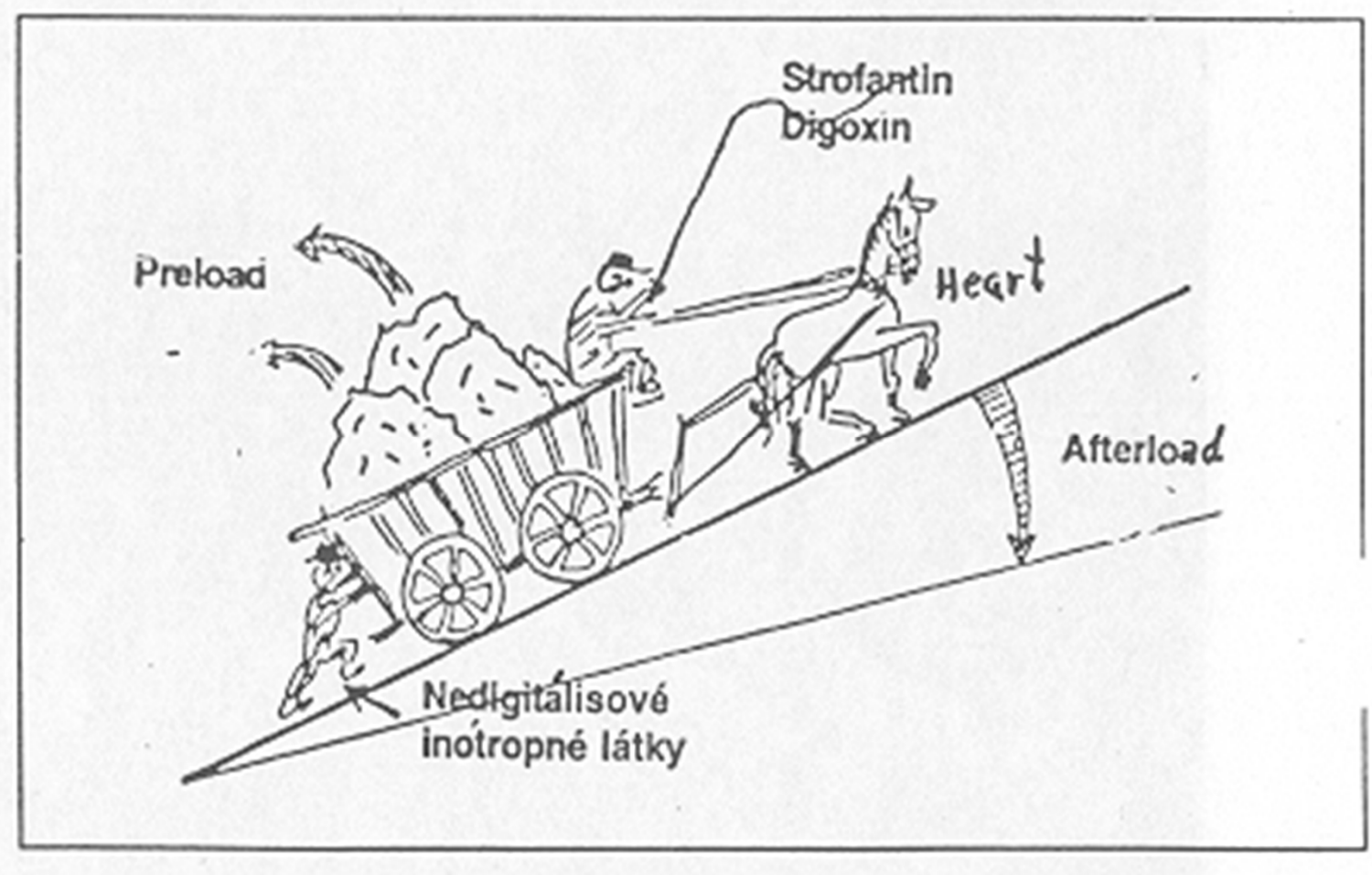
HEART FAILED

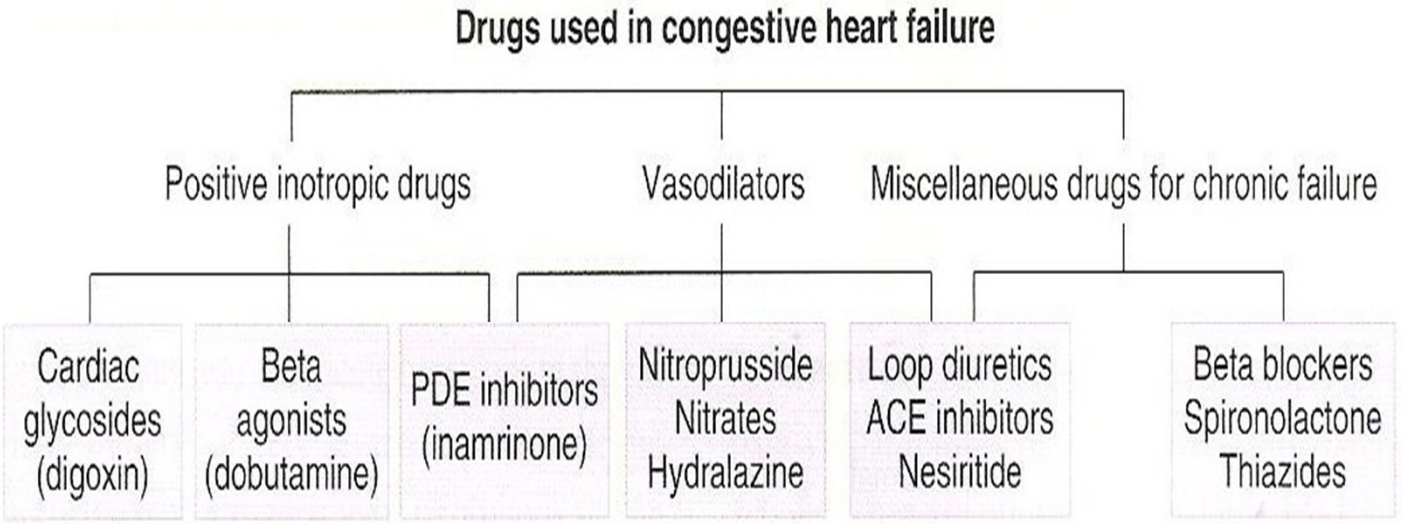
- **H**ypertension (common)
- **E**ndocarditis/environment (e.g. heat wave)
- **A**nemia
- **R**heumatic heart disease and other valvular disease
- **T**hyrotoxicosis
- **F**ailure to take meds (very common)
- **A**rrhythmia (common)
- **I**nfection/ischemia/**I**nfarction (common)
- **L**ung problems (PE, pneumonia, COPD)
- **E**ndocrine (pheochromocytoma, hyperaldosteronism)
- **D**ietary indiscretions (common)

Pharmacologic Management of HF

1. Removal of retained salt and water with ***diuretics***
2. Reduction of afterload and salt and water retention by means of ***angiotensin-converting enzyme (ACE) inhibitors***
3. Reduction of excessive sympathetic stimulation by means of ***blockers***
4. Reduction of preload or afterload with ***vasodilators***
5. Systolic failure, direct augmentation of depressed cardiac contractility with positive ***inotropic drugs*** such as digitalis glycosides.

Pharmacologic Management of HF




Drugs used in congestive heart failure
Positive inotropic drugs
Vasodilators
Miscellaneous drugs for chronic failure
Cardiac glycosides (digoxin)
Beta agonists (dobutamine)
PDE inhibitors (inamrinone)
Nitroprusside Nitrates Hydralazine
Loop diuretics ACE inhibitors Nesiritide
Beta blockers Spironolactone Thiazides

Diuretics

- First-line therapy for both systolic and diastolic failure and are used in heart failure before digitalis and other drugs are considered.
- **Furosemide** is a very useful agent for immediate reduction of the pulmonary congestion and severe oedema associated with acute heart failure and for moderate or severe chronic failure.
- **Spironolactone** and eplerenone (aldosterone antagonist diuretics) have significant long-term benefits and can reduce mortality in chronic failure.

Diuretics

- ***Classification***
  - Loop diuretics(eg, furosemide)
- ***Mechanism of Action***
  - Block Na/K/2Cl transporter in thick ascending limb
- ***Clinical Applications***
  - Hypertension, heart failure, oedema, hypercalcaemia
- ***Pharmacokinetics***
  - Oral, parenteral Duration: 2–3 h
- ***Toxicities, Interactions***
  - Hypokalemia, hypovolemia, ototoxicity

Diuretics

- ***Classification***
  - Potassium-sparing diuretics(eg, Spironolactone, eplerenone, Amiloride)
- ***Mechanism of Action***
  - Inhibitors of cytoplasmic aldosterone receptor in cortical collecting ducts; reduce K^+ excretion (Spironolactone & Eplerenone)
  - Inhibitor of ENaC epithelial sodium channels in cortical collecting duct, reduces Na^+ reabsorption and K^+ excretion(Amilioride)
- ***Clinical Applications***
  - Hypertension, heart failure, oedema in cirrhosis
  - To reduce the loss of potassium when they are used with thiazides(Amiloride)
  - Amiloride, an epithelial sodium-channel blocker, is reportedly more effective than spironolactone as therapy in blacks who have resistance to treatment.
- ***Pharmacokinetics***
  - Oral Duration: 24–36, 48 h (Spironolactone & eplerenone)
  - Oral Duration: 10–12 h(Amiloride)
- ***Toxicities, Interactions***
  - Hyperkalemia; gynecomastia (spironolactone only)

Angiotensin Antagonists

- Reduce aldosterone secretion, salt and water retention, and vascular resistance.
- Used, along with diuretics, as first-line drugs for chronic heart failure.
- The angiotensin receptor blockers (ARBs, eg, **losartan**) appear to have the same benefits as ACE inhibitors (eg, **captopril**), although experience with ARBs is not as extensive as with ACE inhibitors.

Angiotensin antagonists

- Angiotensin Converting Enzyme Inhibitors
  - ***Subtypes***
    - Class I: Captopril-like (eg, captopril)
    - Class II: Prodrugs (eg, Enalapril, Perindopril, Ramipril)
    - Class III: Water-soluble(eg, Lisinopril)
  - ***Mechanism of Action***
    - ACE inhibitor; reduces angiotensin II synthesis
    - It causes venodilation and induces natriuresis
  - ***Clinical Applications***
    - Hypertension, diabetic renal disease, heart failure
  - ***Pharmacokinetics***
    - Oral Half-life: 2.2 h but large doses provide duration of 12 h
  - ***Toxicities, Interactions***
    - Hyperkalemia; teratogen; cough, angioedema, acute renal failure (particularly in patients with bilateral renal artery stenosis or stenosis of the renal artery of a solitary kidney) CONTRAINDICATED

Angiotensin antagonists

- Angiotensin II receptor blockers (ARBs)
  - **Examples**
    - Losartan, Valsartan,Candesartan,Irbesartan,Telmisartan
  - ***Mechanism of Action***
    - Blocks AT_1 receptors
  - ***Clinical Applications***
    - Hypertension. ACEi intolerant patients due to intractable cough or who develop angioedema.
  - ***Pharmacokinetics***
    - Oral Duration: 6–8 h
  - ***Toxicities, Interactions***
    - Hyperkalemia; teratogen

Beta-Adrenoceptor Antagonists

- Several β blockers (**carvedilol, labetalol, metoprolol**) have been shown in long-term studies to reduce progression of *chronic* heart failure.
- This benefit of blockers had long been recognized in patients with hypertrophic cardiomyopathy but has now been shown to occur also in patients without cardiomyopathy.
- **Nebivolol**, a newer blocker with vasodilator effects, is investigational in heart failure.
- Beta blockers are not of value in acute failure and may be detrimental if systolic dysfunction is marked.

β1 selective blockers

- ***Examples***
  - Bisoprolol
- ***Mechanism of Action***
  - Competitive block of β_1 receptors
- ***Clinical Applications***
  - Hypertension, heart failure, angina , arrhythmias
- ***Pharmacokinetics***
  - Oral Duration: 6–9 h
- ***Toxicities, Interactions***
  - Atrioventricular block, CNS sedation, lethargy, sleep disturbances,bronchospams beware in Asthma

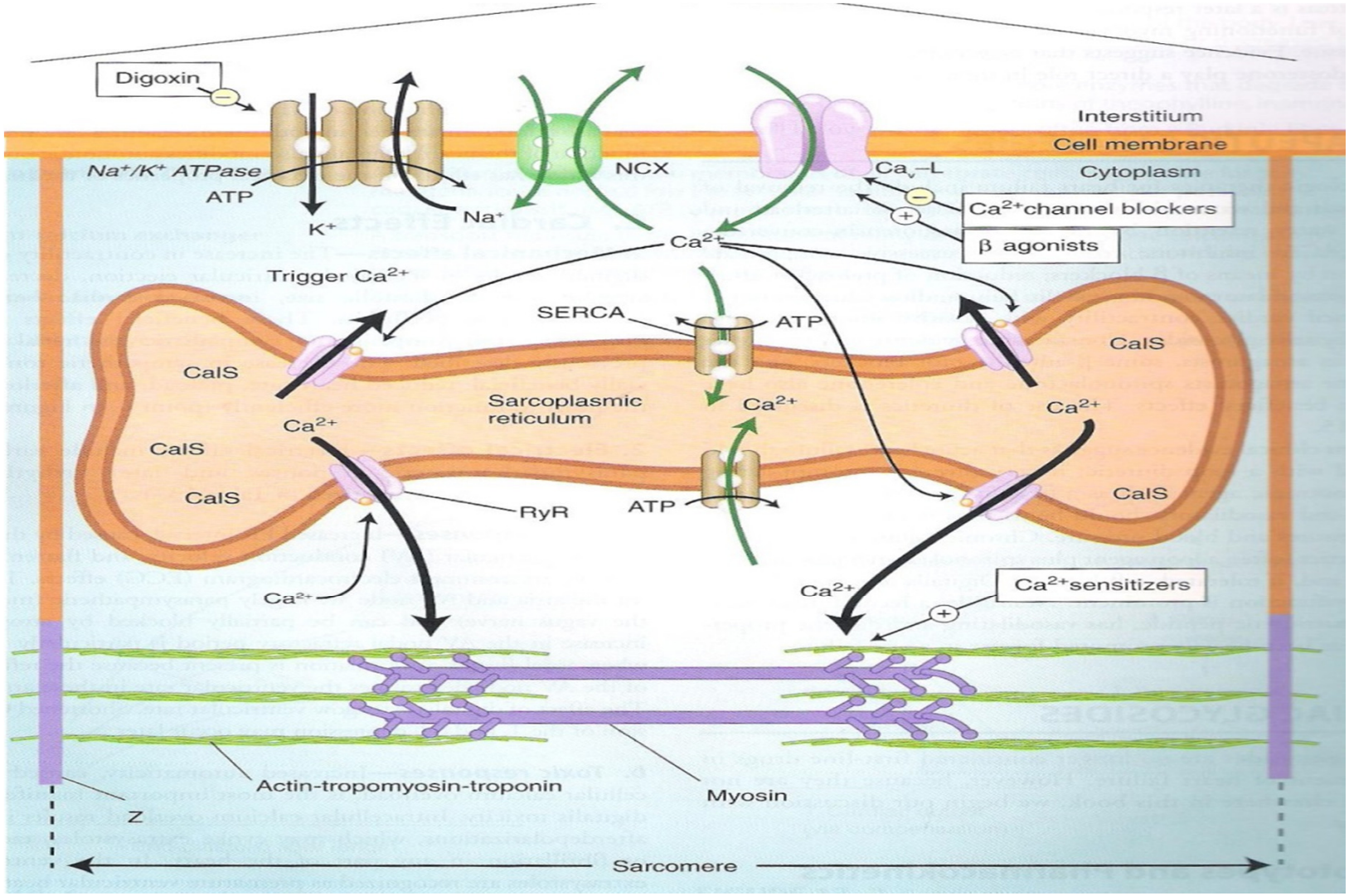
Alpha+beta blockers

- ***Examples*** (Labetalol, Carvedilol)
- ***Mechanism of Action***
  - Four isomers; 2 bind and block both α and β receptors
- ***Clinical Applications***
  - Hypertension, heart failure, hypertensive emergencies (IV)
- ***Pharmacokinetics***
  - Oral and IV Duration: 5 hours
- ***Toxicities, Interactions***
  - Excessive β blockade: bronchospasm (can be fatal in asthmatics), atrioventricular block, heart failure; CNS sedation, lethargy, sleep disturbances

Inotropic Drugs

- ↑ cardiac contractility → ↑ CO
- ↑ cytoplasmic calcium → ↑ contractility
- Examples
  - Digitalis glycosides
  - β- adrenergic agonists
  - Phosphodiesterase inhibitors

Cardiac contraction



Digitalis glycosides

- Digoxin most widely used
- Inhibits Na+/K+ ATPase sodium pump and increases intracellular Na+, decreasing Ca2+ expulsion and increasing cardiac contractility
- Enhances inotropy of cardiac muscle
- ↑ PSNS activation & ↓activation of SNS and RAAS
- ↑automaticity of the heart
- Stim of baro- and chemorecptors → vasodilation with a ↓ in afterload.
- Oral, parenteral formulations. Duration of action : 40 hrs
  - Not extensively metabolized in humans
  - Almost two thirds is excreted unchanged by the kidneys. Its renal clearance is proportionate to creatinine clearance.
  - Equations and nomograms are available for adjusting digoxin dosage in patients with renal impairment

Digitalis glycosides

- ***Therapeutic uses of digoxin***
  - Congestive cardiac failure esp. in atrial fibrillation
  - Control of ventricular rate in chronic persistent atrial fibrillation in the elderly
  - Atrial flutter
- ***Adverse effects of digoxin***
  - Cardiac effects
    - bradycardia in normal hearts due to ↑vagal tone
    - ↑automaticity → dysrrhythmias
    - ↓ K predisposes to these adverse effects
  - GIT effects
    - Nausea and vomiting
  - CNS
    - Headaches , fatigue , confusion, blurred vision
  - Digoxin toxicity

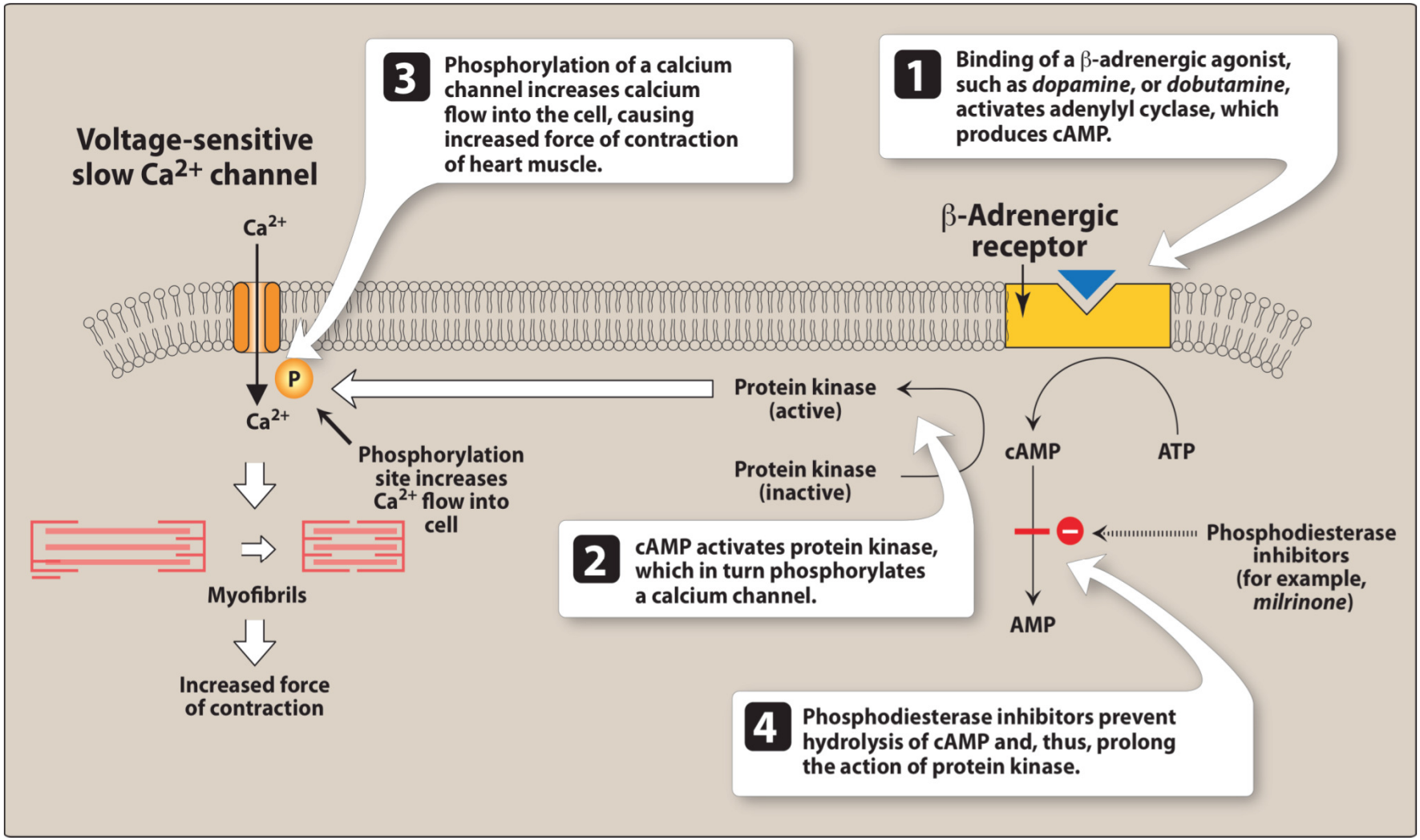
Digoxin toxicity

- Major signs of digitalis toxicity
  - Arrhythmias, nausea, vomiting, and diarrhea. Rarely, confusion or hallucinations and visual aberrations may occur.
- Chronic intoxication is an extension of the therapeutic effect of the drug and is caused by excessive calcium accumulation in cardiac cells (calcium overload). This overload triggers abnormal automaticity and arrhythmias. Severe, acute intoxication results in cardiac depression leading to cardiac arrest rather than tachycardia or fibrillation.
- Treatment of digitalis toxicity includes several steps, as follows.
  1. Correction of Potassium or Magnesium Deficiency. Severe acute intoxication (as in suicidal overdoses) usually causes marked hyperkalemia and should not be treated with supplemental potassium.
  2. Antiarrhythmic Drugs
  3. Digoxin Antibodies

Other inotropes

- **Beta$_1$-Adrenoceptor Agonists**
  - **Dobutamine** (β_1-selective) and **dopamine** useful in acute failure in which systolic function is markedly depressed.
  - Not appropriate for chronic failure because of tolerance, lack of oral efficacy, and significant arrhythmogenic effects.
  - Tachyphylaxis may occur, partially because of receptor desensitization, with infusions of more than 24 to 48 hours
- **Phosphodiesterase Inhibitors**
  - **Amrinone** and **milrinone** are the major representatives
  - Increase cyclic adenosine monophosphate (cAMP) by inhibiting its breakdown by phosphodiesterase and cause an increase in cardiac intracellular calcium similar .
  - Cause vasodilation, which may be responsible for a major part of their beneficial effect. At sufficiently high concentrations, these agents may increase the sensitivity of the contractile protein system to calcium.
  - Not used in chronic failure.

β- adrenergic agonists



Vasodilators

- **Nitroprusside** or **nitroglycerin** is often used for acute severe failure with congestion.
- Vasodilator therapy can be dramatically effective, especially in cases in which increased afterload is a major factor in causing the failure (eg, continuing hypertension in an individual who has just had an infarct).
- The natriuretic peptide **nesiritide** acts chiefly by causing vasodilation, although it does have natriuretic effects as well. It is given by IV infusion for acute failure only.
- ***Nesiritide has significant renal toxicity and renal function must be monitored.***
- Chronic heart failure sometimes responds favourably to oral vasodilators such as **hydralazine** or **isosorbide dinitrate** (or both), and the combination has been shown to reduce mortality in Africans. Calcium channel blockers (eg, verapamil) are of no value in heart failure.

Acute pulmonary oedema Mx

Treat acute precipitating factors (e.g. ischaemia, arrhythmias)

- **L** – furosemide 40-500 mg IV
- **M** – morphine 2-4 mg IV – decreases anxiety and preload (venodilation)
- **N** – nitroglycerin – topical/IV/SL
- **O** – oxygen
- **P** – positive airway pressure (CPAP/BiPAP) – decreases preload and need for ventilation
- **P** – position – sit patient up with legs hanging down unless patient is hypotensive

Heart failure – long term Mx