pharmacology

summary

made by : ebaa alzubi

Antihypertensives drugs

Hypertension is a silent disease cause end organ damage : congestive heart failure, myocardiac infarction, renal damage, cerebrovascular accidents

hypertension is above 140/90 , elderly above 150/90 , 3 stages of hypertension .

Lifestyle Modification is more beneficial than drugs with side effect .

neural stimulation & local factors affect faster in emergency on cardiac output (CO) and total peripheral resistance (TPR)

drugs - location - decrease BP

methyldopa+ clonidine - vasomotor center in brain
propranolol - B blockers - heart
losartan - angiotensin receptors - vessels
minoxidil+ nitroprusside + ca+ blockers - smooth muscle of vessel
fenoldopam - stimulates dopamine
thiazide - inhibits Na+ reabsorption in renal tubules → **more efficacy in black people**
ACE inhibitors - prills - inhibit angiotensin conversion
Alpha 1 blockers - on vessels - men >50 , enlarged prostate.

diuretics lower blood pressure by 10–15

Thiazide Diuretics

increase Na+ excretion , Acute decrease in CO ,Chronic decrease in TPR
lower doses (25–50 mg) , dose independent , rare Orthostatic hypotension
Chlorothiazide & Hydrochlorothiazide = orally
Adverse effect : hypokalemia , hyperuricemia (like gout) , hyperglycemia (diabetes) hypercalcemia

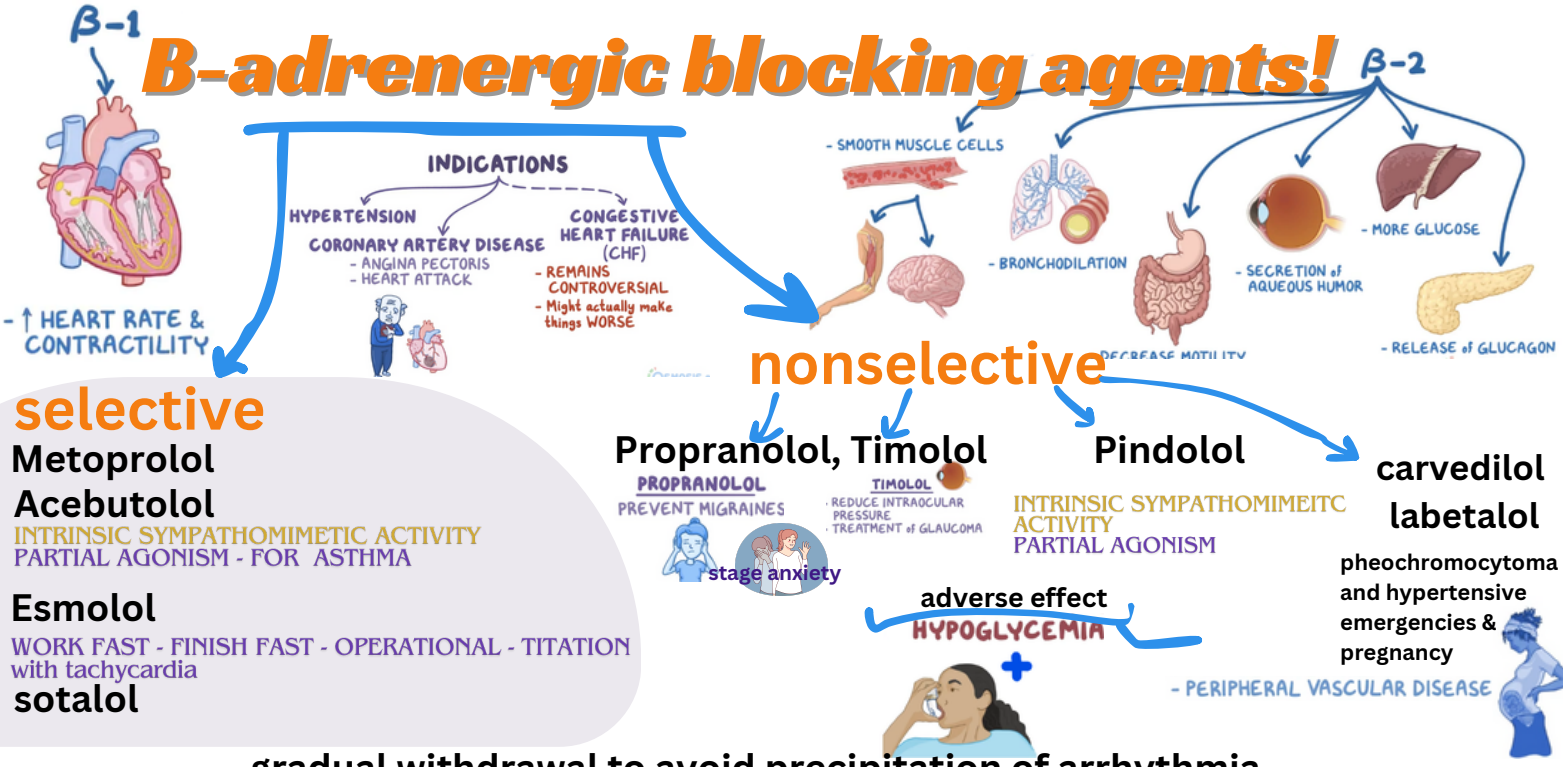
1/4 ml of digoxin can be fatal with hypokalemia + Na+ supplements .

for whom can't take thiazides = kidney compromised = give Loop diuretics like :

effective if CrCl <30

Furosemide (Lasix) - unless they had sulfa hypersensitivity.
ethacrynic acid, and bumetanide (preferable) .
cause dry mouth , Ototoxicity with aminoglycosides , nocturia , hypocalcemia

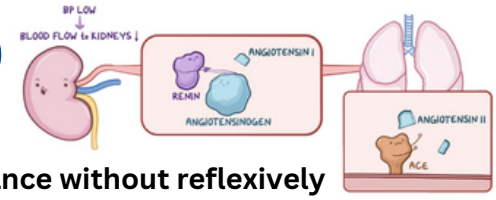
B-adrenergic blocking agents!

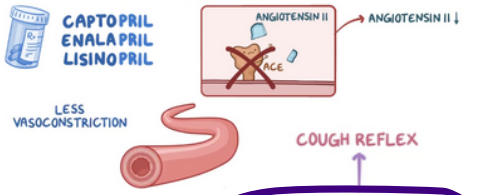


gradual withdrawal to avoid precipitation of arrhythmia

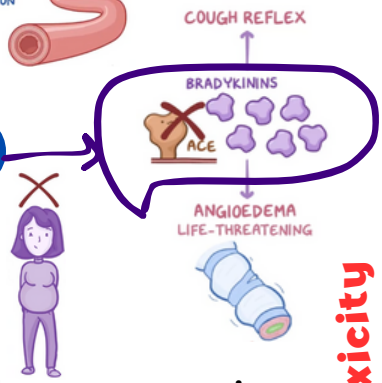
ACE Inhibitors

first - line agents





reducing peripheral vascular resistance without reflexively increasing cardiac output



hyperkalemia + dry cough + angioedema(first-dose syncope)

combinations : ACE inhibitors or ARBs and thiazides

useful for hypertensive + diabetic black people

(ACEIs) are relatively contraindicated in patients with bilateral renal artery stenosis

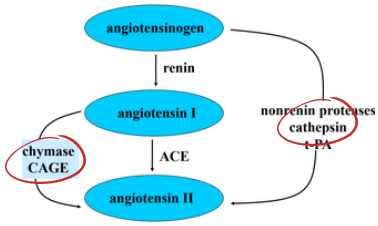
fetal renal toxicity

ANGIOTENSIN II-RECEPTORS ANTAGONISTS

Losartan , for whom can not use ACE .

do not increase the bardykinin levels

low risks of cough and angioedema



potassium accumulation : hyperkalemia

Calcium channel blockers

vasodilation effect

binding to the L-type channels

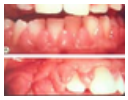
first line for blacks - except patient with angina and diabetes = then ACE are first line with thiazide except in England & Australia . cardio-selective : negative chromo , intropo

	NIFEDIPINE*	DILTIAZEM	VERAPAMIL
coronary arteries dill	+ +	+ +	+ +
peripheral arteries dill	+ + + +	+ +	+ + +
negative inotropic	+	+ +	+ + +
slowing AV cond	↔	+ + +	+ + + +
heart rate reflux tachycardia	↑ ↔	↓ ↔	↓ ↔
↓ blood presure	+ + + +	+ +	+ + +
depression of SA	↔	+ +	+ +
increase in cardiac output	+ +	↔	↔

a. Diphenylalkylamines, Varapamil.
b. Benzothiazepines, Diltiazem
c. Dihydropyridines, Nifedipine

Drug	Effect on heart rate	Adverse effects
Nifedipine	↑	Headache, flushing, ankle swelling
Amlodipine	↑	Ankle swelling
Nimodipine	±	Flushing, headache
Diltiazem	±	Generally mild
Verapamil	↓	Constipation, marked negative inotropic action

THEY CAUSE ORTHOSTATIC HYPOTENSION & GINGIVAL HYPERPLASIA .



LONG HALF-LIFE , MOST USEFUL

verapamil and nimodipine also used to decrease migraine , or brain hemorrhage

Selective a1 -blockers

Alfuzosin, doxazosin, prazosin, terazosin = FOR HYPERTENSION + PROSTATE HYPERPLASIA

•Silodosin = FOR PROSTATE HYPERPLASIA

Centrally acting adrenergic drugs

a2 agonist

Clonidine

for whom can not with diuretics alone

useful in renal disease

sodium and water retention

lowers heart rate

DRY MOUTH, SEDATION

Rebound hypertension occur following sudden withdrawal

time to rebuild receptors

Methyldopa

useful in renal disease

methylnorepinihrine

SAFE

DRY MOUTH, SEDATION

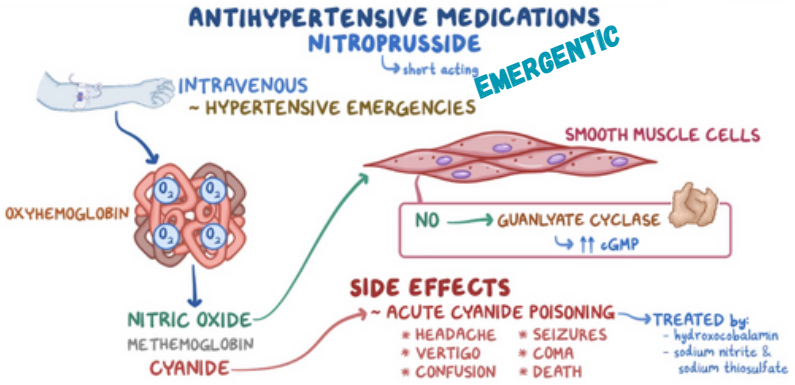
VASODILATOR

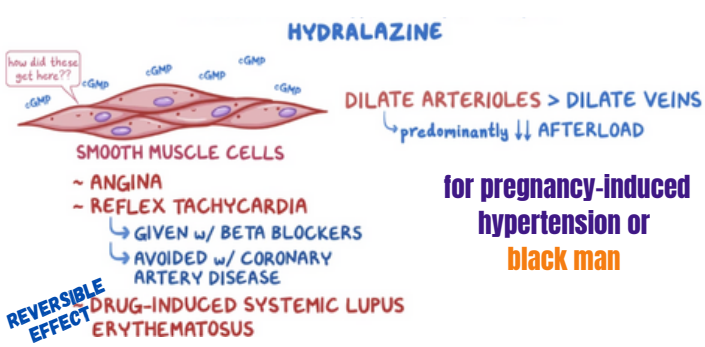
smooth muscle relaxants

sodium and water retention

no unwanted effects =give B blockers

prompt angina, Myocardiac Infarction





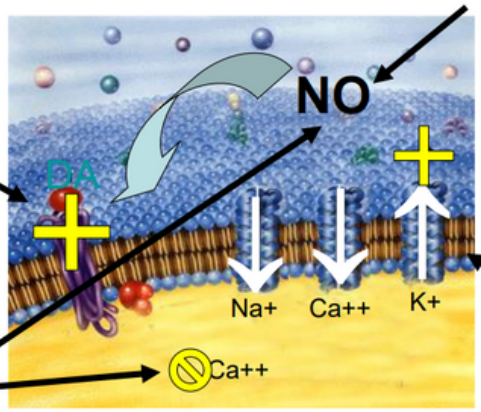
for pregnancy-induced hypertension or black man

nitroprusside

beneficial in patients with renal insufficiency

fenoldopam

causes arterial/arteriolar vasodilation leading to a decrease in blood pressure by activating peripheral D 1 receptors. It decreases afterload and also promotes sodium excretion



hydralazine

minoxidil

diazoxide

potent openers of the K+ ATP channels. Opening these channels leads to decrease in calcium influx,

Hypertension emergency

150/210

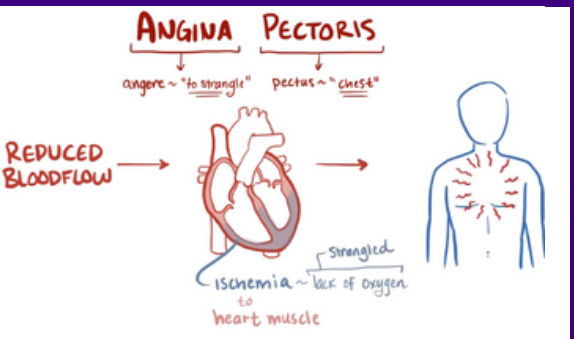
- It is rare but life threatening, in which DBP is > 150 mm Hg with SBP > 210 mm Hg (healthy person), or DBP of > 130 mm Hg in individual with pre-existing complications, such as encephalopathy, cerebral hemorrhage, and left ventricular failure, or aortic stenosis.
- **Sodium nitropresside** (onset 1-2 min), is administered intravenously and causes sudden vasodilation and reflex tachycardia, it is effective in all patients regardless the cause.

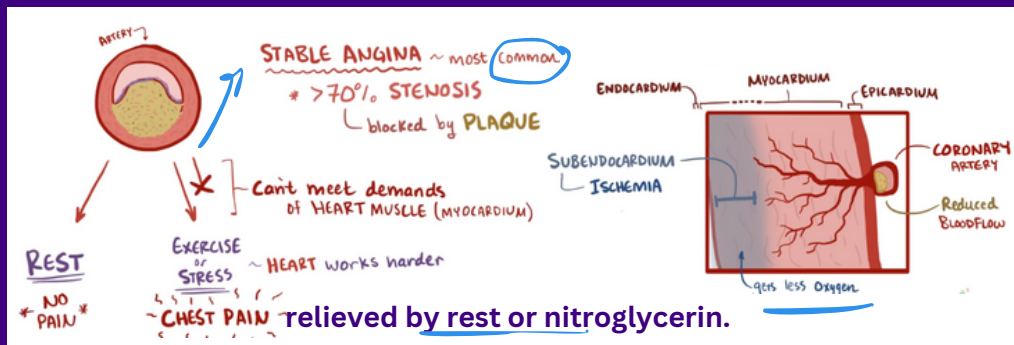
It metabolized rapidly (half life of minutes) and require continuous perfusion. An overdose can cause hypotension.

angina

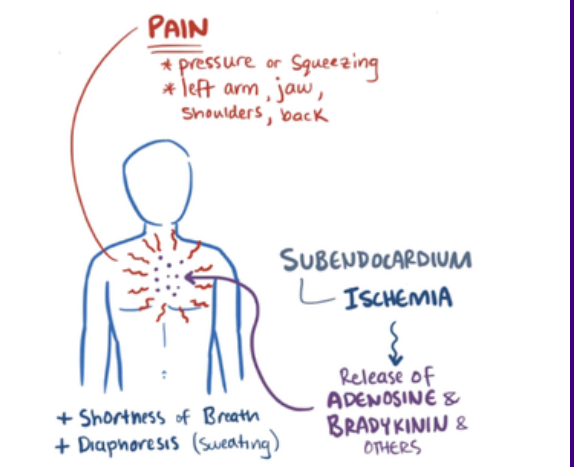
الذبحة الصدرية

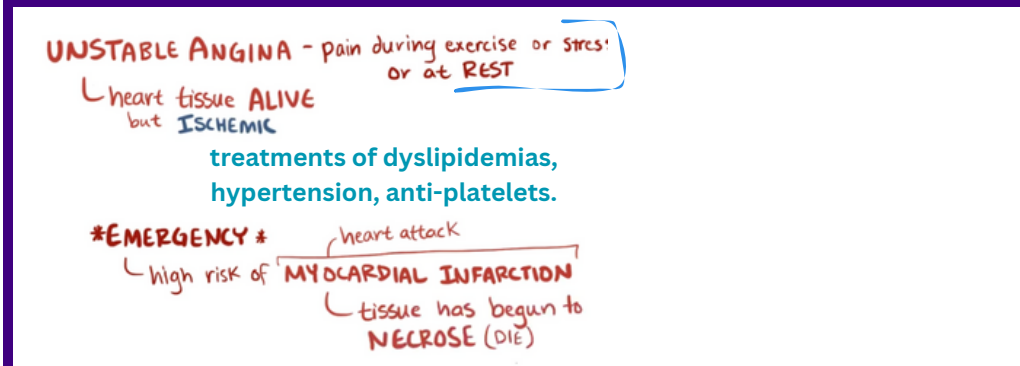
تتمثل أعراض الذبحة الصدرية في ألم أو ضيق في الصدر يحدث عندما لا يحصل القلب على ما يكفي من الأكسجين. يمكن أن يوصف ألم الذبحة الصدرية بأنه شعور بالضغط أو الامتلاء أو الثقل أو الضيق في الصدر. كما يمكن أن يمتد الألم إلى مناطق أخرى من الجسم، مثل الكتف أو الذراع أو الرقبة أو الفك أو الظهر.



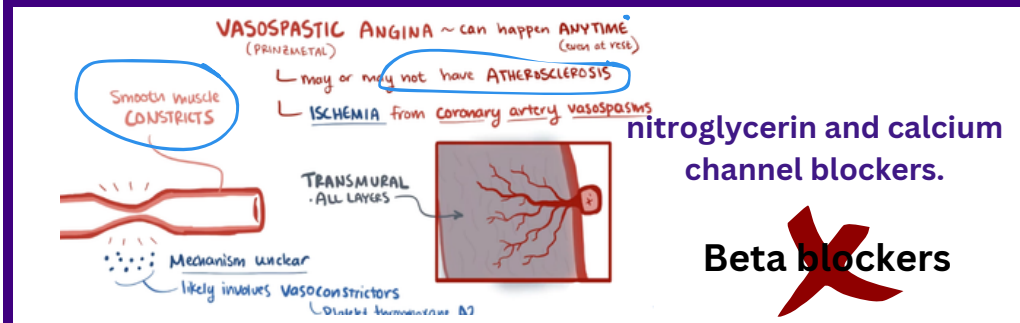


relieved by rest or nitroglycerin.





treatments of dyslipidemias, hypertension, anti-platelets.



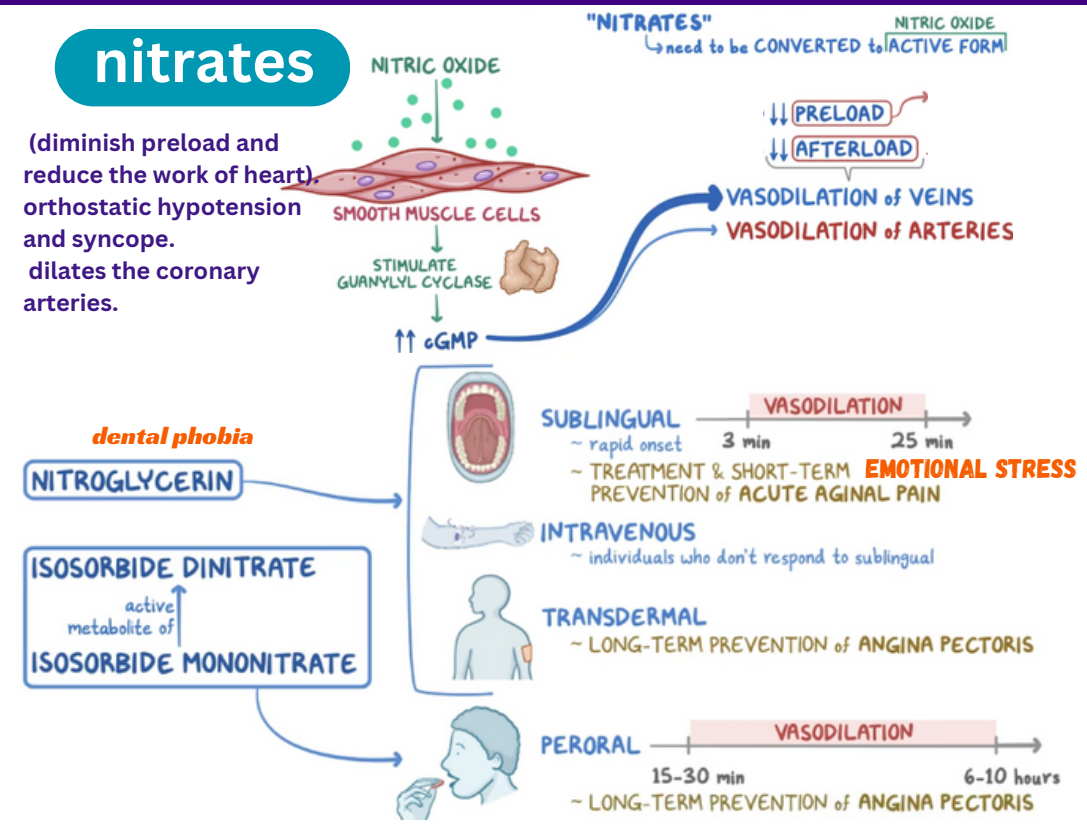
nitroglycerin and calcium channel blockers.

Beta blockers

ANTIANGINALS

nitrates

(diminish preload and reduce the work of heart), orthostatic hypotension and syncope.
dilates the coronary arteries.

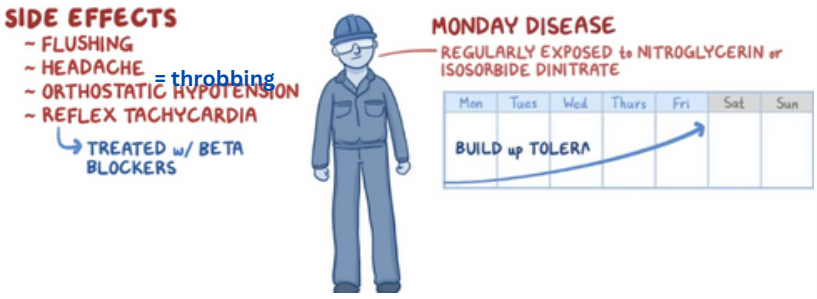


Pharmacological mechanism

Organic nitrates
↓
NO
↓
guanylyl cyclase
↓
cGMP ↑
↓
cGMP dependent protein kinase
↓
intracellular Ca^{2+} ↓
↓
vascular smooth muscle relaxation

Sildenafil (Viagra) inhibits phosphodiesterase -> thus increases levels of cGMP -> myosin molecules are further apart -> relaxation

NEVER combine nitrates with sildenafil because -> this leads to a major drug-drug interaction & **hypotension shock** (tachycardia, circulatory collapse) - they both also cause headaches / **any vasodilator causes headaches as well!**



	Result
1. Potential beneficial effects	
Decreased ventricular volume Decreased arterial pressure Decreased ejection time	Decreased myocardial oxygen requirement decreased oxygen demand
Vasodilation of epicardial coronary arteries Dilation (انفراج او انفتاح) at connection point of coronary arteries .	Relief of coronary artery spasm →
Increased collateral flow in cases of stenosis, angiogenesis occurs leading to increase in collateral flow	Improved perfusion to ischemic myocardium
Decreased left ventricular diastolic pressure	Improved subendocardial perfusion
2. Potential deleterious effects	
Reflex tachycardia (On the level of the vein) ←	Increased myocardial oxygen requirement
Reflex increase in contractility	
Decreased diastolic perfusion time due to tachycardia	Decreased coronary perfusion

Thiol compounds are limited, so depletion due to continuous administration of nitrates= tolerance can be overcame by providing a daily "nitrate free intervals"

kept in tightly closed glass ,not require refrigeration

Thereby, high dose of beta blocker + nitrates is prescribed to every patient with angina pectoris (both stable and unstable angina ONLY)

B-adrenergic blocking agents

- The cardioselective β 1agents, such as acebutolol and atenolol and metoprolol are preferred.
- Try to avoid drugs with intrinsic sympathomimetic activity
  - as they increase cardiac oxygen demand, because they are partial agonists .
- First line therapy in all patients with stable angina

  Ventolin (Salbutamol)(Beta 1+2 agonist): 5% experience palpitation.

2.clinical uses

stable and unstable angina

myocardia infarction

3.contraindication

variant angina,

bronchial asthma,

bradycardia,

Calcium-channel blockers, digoxin, and beta-blockers are contraindicated in people with Wolff-Parkinson-White (WPW) syndrome

Calcium channel blockers

USEFUL IN THE TREATMENTS OF ANGINA CAUSED BY SPONTANEOUS CORONARY SPASM (VARIANT ANGINA).

Verapamil: Avoided in congestive heart failure

Verapamil and Diltiazem

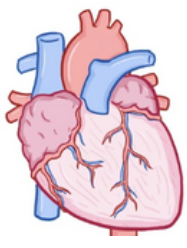
antiarrhythmic effects
Treating angina (not hypertension)

Effect	Nitrates Alone	Beta-Blockers or Channel Blockers Alone	Nitrates Plus Beta-Blockers or Channel Blockers
Heart Rate	*Reflex Increase*	Decrease*	Decrease
Afterload	Decrease	Decrease	Decrease
Preload	Decrease	*Increase*	None or decrease
Contractility	*Reflex increase*	Decrease*	None
Ejection time	Decrease	*Increase*	None

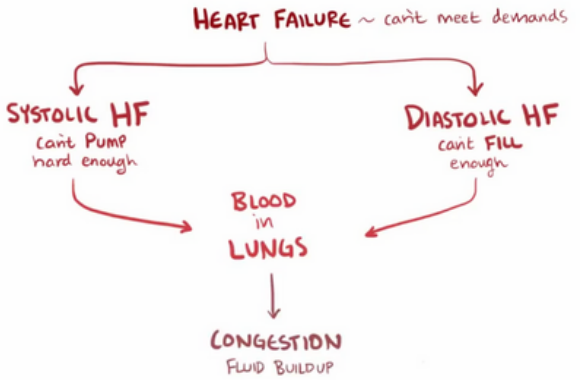
Calcium Channel Blockers Mechanisms of Action

- Arterial dilation/after-load reduction
- Coronary arterial vasodilation
- Prevention of coronary vasoconstriction
- Enhancement of coronary collateral flow
- Improved subendocardial perfusion
- Slowing of heart rate with diltiazem, verapamil

NON-DIHYDROPYRIDINES
~ VERAPAMIL
~ DILTIAZEM
* GREATER EFFECT on the HEART
* LESS EFFECTIVE for VASODILATION



HEART FAILURE



- A complex clinical syndrome characterized by the heart's inability to effectively fill and/or eject (pump) blood
- Normal preload, ↓ contractility (inotropy; force of contraction) → inadequate emptying of ventricles during systole → ↓ EF ≤ 40 (HFrEF); often also have some degree of diastolic dysfunction

(can't pump enough) low preload & low afterload cause heart hypertrophy till these fibers dies (can't pump at all).
so give drugs to lower hypertension in periphery + dilation in coronary to keep the heart alive .

ACE INHIBITORS + BETA BLOCKERS IMPROVE SURVIVAL NORMALLY BUT IN BLACK PEOPLE WE GIVE HYDRALAZINE & MONONITRATES .

- **African-American patients with advanced heart failure due to left ventricular systolic dysfunction should be considered for treatment with hydralazine and isosorbide dinitrate in addition to standard therapy.**

Heart failure drugs

(1) ACE inhibitors, → for symptomatic or non symptomatic
(2) β-adrenergic blocking agents,
(3)diuretics, → for symptomatic or non symptomatic
(4) inotropic agents,
(5) direct vasodilators, → Minoxidil cause fluid retention so needs loop diuretics to remove this fluid
(6) aldesterone antagonist → SPIRONOLACTONE → ANTIANDROGENIC SIDE EFFECTS (e.g. gynecomastia & impotence)
eplerenone

مهم

Spironolactone

Generally Patient with advanced heart disease have elevated levels of aldosterone due to angiotension II stimulation and decrease hepatic clearance of this hormone.

THEY CAUSE HYPERKALEMIA , SO KEEP AN EYE ON CREATININE LEVEL < 2,5 IN MEN , <2,0 IN WOMEN , K < 5

Spironolactone is a direct antagonist of aldesterone, and so prevent sodium retention, myocardial hypertrophy, and hypokalemia.

Spironolactone should be preserved for the most advanced cases of HF.

The dose of spironolactone should be no more than 25-50 mg/day and it is only recommended in those with moderate to severe heart failure due to LVSD.

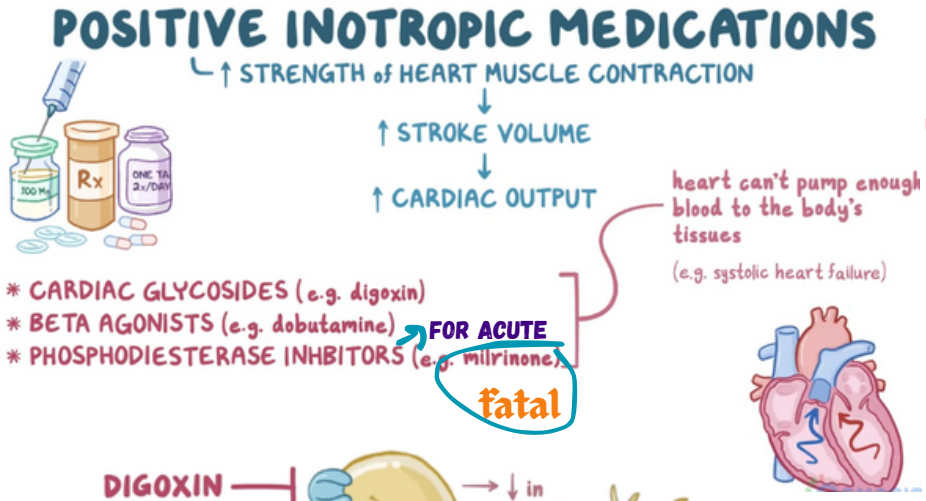
Main side effects include CNS effects, such as confusion, endocrine abnormalities, and gastric disturbances like peptic ulcer.

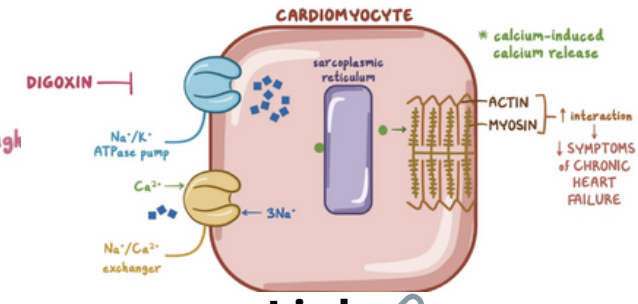
Eplerenone can be substituted for spironolactone in patients who develop gynaecomastia

diagnoses → mild- management → ACE (vasodilators in blacks)& diuretics & beta blockers → SEVERE → SPIRONOLACTONE OR EPLERENONE

after years of managment , when nothing is efective we give the magic :
digoxin

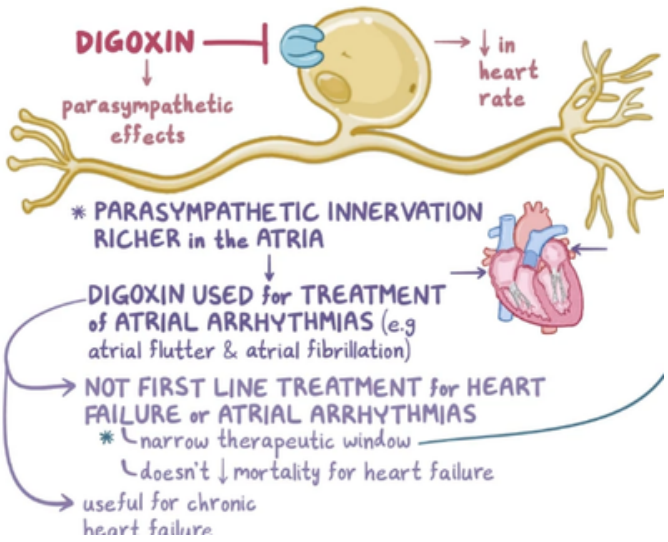
Positive inotropic medications





Link 🔗

inhibits K / Na pump = Influence the sodium and calcium ions=increase Ca+ in cell = Increase the contractibility



- Digoxin also has a rapid onset of action, making it useful in emergency condition, in which the drug in given intravenously, and the onset of action will be within 5-30 minutes.

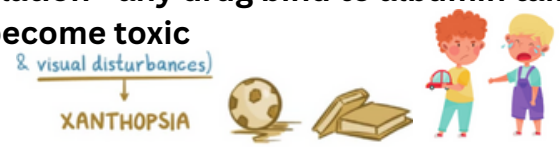
side effect :

narrow window

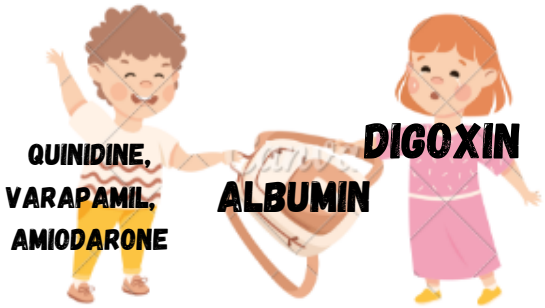
depletion of serum K + due to diuretic therapy

toxic accumulation - any drug bind to albumin take his place so become toxic

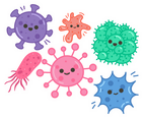
toxicity :



1. Anorexia, nausea and vomiting and diarrhea.
2. Vision changes (xanthopsia), fatigue and headache.
3. cardiac effects that include: premature ventricular contraction, and ventricular tachycardia and fibrillation. Arrhythmia and atrial tachycardia.



Macrolide and tetracycline antibiotics should be avoided because they elevate digoxin serum concentration and enhance the risk for digoxin toxicity



antidote : treat toxicity : Digifab , Digibind

Dobutamine is a B1 adrenergic agonist , for acute heart failure , increase inotropic , cause vessel dilation , hhaha , we dont need dilation so we give some noradrenaline to affect vessels .

Calcium-channel blockers, digoxin, and beta-blockers are contraindicated in people with Wolff-Parkinson-White (WPW) syndrome

Newer antianginal drugs

Ivabradine

SELECTIVELY INHIBITS THE IF CURRENT , DECREASE HEART BEAT , DECREASE O2 DEMAND , NO AFFECT ON HYPERTENSION OR VESSELS , REDUCTION OF ANGINAL SYMPTOMS .

induce CYP3A4 , so will interact with any drug inhibit it like anti-bacterial ,verapamil and diltiazem

Used in HF if beta blockers are not enough , when LVEF lower than 35 percent

manage HF , hb >70 in min .

Ih ion channels in *retina* get affected like heart , which cause luminous phenomena = yellow blurred vision : 14.5%

5% headaches ,bradycardia

Ranolazine

selectively inhibits the late sodium influx ,reducing calcium ,reduced contractility , no effect on heart rate

improves exercise tolerance ,myocardial ischemia , no affect on bp

ischemia= increase o2 demand = increase late Na + Ca + = increase contractility - so we give ranolazine

QT-prolongation (dose-related)

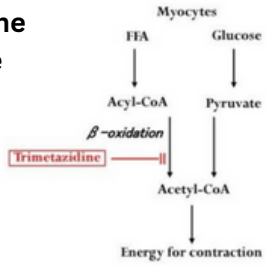
QT interval is increased in the setting of liver dysfunction (contraindecated)

Calcium overload causes diastolic relaxation failure, which:
- Increases myocardial oxygen consumption
- Reduces myocardial blood flow and oxygen supply
- Worsens ischemia and angina

Trimetazidine

ischemia=increase fatty acid oxidation= increase o2 demand = increase contractility - so we give Trimetazidine to inhibit beta oxidation .

Inhibition of the reduction of adenosine triphosphate, stimulation of glucose consumption by the myocardium



cause restless leg syndrome

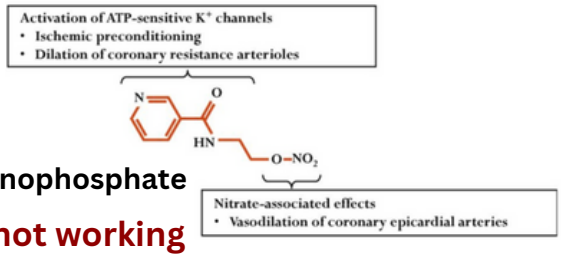
contraindicated in Parkinsonian

Nicorandil

tow parts :

1- nitrate

2- potassium part : open channel - increases cyclic guanosine monophosphate



second-line option if beta blockers &calcium blockers not working

STOP if it cause gastrointestinal, skin and mucosal ulcerations