Pathophysiology of Heart Failure:

Heart Failure (HF) → decreased cardiac output (CO ↓)

$BP = CO \times SVR$

∴ BP ↓

stimulates the baroreceptors

medulla (cardiac & vasomotor centres)

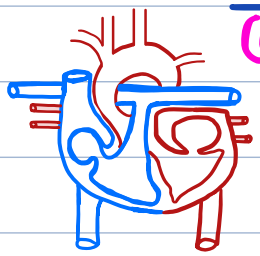
increased sympathetic outlet

increased release of norepinephrine & epinephrine at

HF with a reduced ejection fraction

HF_rEF (Systolic Type)

(due to ↓ systolic function)



HF with a preserved ejection fraction

HF_pEF (Diastolic Type)

(due to ↓ filling of heart)

β_1 receptors of heart

- Increases heart rate
- Increases contractility

→ increased oxygen demand
- decreased duration of diastole

→ decreases coronary perfusion

α_1 receptors of arteries & veins

arteries: vasoconstriction → ↑ systemic vascular resistance (SVR) → ↑ afterload → compensatory left ventricular hypertrophy (LVH)

veins: venoconstriction → ↑ venous return → ↑ preload → left ventricular dilation (LVD)

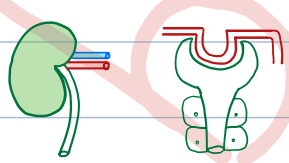
β_1 receptors on JG cells of the kidney

renin

Angiotensinogen → Angiotensin I (AT-I)

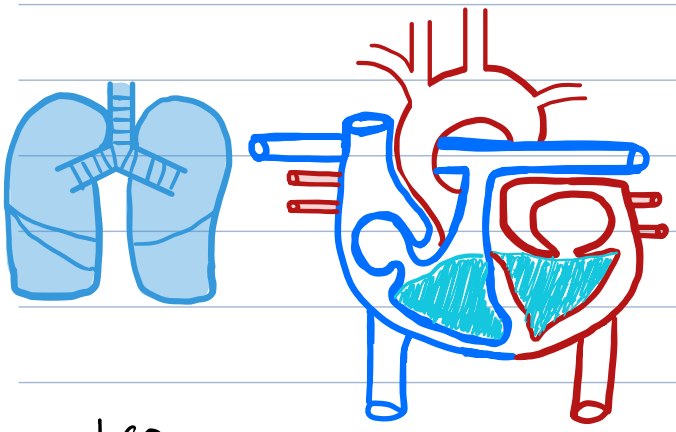
AT-I —ACE→ AT-II

- **Vaso-Constriction** → ↑ SVR → ↑ afterload → ↑ LVH
- **veno-constriction** → ↑ venous return → ↑ preload → ↑ LVD
- Increases ADH production
- increase aldosterone production → Na^+, H_2O retention → hypervolemia → edema / ↑ preload → ↑ LVH
- efferent arteriole vaso-constriction → ↑ kidney perfusion → glomerular BP ↑ *



* ↑ GFR
- ↑ proteinuria
- ↑ thickening of glomerular basement membrane

→ ↑ risk of CKD.



↓CO

↑ volume of blood in LV (overload)

stimulates the ventricular myocardium to release BNP (brain natriuretic peptide)

BNP blocks AT-II action

↓CO

↑ volume of blood in LV (overload)

blood starts entering the LA

retrograde flow from LA into pulmonary venous circulation

pulmonary edema

↓CO

↑ volume of blood in LV → venous congestion in RV

retrograde blood flow into jugular veins / inferior vena cava

jugular vein distension & peripheral edema

HF → ↓CO

compensation mechanisms

↑ HR

↑ contractility of myocardium

↑ LVH

↑ LVD

- ↑ O_2 demand
- ↓ coronary perfusion

- ↑ mortality
- ↑ morbidity

↓CO

↓ mean arterial pressure (MAP)

↓ tissue perfusion

Cardiogenic shock → multi-system organ failure → death

Skin → cold, pale skin

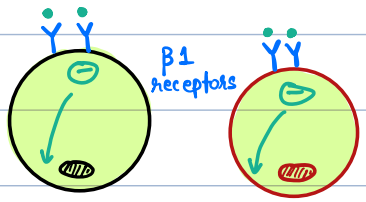
Kidney → ↓ urination → ↑ risk of acute kidney injury (AKI)

Skeletal Muscles → Fatigue, dyspnoe on exertion

β-Blockers:

- Metoprolol (β1) — tartarate / succinate → better for CHF
- Bisoprolol (β1)
- Carvidolol (β1 + α1)

} ↓ mortality

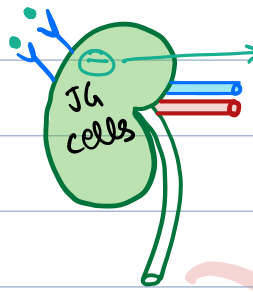


↓ HR — ↓ Contractility

↓ O_2 demand

↑ coronary perfusion

↑ duration of diastolic filling

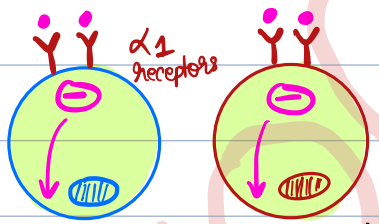


↓ renin production → ⊖ RAAS

Indications:

1. HF, EF +/- Post-MI +/- CAD
2. β-blockers will cause an initial decrease in EF; later it'll ↑↑ EF & CO.

Carvidolol •



Venous smooth muscle cell → ↓ venoconstriction → ↓ preload → ↓ left ventricular dilation

Arterial smooth muscle cell → ↓ vasoconstriction → ↓ SVR → ↓ afterload → ↓ left ventricular hypertrophy

Adverse effects:

- Bradycardia (due to falling HR)
- Hypotension (due to decreased contractility) ⇒ which may lead to shock

  ∴ C/I = decompensated heart failure
- Propranolol ($\beta_1 + \beta_2$) block β_2 receptors in bronchial smooth muscles

⇒ bronchospasm C/I = COPD, asthma

- Normally, stimulation of sympathetic system by hypoglycemia causes glucagon release; in case of β-blocker, sympathetic outflow is inhibited

  ∴ patient develops Hypoglycemia unawareness ∴ C/I in DM.

C/I: • Asthma / COPD • Heart Block / Bradycardia • PVD • Pregnancy

Indications:

- HTN
- Angina
- Arrhythmias
- Heart failure
- MI
- Migraine prophylaxis
- Essential tremors
- Anxiety (particularly performance anxiety)

RAAS Inhibitors: ↓ mortality

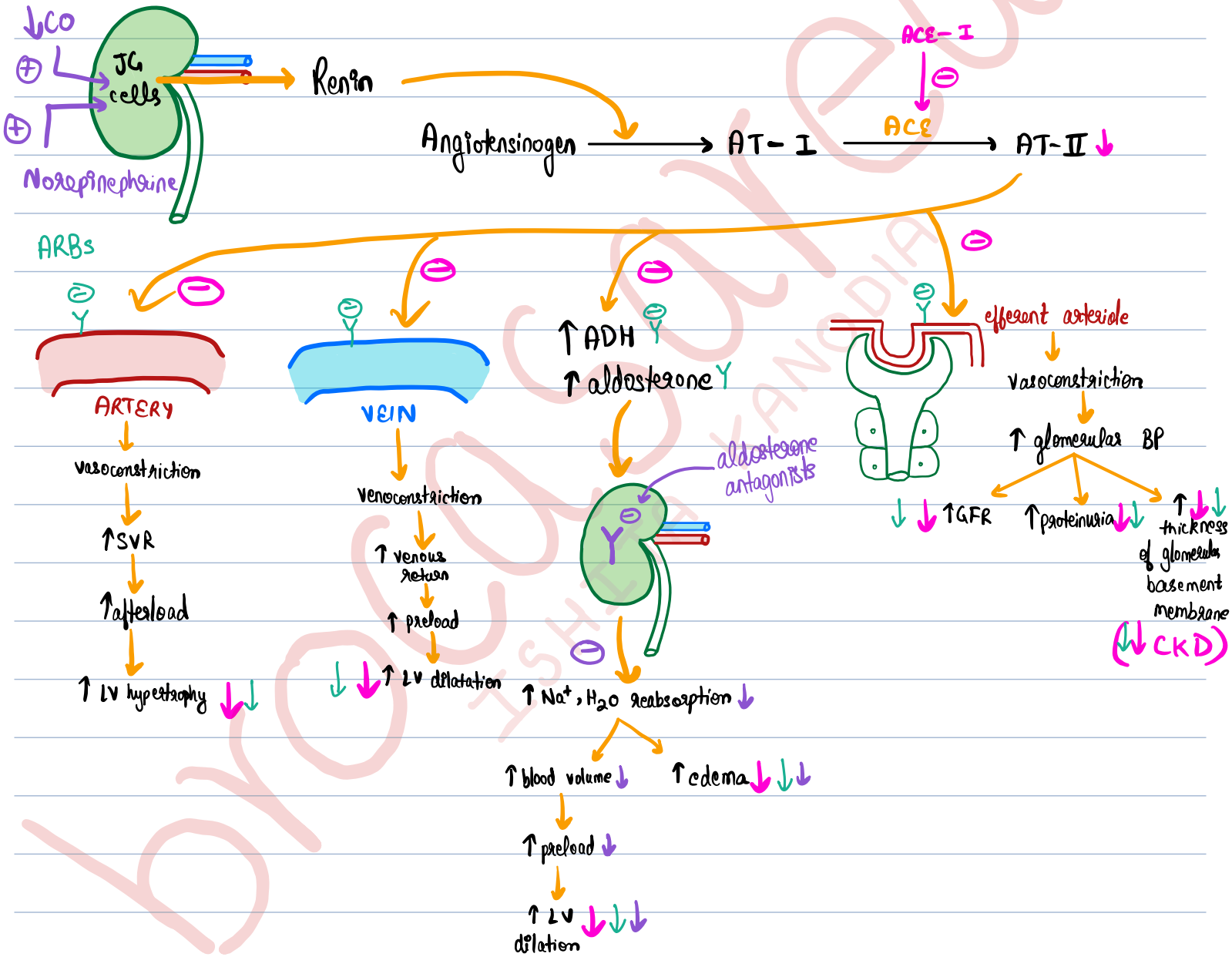
First Line → HFrEF, HFpEF } + HTN [ACE-I or ARBs]

Aldosterone Antagonists ⟹ add-on therapy

ACE Inhibitors: Lisinopril, Captopril, Enalapril, Benzopril

ARBs: Losartan, valsartan, Candesartan

Aldosterone Antagonists: Spironolactone, Eplerenone



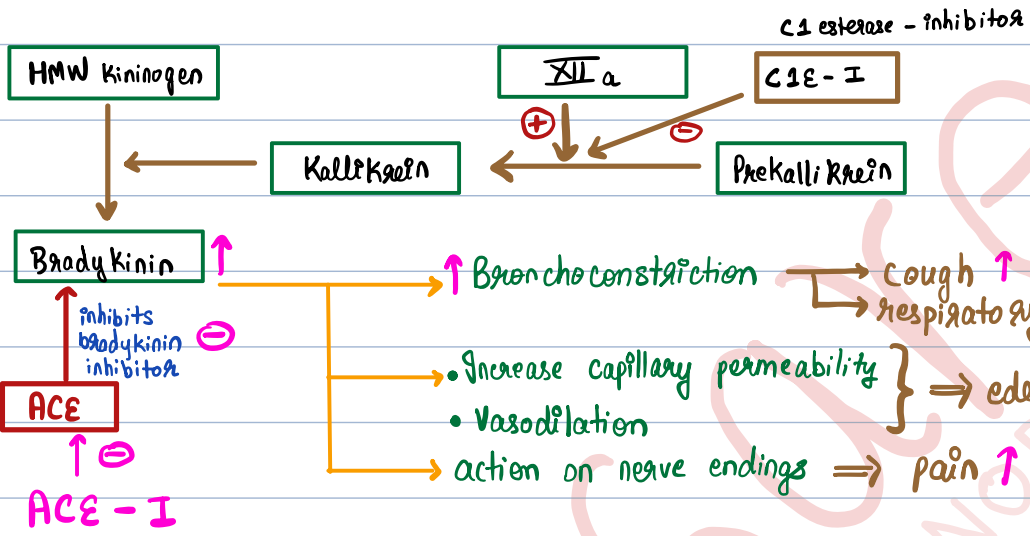
Adverse Effects: ① Hyperkalemia

② Hypotension

③ Angioedema & dry cough (severe reaction to ACE-I)

↓ ↓ ↓

∴ ACE-I are contraindicated in C1E-I deficiency (autosomal dominant trait)



④ First-dose hypotension

⑤ Dysguesia (altered taste sensation)

⑥ Granulocytopenia

Contraindications:

- C1E-I deficiency
- Angioedema
- Pregnancy (teratogenic)
- Bilateral renal artery stenosis
- Severe CKD
- Serum creatinine > 3.5 mg/dL

- Caution while giving multiple anti-HTN drugs ⇒ hypotension may occur
- K^+ sparing diuretics (aldosterone antagonists) with ACE-I/ARBs ⇒ severe hyperkalemia
- NSAIDs increase Na^+ & H_2O retention & counteract anti-hypertensive action of ACE-I/ARBs
- Lithium (used in bipolar disease) toxicity with ACE-I/ARBs since they decrease Lithium excretion.

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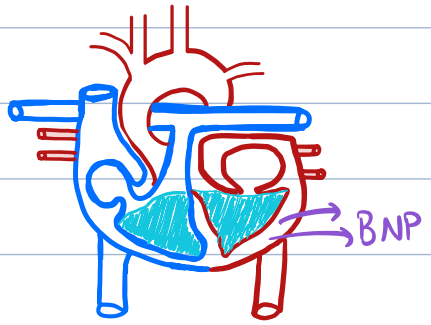
↳ alternative to ACE-I or ARB

BNP Enhancers: ↓ mortality



↓CO → ↑ volume of blood in LV (overload) → stimulates the ventricular myocardium to release BNP (brain natriuretic peptide) → ↑↑ BNP blocks AT-II action

Neprolysin ⊖ ↑↑BNP → inactive metabolite ↓↓

- Sacubitril + ARB - valsartan } Neprolysin inhibitors

ARNi (ENTRESTO)
(Angiotensin receptor blocker with neprolysin inhibitor)

↓CO
⊕ JG cells → Renin
⊕ Norepinephrine

Angiotensinogen → AT-I —ACE→ AT-II ↓↓↓

⊖ ARTERY → vasoconstriction → ↑SVR → ↑afterload → ↑ LV hypertrophy ↓

⊖ VEIN → venoconstriction → ↑ venous return → ↑ preload → ↓↑ LV dilatation

⊖ ↑ADH ↑aldosterone → ↑ Na^+, H_2O reabsorption → ↑ blood volume → ↑preload → ↑ LV dilation ↓
↑ blood volume → ↑ edema ↓

⊖ efferent arteriole → vasoconstriction → ↑ glomerular BP → ↓↑GFR, ↑proteinuria ↓, ↑↓ thickness of glomerular basement membrane (↓CKD)

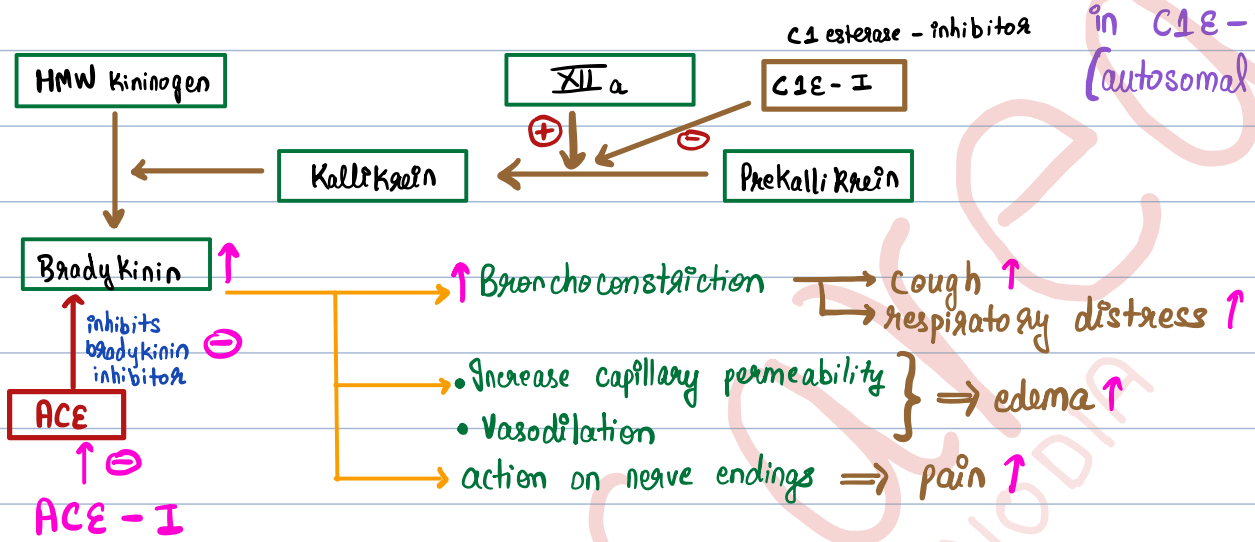
Adverse Effects: ① Hyperkalemia

② Hypotension

③ Angioedema & dry cough (severe reaction to ACE-I)

↓ ↓ ↓

∴ ACE-I are contraindicated in C1E-I deficiency (autosomal dominant trait)



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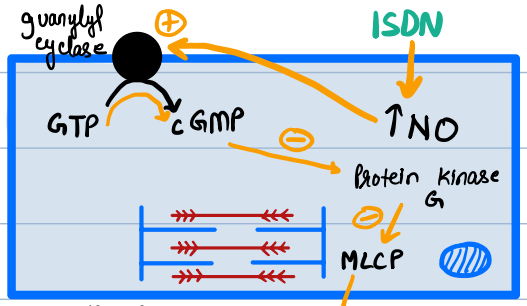
- Lithium (used in bipolar disease) toxicity with ACE-I/ARBs since they decrease Lithium excretion.

Vasodilators (Direct):

↓ mortality in AHF patients of African-American origin

Arterial Dilators: • Hydralazine

Venous Dilators: • Isosorbide dinitrate (ISDN)



ϕ orthostatic hypotension

inhibition of smooth muscle contraction

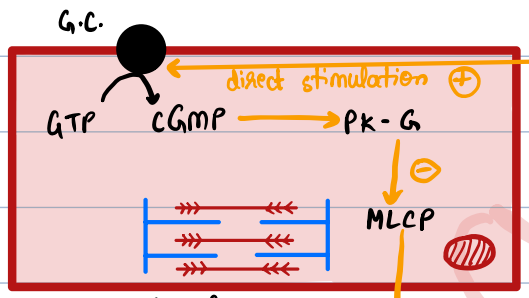
relaxation of smooth muscle (venodilation)

venous return ↓

↓ preload

Indication:

- Alternative therapy (to ACE-I or ARBs)
  - In case of decreasing renal function (ACE-I & ARBs further decrease renal function)
  - In case of AHF in African-American, these are preferred to ACE-I & ARBs



ϕ reflex tachycardia

inhibition of smooth muscle contraction

relaxation of smooth muscle (vasodilation)

↓ SVR

↓ afterload

(HDL2)

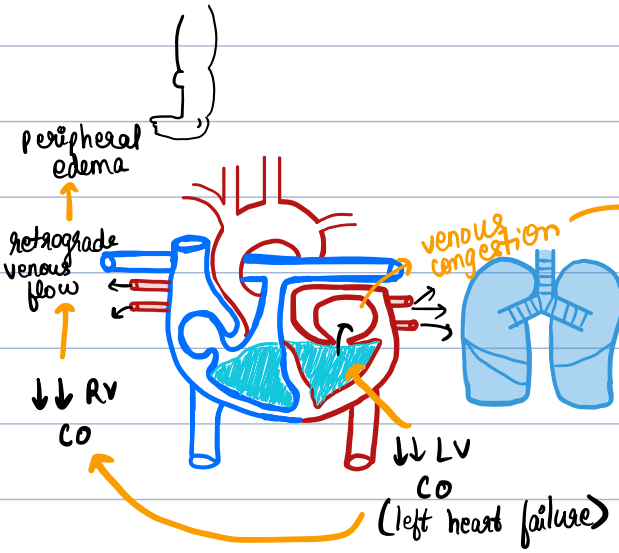
C/I of Hydralazine: • Pregnancy & breastfeeding

- CAD (HDL2 can worsen ischaemia due to blood flow redistribution in the heart)
- Severe hepatic impairment (dose adjustment)
- Cerebral vascular disease (HDL2 ↑ risk of cerebral ischaemia/stroke in case of history)
- SLE-like syndrome
- Mitral valve rheumatic heart disease (HDL2 ↑ regurgitation of mitral valve in RHD patients)

Diuretics: ↓ edema symptoms (pulmonary venous congestion, peripheral edema)

Loop: Furosemide, Bumetanide, Torsemide

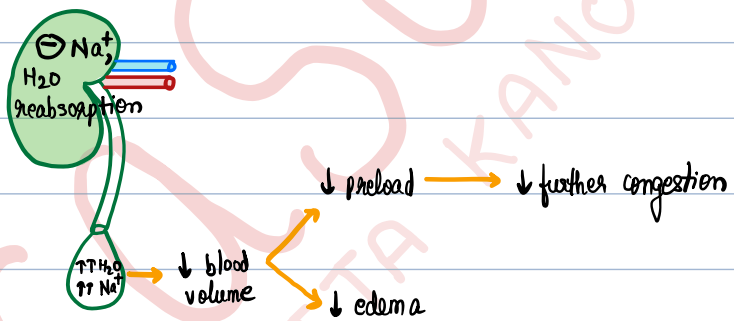
Thiazide: Hydrochlorothiazide, chlorothalidone, metolazone



Pulmonary edema
- dyspnoea
- Paroxysmal nocturnal dyspnoea
- Orthopnoea
- hypoxic respiratory failure

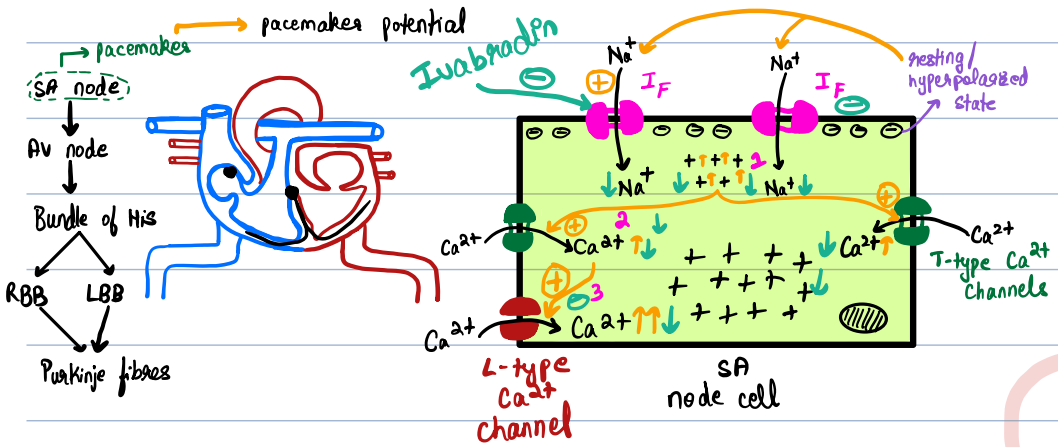
Indications:

- To ↓ Edema symptom
  - Pulmonary congestion
  - peripheral pitting edema
  - increasing daily weight

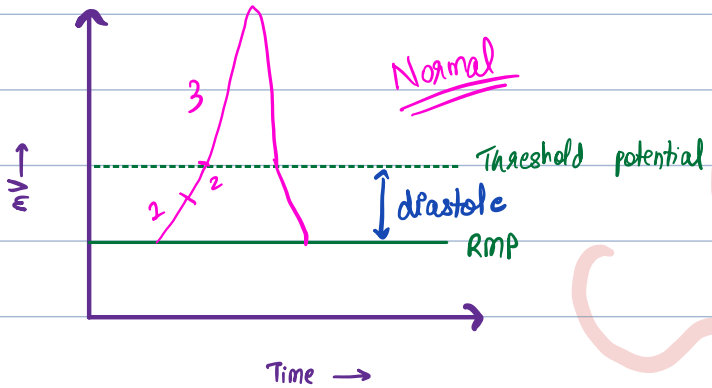


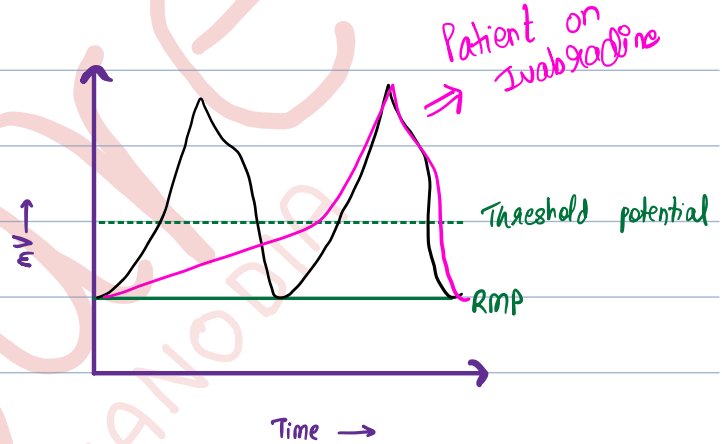
- ϕ Metabolic alkalosis
- ϕ Hyponatraemia
- ϕ Hypokalemia
- ϕ Hyperuricemia & gout
- ϕ Ototoxicity

Ivabradine: used in Refractory CHF (HFrEF; EF ≤ 35%)



I_F = inward (funny) Na^+ Channels





- ↓↓ HR
- ↑↑ diastolic filling → ↑ ventricular filling → ↑ coronary perfusion, ↑ CO, SV

Indications:

- EF ≤ 36% + Normal sinus rhythm + HR ≥ 70 bpm + maxed on β-blockers or C/I to β-blockers

ϕ Bradycardia

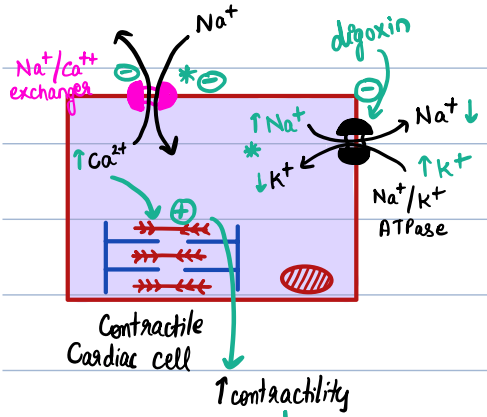
ϕ Blurry luminous changes (bright vision changes)

Positive Inotropic Agents: ↑ contractility.

[utilized in refractory $HF_{r}EF$]

1 Digoxin: refractory $HF_{r}EF$ (ACE-I, ARBs, ARNi's, β-blockers, aldosterone antagonists, Hydralazine & isosorbide dinitrate, diuretics

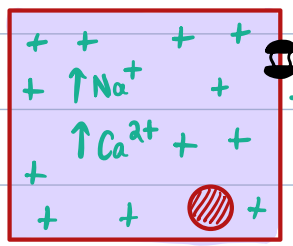
* high Na^+ inside the cell
∴ Na^+ cannot move down the conc. gradient with Na^+/Ca^{2+} exchanger ∴ this exchanger is inhibited



↑contractility

∴ +ve inotrope

↑SV, ↑CO

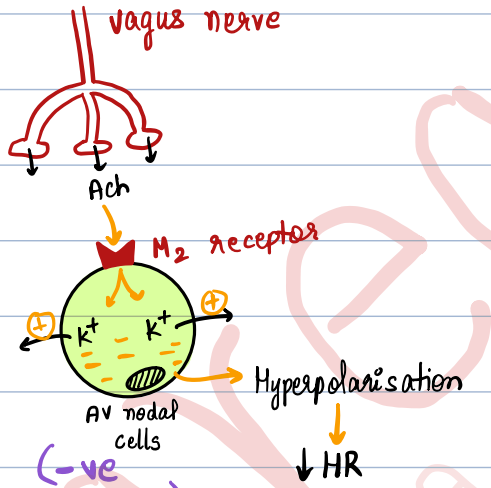


→ ↑RMP → ϕ ↑arrhythmia

↑K^+ → ϕ hyperkalemia

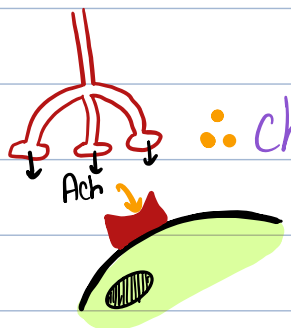
- K^+ & digoxin compete with each other at Na^+/K^+ ATPase pum

∴ ϕ hypokalemia ⟹ digoxin toxicity ↑



(-ve chronotrope)

∴ indicated to ↓HR in patients with atrial fibrillation + $HF_{r}EF$



∴ Cholinergic side effects

- nausea
- vomiting
- diarrhoea
- vision changes (bright yellow vision)

Drug Interactions:

- Digoxin toxicity with Verapamil & Amiodarone (due to decreased renal clearance of digoxin)

↑↑ digoxin levels ⟹ ↑↑ mortality in $HF_{r}EF$

antidote: digibind

Adverse Effects: (therapeutic index 1.5–3)

Extracardiac: • Nausea • Vomiting • Abdominal pain • Diarrhoea • Gynecomastia • Skin rashes

Cardiac: • Arrhythmia • Pulsus bigeminus • Partial to complete AV block

Precautions & C/I: • Elderly patients • Renal/hepatic disease • Ventricular tachycardia • Hypokalemia • Partial AV block • WPW syndrome

Digoxin Toxicity – Management:

For tachyarrhythmias: • Infuse KCl 20 mmol/hr (max. = 100 mmol) I.V

• K^+ is C/I if higher degree of AV block is present

For ventricular arrhythmia: • Lidocaine I.V.

• C/I drugs: Quinidine, procainamide, propafenone

For supraventricular arrhythmia: • Propranol I.V. or orally

For AV block & bradycardia: • Cardiac pacing through a temporarily-inserted pacemaker

• Atropine 0.6 – 1.2 mg I.M.

Drug Interactions:

① Diuretics: cause hypokalemia ⟶ increased risk of digitalis arrhythmia (give K^+ supplements)

② Calcium: synergizes with digoxin ⟶ precipitates toxicity

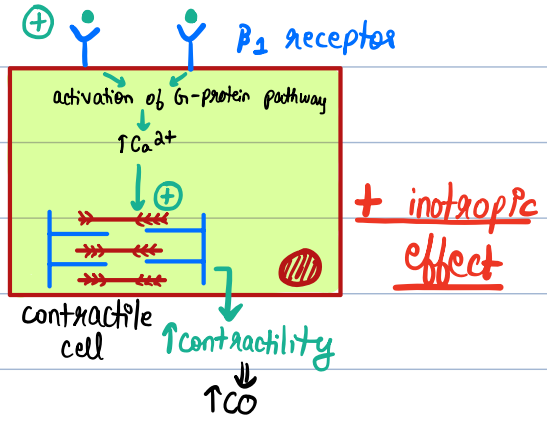
③ Quinidine: reduces digoxin tissue-protein binding & renal & biliary clearance ⟶ toxicity

④ Propranolol, verapamil: oppose positive inotropic effect

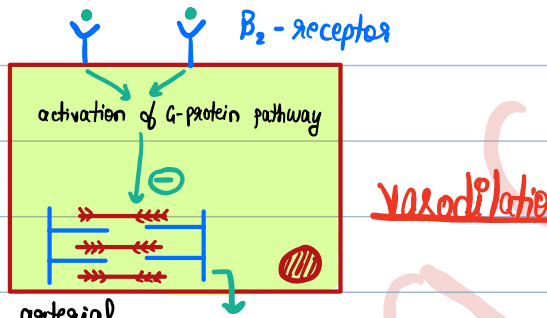
II Dobutamine: (β1 + β2 agonist)

↑↑ mortality ← i.v. infusion

Indication: AHF progressing to cardiogenic shock



+ inotropic effect



vasodilation

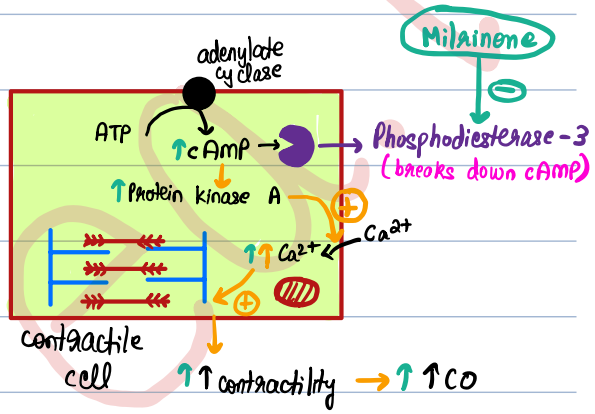
ϕ Tachycardia (↑HR)

ϕ Stress (takotsubo) cardiomyopathy (↓↓EF)

ϕ vasodilation → ↓ BP ∴ +/- Norepinephrine (for pressor action)

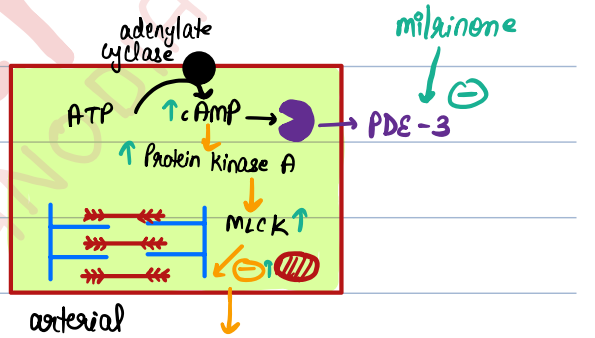
III Milrinone: (PDE-3 inhibitor)

Indication: AHF progressing to cardiogenic shock



+ inotropic effect

Inamrinone
milrinone



vasodilation

ϕ ARF (↑ levels of milrinone in ARF due to renal excretion of milrinone)

ϕ vasodilation → ↓ BP ∴ +/- Norepinephrine (for pressor action)

Adverse effects:

- Thrombocytopenia
- Nausea
- Diarrhoea
- Abdominal pain

Chronic Heart Failure Management:

[NYHA = New York Heart Association Classification]

[NYHA - A]: ⊖ Symptomatic , ⊖ Structural Heart Disease (LVH/LVD/myopathy) , ⊕ Risk factors for HF (HTN, CKD, etc.)

↳ ACE-I or ARB

(symptoms: dyspnoea, fatigue, venous congestion, etc.)

[NYHA - B]: ⊖ Symptomatic , ⊕ Structural Heart Disease , ⊕ Risk factors

↳ ACE-I or ARB

⊕ β-blocker (if ↓EF, Post-MI, CAD)

[NYHA-C]: ⊕ symptomatic , ⊕ Structural Heart Disease , ⊕ Risk factors

↳ ACE-I or ARB

↳ β-blocker (if ↓EF, Post-MI, CAD)

⊕ Aldosterone Antagonist

⊕ if refractory to max ACE-I/ARBs: ARNi

⊕ if patient is African-american / has ARF: ⊗ ACE-I/ARBs

↳ Hydralazine & Isosorbide dinitrate

⊕ if lots of central & peripheral venous congestion present → Diuretics

[NYHA-D]: Refractory to all of the above

↳ ACE-I or ARB

↳ β-blocker (if ↓EF, Post-MI, CAD)

→ Aldosterone Antagonist

→ if refractory to max ACE-I/ARBs: ARNi

→ if patient is African-american / has ARF: ⊗ ACE-I/ARBs

↳ Hydralazine & Isosorbide dinitrate

→ if lots of central & peripheral venous congestion present → Diuretics

⊕ Ivabradine (if EF < 35%, NSR > 70 bpm, max. β-blockers)

⊕ Positive inotrope (especially if AF present)

(digoxin)

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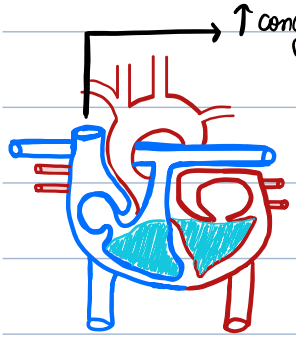
Acute Heart Failure Management:



↑ congestion
- peripheral pitting edema
- jugular venous distension
- pulmonary edema → Hypoxia (↓ O_2) *

↓CO
+ exacerbation
- MI
- medication non-compliance
- ARF
- Hypertension crisis

↓↓↓↓ CO

↓↓↓ perfusion
- cool, pale skin
- decreased urine output
- ↓↓↓↓ BP * → MSOF } cardiogenic shock

PERFUSION

• N perfusion • ↓ congestion ∴ warm (extremities) + DRY (lungs) stable	• N perfusion • ↑ congestion Warm + Wet aim: ↑ diuresis
• ↓ perfusion • ↓ congestion COLD + DRY start inotropes	• ↓ perfusion • ↑ congestion COLD + WET multiple interventions *

CONGESTION

* Intervention for Cold, Wet Type

Aim:
- ↑ perfusion
- ↓ congestion

① ↓ Congestion

↓ Preload

↓↓↓ Na^+, H_2O reabsorption
- Diuretics (Loop + thiazide) I.V.
(1st line)

↓ venous return
venodilation
- NTG
- Morphine
(2nd line)

② ↑ Perfusion:

Hypertensive AHF
[↑↑SVR, ↓↓↓CO]
(aka flash pulmonary edema, sympathetic crashing acute pulmonary edema)
aim: dilate arteries / ↓ afterload
- High dose NTG
- Hydralazine + isosorbide dinitrate
- ACE-I or ARB
ϕ ARF

Hypotensive AHF
(Cardiogenic shock)
N SVR, ↓↓↓↓ CO
aim: increase contractility
- + inotropes (dobutamine, milrinone)
ϕ β-blocker
↓
↓SVR
↓
ϕ BP
∴ +/- pressor (norepinephrine) to ↑ BP.

Drugs for Congestive Heart Failure

Inotropic Drugs

- Cardiac glycosides
  - Digoxin
  - Ouabain
- Sympathomimetics
  - Dobutamine
  - Dopamine
- PDE-3 inhibitors
  - Inamrinone
  - Milrinone

Diuretics

- High Ceiling
  - Furosemide
  - Bumetadine
- Thiazide-like
  - Hydrochlorothiazide
  - Metolazone
  - Xipamide

β-adrenergic blockers

- Metoprolol
- Bisoprolol
- Nebivolol
- Carvedilol

Aldosterone Antagonists

- Spironolactone
- Eplerenone

Renin-Angiotensin Inhibitors

ACE-I

- Enalapril
- Ramipril etc.

ARBs

- Losartan
- Candesartan
- Telmisartan etc.

Vasodilators

- Venodilators
  - GTN
  - Isosorbide dinitrate
- Arteriolar Dilator
  - Hydralazine
- Arteriolar + venodilator
  - Sodium nitroprusside

PDE-3 Inhibitors: Amrinone, Milrinone, Levosimendan

Adverse effects
- Cardiac arrhythmias
- GI: nausea & vomiting
- Dose-dependent thrombocytopenia
- Sudden death