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Congestive Heart failure

→ Please note that **all** heart diseases fall into one of these 4 categories. But for sure, the patient might have overlapping heart disease; in which he'd have more than one of the following diseases. This is because one condition can lead to the other (eg: Ischemic heart disease if it progresses to Myocardial infarction may cause heart failure).

Heart diseases

- Structural/Anatomical abnormalities → Abnormal valves, congenital defects and anomalies.
- Improper blood flow to the heart → Ischemic heart diseases (CAD)
- Improper pumping ability of the heart muscle with abnormal CO → Congestive heart failure (CHF)
- Arrhythmias (Problems in the electroconducting properties of the heart).

↱ Cardiac output < 5L/minute.

- **Heart failure:** The heart is not able to pump enough blood to match our body needs. Thus cardiac output would decrease, less blood would flow to the tissues, those organs would suffer from ischemia.

⟶ We can also define heart failure by saying it's when the patient's left ventricular ejection fraction (LVEF) is less than **40 %** **.

* Ejection fraction = $\frac{\text{Stroke volume}}{\text{End-diastolic volume}}$; it normally ranges between (50-70%)

Since the heart is not able to pump blood well; then the stroke volume definitely decreases in relation to the end-diastolic volume ; thus ejection fraction decreases.

- Normally:
  - ⟶ Stroke volume : 70mL
  - ⟶ End-diastolic volume = 120mL

} EF = 60%

→ Classification of heart failure:

Anatomical classification into left-sided and right-sided heart failure.

① Left-sided heart failure:

→ There are many causes of left-sided heart failure. The most common of which include **systemic hypertension**

A patient with systemic HTN would have very high resistance in his arteries. This would make it very hard for the left ventricle to pump the blood into the aorta since it'd need to overcome this extra pressure. (Afterload is v.high in this patient). As a compensatory mechanism, the left ventricle would undergo hypertrophy to try to overcome this increased afterload (Left ventricular hypertrophy). This would increase to a point that the pt now has cardiomegaly.

Moreover, as the left-side of the heart increases more and more, the mitral valve would "loosen-up" and starts allowing some blood to leak back into the left atrium. This is

Known as mitral valve regurgitation. In fact, after blood regurgitates back into the left atrium, blood would build up there and then move into the pulmonary veins.
With time, this would lead to pulmonary HTN; it'd become easier now for blood to leak out of the pulmonary capillaries leading to pulmonary edema. This will make it very hard for the pt to breathe. That's why symptoms of left-sided heart failure are mainly pulmonary-related.

Symptoms include: 1) Tachypnea. (The pt breathes at a faster rate than normal).

2) Dyspnea. (Difficulty breathing).

3) Orthopnea. (Difficulty breathing when lying down in the supine position; thus the pt would sleep on a chair or in a 45° manner; not supine

4) Paroxysmal nocturnal dyspnea (PND).
We said that the pt might have orthopnea; and thus can only sleep in the 45° position. However, the pt starts his sleep in this 45° position then slips into the supine position during his sleep (طبيعي المريض تقلب و هو نايم)
So the pt wakes up على الفجر with severe, intolerable chest pain.

⟶ Also, due to left ventricular hypertrophy. The mitral valve won't close at the same time as the tricuspid valve. This results in splitting of the (S_1) sound which is known as the galloping rhythm.
(galloping rhythm would also be heard with right ventricular hypertrophy, the idea is that the ventricular hypertrophy prevents the valves from closing at the same time).

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② Right-sided heart failure

⟶ The right ventricle is not able to pump its blood content away into the lungs. This might be due to conditions like increased venous return. This would be associated with conditions like increased blood content all over the body.
Another major cause of right-sided heart failure is a pulmonary disease. If the pt has pulmonary fibrosis, pulmonary HTN, or any other disease in the lungs and pulmonary circulation which is limiting the flow of blood from the

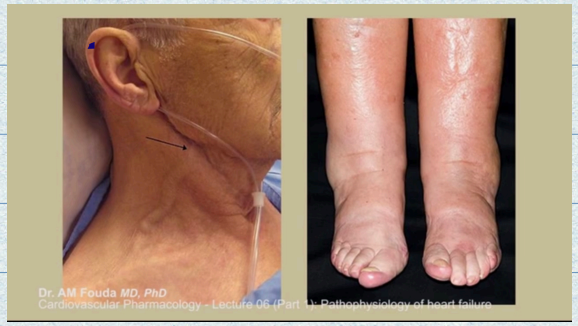
heart into the lungs causing blood to flow backwards into the right ventricle.

Left-sided heart failure can cause pulmonary damage which then leads to right-sided heart failure.

- So; this causes blood to accumulate in the right ventricle causing right ventricular hypertrophy. This hypertrophy would ultimately lead to dilatation of the right ventricle so the right ventricle won't be able to pump blood into the lungs.

- Blood would then accumulate in the right ventricle → right atrium → superior + inferior venacava. Then from those venacava, blood would accumulate in the peripheral veins of the body; causing Systemic congestion. (Blood can accumulate in the peripheral veins of the legs / veins of the neck.) This causes distention in those veins with edema seen as follows:

Ofc, other veins can also get distended like those in the abdomen causing the pt to suffer from dyspepsea.



The patient has congested neck veins with edema of the lower limbs.

Thus the cardinal sign of right-sided heart failure is Systemic congestion.

So, to sum up :-

a) The cardinal sign of Left-sided HF is pulmonary congestion. This pulmonary congestion due to Left-sided HF is the most common cause of right-sided heart failure.

Our main therapeutic goal when dealing with a pt with pulmonary congestion is to reduce the afterload.

b) The cardinal sign of right-sided heart failure is systemic congestion.

↙

manifests as edema and distended veins.

Our main therapeutic goal when dealing with a pt with systemic congestion is to reduce the preload.

- Pathological classification of heart failure:

Systolic heart failure

the problem is with the heart's ability in pumping the blood; the problem is in contractility. Less contraction → less pumping of blood → ↓ SV → ↓ cardiac output.

This classification is not imp. from a pharmacological point of view.

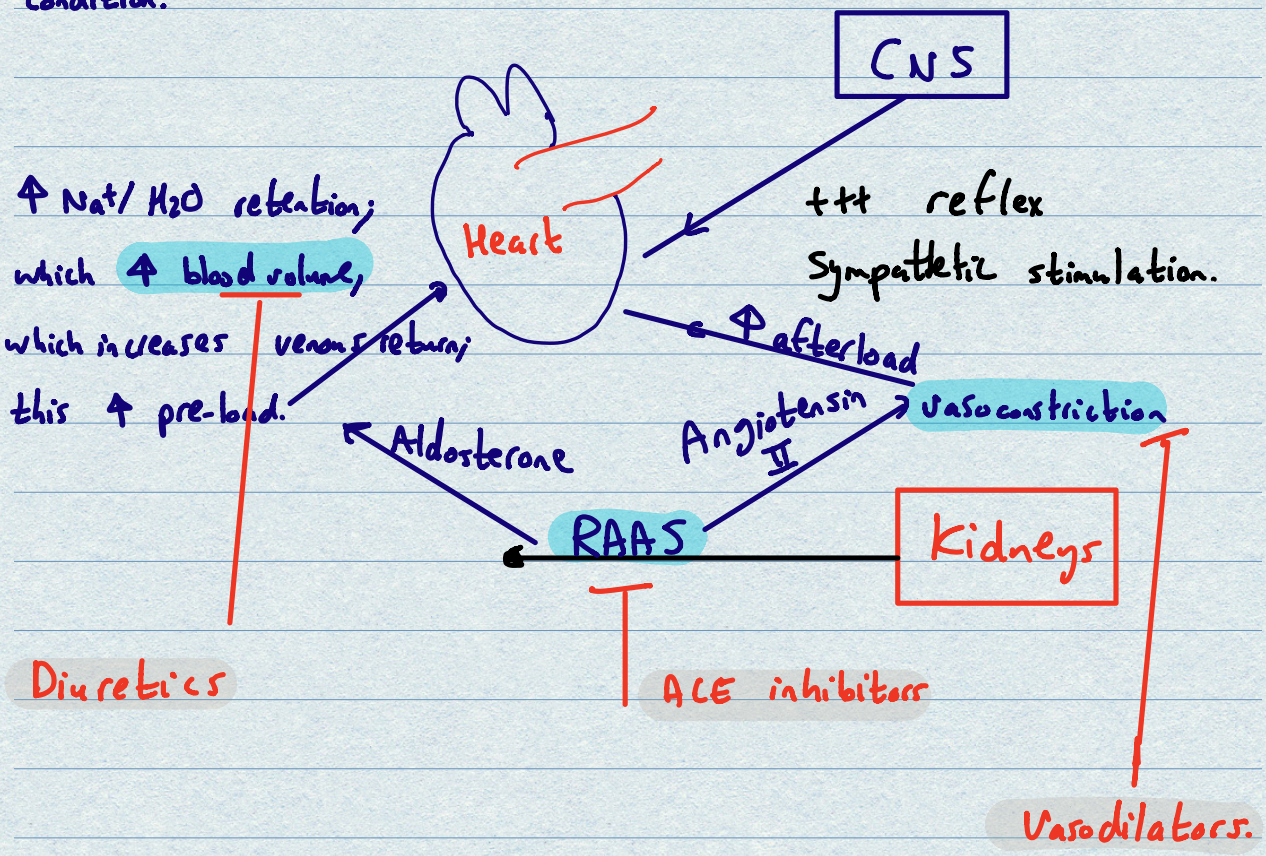
Diastolic heart failure

the problem is with the heart's ability in receiving the blood during diastole. This could be due to infiltration by fibrous tissue / fatty tissue into the ventricles, constrictive pericarditis, ventricular hypertrophy, ... etc ...

(Mainly any condition that reduces the capacity of the heart in receiving blood during diastole, ↓ EDV). Since the EDV is reduced; thus less blood could be pumped from the heart. → Ejection fraction ↓

The effects of heart failure and how to approach its treatment?

→ After heart failure, the amount of blood pumped from the heart to rest of the body decreases (cardiac output decreases). This means that all body tissues would suffer from ischemia and Hypoxia. However, 2 organs in specific would play a central role in the deterioration of the pt's condition.



1) Since less oxygenated blood flows into the CNS; the brain responds by increasing the sympathetic reflex in an attempt to increase the heart rate to supply the brain with more blood.
Thus heart failure pt would have low pulsation at examination due to ↓ cardiac output but has tachycardia.

2) The kidneys respond to the ischemia + hypoxia by increasing the production of RAAS. Angiotensin II would act as a vasoconstrictor thus increasing the systemic resistance and thus increasing the afterload.
- Aldosterone produced would also cause sodium/H_2O retention thus increasing the blood volume. This would then cause an increase in venous return with an increase in preload.

Those effects would worsen the heart's function; which would enter a vicious cycle causing the heart's function to decrease day by day.

Thus, we can give drugs to break this vicious cycle. We should start by aiming to decrease the afterload and preload, so start by giving ACE inhibitor which decrease preload (↓ Aldosterone), and decrease angiotensin II (↓ afterload).

- We can also give diuretics along with the ACEIs to decrease the blood volume and thus decrease the preload on the heart.
- Vasodilators can be given too to decrease systemic resistance thus ↓ afterload.

- +ve inotropic agents like digitalis can be given to ↑ the heart's contractility to ↑ Cardiac output. But beware!!!

- NEVER start with +ve inotropic agents. You must first reduce the preload and the afterload and only then give a drug that increases the heart's contractility.

PLEASE, do NOT start therapy with Digitalis.

- β-blockers can be given too to dampen down the reflex sympathetic tone from the brain.

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Cardiac glycosides

- Let's start our discussion with discussing cardiac glycosides. (remember it's never given as initial therapy before decreasing the preload and the afterload).

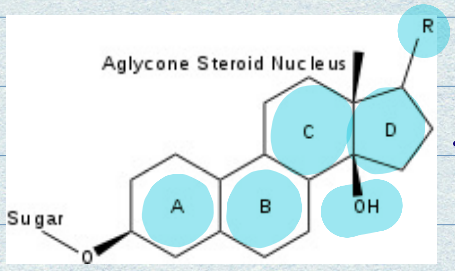
→ History: In 1775, a lady called "Mother Hutton" used to treat heart failure pts with some herbs. Those herbs were then identified as part of the Digitalis plants. Thus digitalis is the general plant name; a specific example on which is called fox-glove from which cardiac glycosides were then isolated.

Cardiac glycosides were classified into 3 examples,

- Digoxin
- Digoxitin
- Ouabain

} those 3 only differed in the type of sugar they have.

These 3 drugs differ only in this sugar moiety which is responsible for differences in pharmacokinetic properties (t½, metabolism,...)



All 3 had the same steroid + lactone structure. Those structures are responsible for the MoA of the cardiac glycosides. So all those 3 drugs have the same MoA

Now, since all those 3 drugs had the same MoA thus the same efficacy and side-effects; and Digoxin had the best pharmacokinetic properties; then we only use Digoxin nowadays; it's the only available cardiac glycoside actually.

→ When Digoxin is given to the pt; it gets concentrated x15 times in the cardiac myocytes than in the plasma.

→ As for Digoxin's MOA, it has both molecular effects as well as effects on the heart muscle organ as a whole.

At the lvl of the cardiac myocyte:

→ On the molecular aspect, Digoxin blocks the Na^+/K^+ ATPase. This inactivates the Na^+/K^+ pump. Subsequently, Na^+ would accumulate inside the cell and K^+ ions would accumulate outside the cell. The increased intracellular Na^+ concentration would subsequently result in an increase in intracellular Ca^{++} ions by several ways.

1) Na^+ ions induce the release of Ca^{++} ions from the Sarcoplasmic reticulum into the cytosol

2) Na^+ ions help in the release of Ca^{++} ions from the Submembranous Ca^{++} ion stores into the cytosol.

3) Na^+ ions would prevent the Na^+/Ca^{++} exchanger from pumping $3\,Na^+$ into the cell and $1\,Ca^{++}$ ion outside the cell. This results in accumulation of Ca^{++} ions inside the cell.

4) Na^+ ions help open certain Ca^{++} ion channels in the cell membrane.

→ Thus, all in all, Digoxin results in :

a) Increased intracellular Ca^{++} levels → this ↑ contractility and CO.

b) Increased intracellular Na^+ ions lvls → this causes ↑ cell depolarization

c) Decreased intracellular K^+ ions lvls → ↓ cell stability. → arrhythmias.

As you can see, the Ca^{++} and Na^{+} ions are tightly connected to one another on the molecular lvl; thus we can never ↑ intracellular Ca^{++} ion lvls unless we ↑ the intracellular Na^{+} ion lvls.

What this implies is the following; I'd benefit from the increased cardiac contractility mediated by the increase in intracellular Ca^{+} ions; but we will also definitely get the inseperable negative effects of arrhythmias due to ↑ Na^{+} lvls intracellularly, with ↓ [K] intracellular.

Now; let's consider the effects of Digoxin on the tissue level; the bigger picture.

1) Digoxin induces vagal stimulation (both directly and indirectly). This results in decreased heart rate; which also opposes the increased sympathetic stimulation that is done by the brain (when the brain received less cardiac output and responded with an increased sympathetic stimulation).
2) Also, since the contractility of the heart increased due Digoxin administration; the cardiac output would've become better thus the brain receives its fair share of blood and won't cause an increased reflex sympathetic stimulation.

- On the lvl of the kidney, after Digoxin results in better cardiac output due to better heart contractility; this means that more blood flows into the kidneys. This means the kidneys won't produce renin as much thus the RAAS system won't be as active (p.s: remember that the kidney used to ↑ the RAAS and subsequently cause the heart to enter the "vicious" cycle as discussed earlier).
Thus less angiotensin II means less vasoconstriction thus less afterload. Less aldosterone means less Na^+/ H_2O retention thus less preload!
Also, since the kidneys now receive proper amounts of blood; (renal blood flow increases); thus there would be more diuresis; further helping the pt reduce his blood volume.
"Some books even say that Digoxin is the best (((diuretic))) to be used in heart-failure pts!"

- ofcourse, as previously stated; the preload and afterlod must first be corrected before giving Digoxin.

- All the other body tissues that suffered previously from ischemia and hypoxia would be much better perfused now.

So, again. Let's discuss the effect of Digoxin on the heart based on:
- contractility
- Heart rate
- Conduction of impulses
- Rhythmicity

① Contractility increases as Digoxin increases the intracellular Ca^{++} ion lvls. So the strength of each contraction; each pump increases (كمية الدم التي تضخ في الضربة الواحدة تزيد)

② Heart rate: Digoxin causes bradychardia. How does that happen?

a) Digoxin causes vagal stimulation.

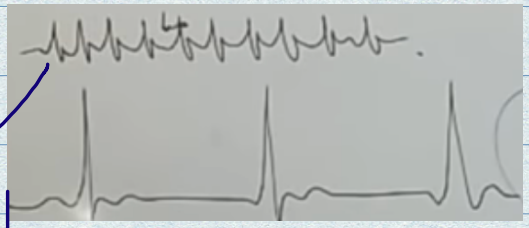
b) Digoxin increases the blood flow to the brain thus there would be less sympathetic stimulation as a reflex mechanism sent from the brain to the heart.

c) Digoxin blocks AV conduction, thus the speed at which impulses reach the ventricles decreases.

d) Since the heart pumps blood better now, this means less stagnant blood will be remaining in the right atrium. So, the

bainbridge reflex (sympathetic atrial reflex) would be less due to less accumulation of blood in the right atrium. Thus; this sympathetic reflex decreases, bradychardia occurs.

Heart failure with tachycardia (short R-R intervals). Also, the peak R-wave is reduced due to weaker contractility in a heart failure pt.



↳ After Digoxin administration:
1) R-R interval is longer → bradychardia
2) The peak of the R-wave is increased thus stronger contractility.

③ Conduction : The resultant vagal stimulation increases the interatrial conduction but decreases the AV conduction.

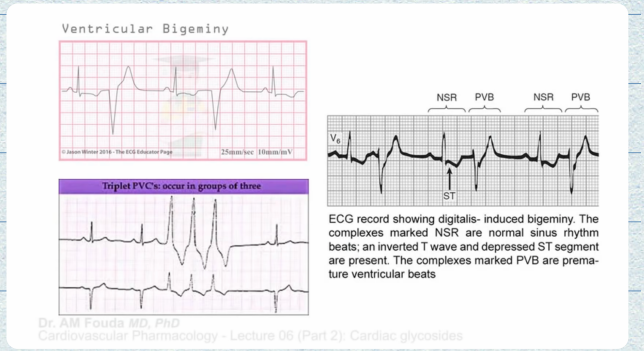
④ Rhythmicity / Excitability / Automacity

- Digoxin would definitely result in arrhythmia developing in the patient. How?

a) The increase in intracellular Na^+ lvls and decrease in intracellular K^+ lvls would definitely result in disruption in the electrical environment of the cardiac myocyte.

b) We also previously said that Digoxin increases the interatrial conduction and reduces the AV conduction (لو حاد الحكي ببسويلك لخبطة بال rhythm كمان)

c) Also, due to these molecular changes in terms of Na^+ and K^+ ions; ectopic foci would appear at the lvl of the ventricles. And those ectopic foci would act as as sources of electrical potential along with the S.A node!! This is called "bigeminy" if one ventricular ectopic focus is formed. 2 ventricular ectopic foci → Trigeminy and so on.



→ What are the ECG changes seen in a patient who takes Digoxin?

1) P-R interval prolongation (due to decreased AV conduction, thus it takes longer for the wave to go from the atria to the ventricles.

2) The R wave becomes longer; this is because ventricular contraction occurs more strongly. So this is seen on the ECG as better ventricular depolarization seen as a higher R-wave.

3) T-wave inversion; due to the intracellular changes of Na^+, K^+ (if they're flipped so the repolarization wave is flipped too).

4) ST depression: this is due to increased myocardial strain as the heart's contractility increases.

5) QT interval gets shorter: this is because each systole is better than the previous one so the time for each contraction (not the heart rate) gets less. This is seen as "narrower" R peak which would result in a shorter QR interval.

6) Any type of arrhythmia can also develop due to the ventricular ectopic foci as stated previously; (Bi/tri/quadra,... geminy).

7) Bradychardia must be seen in the ECG of a patient on Digoxin therapy.

→ How does Digoxin affect the blood pressure? It causes **normalization** of the blood pressure value.

Therapeutic uses of Digoxin

→ If the patient only has congestive heart failure, then you should know by now that Digoxin is <u>not</u> used as the first drug. We need to decrease the preload and the afterload first using ACE inhibitors or diuretics. Then we wait for a few days; most patients would get treated by the ACE inhibitors or diuretics alone without the need for Digoxin all together! However, if the pt is still not treated, Digoxin can be given as the 4th drug.

However, in cases of congestive heart failure with supraventricular arrhythmia like (atrial flutter/atrial fibrillation) then Digoxin becomes **MANDATORY.**

why?

Atrial flutter/fibrillation → the rate of impulses in the atria is extremely rapid. However, this on its own is not a problem, what we fear is this high rate of impulses

getting transmitted via the AV node → AV bundle → into the ventricles; which would then cause Ventricular tachycardia.

So we need a drug that reduces the AV conduction thus preventing those (extra) impulses from flowing from the atria to the ventricles.

At the same time; this patient has congestive heart failure! So, we need a drug that can both increase the contractility of the heart and decrease AV conduction.

The only drug with both those properties is **Digoxin**

- Contraindications of Digoxin use:

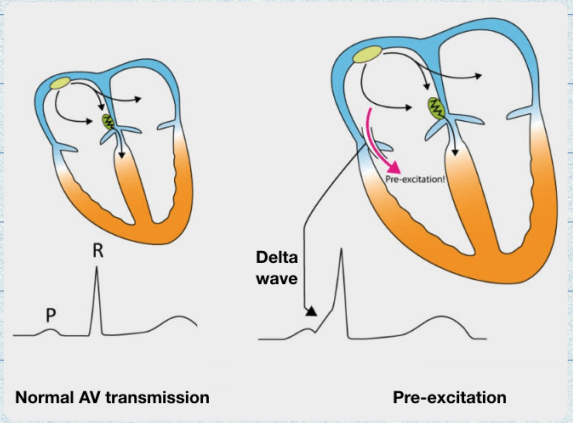
- Absolute contraindications (يحرم عليك استعمال الDigoxin)
- Relative contraindications (استعمال الDigoxin مكروه)

- Absolute contraindications:-

a) Heart block. ⟶ Whatever the degree of heart block (whether 1st/2nd/3rd degree); giving digoxin will result in further AV blockade. Remember that Digoxin reduces AV conduction! (Digoxin has -ve dromotropic effect).

b) WPW syndrome. In this syndrome, the child is congenitally born with an accessory conduction bundle between the atria and the ventricles called the bundle of Kent; which is present either on the right or the left side. And this abnormal conduction pathway would definitely lead to arrhythmias. Remember that any drug that decreases the normal AV conduction in the heart; would subsequently

result in more conduction occuring in this abnormal conduction pathway. So, any drug with -ve dromotropic effects is contraindicated in WPW syndrome. Examples include Digoxin, Verapamil, and Beta-blockers.



Abnormal bundle of kent in Wolf-parkinson white patients.

c) Hypertrophic obstructive cardiomyopathy (HOCM).

Those pts are congenitally born with an AV valve which is thicker than normal. This causes stenosis of the aortic valve, reducing blood outflow into the aorta. Thus; any drug that increases the contractility of the heart is contraindicated in HOMC patient. Examples of such contraindicated drugs includes Dopamine, Adrenaline and Digoxin. (All drugs with a +ve inotropic effect are contraindicated in HOMC pts).

d) Ventricular arrhythmias. Remember that Digoxin induces ventricular ectopic foci formation. Thus definitely, any pt with ventricular arrhythmia should never take Digoxin!

Relative contraindications

① Any cause of bradychardia; this is because Digoxin also causes further bradychardia!

Examples on things associated with bradychardia:

- Pt on Beta blockers, Verapamil therapy
- Hypersensitive carotid sinus; the baroreceptors in the carotid sinus are abnormally sensitive to pressure
- Myxedem (Hypothyroidism pt)
- Sick sinus syndrome (SSS); the SA node is not producing impulses at a fast enough rate.

(eg: المريض بنزل ضغطه و بغمى عليه
(أول ما يلبس الكرافة أو يحلق دقنه)

② Pt who has systemic HTN or pulmonary HTN.

↓ You can never give digoxin before you correct the preload + afterload as previously stated. otherwise, contracting the heart against an already high resistance would cause even more heart failure! So correct the HTN (systemic / pulmonary) first before giving Digoxin

③ Renal failure ↓

Digoxin is excreted in the kidneys. Thus if the pt has renal failure; then Digoxin will get accumulated in the body causing Digitalis toxicity.

or Hepatic failure ↓

Digitoxin is excreted in the liver; so should not be used in cases of hepatic failure.

④ A patient who got cardiac arrest in the I.C.U; the doctor will use (D.C cardioversion) to correct for this cardiac arrest. After the heart "wakes up" from this arrest, it's likely to get arrhythmic. Thus giving Digoxin would further worsen the arrhythmia.

⑤ Myocardial infarction. → Digoxin would increase the contractility of the heart thus more oxygen would be needed by the infarcted heart; further worsening the MI !

⑥ Myocarditis in children with acute rheumatic fever.

Drug - drug interactions with Digoxin

Drug	How does the drug interact with Digoxin ?
-Antacids - Kaolin - Cholestyramine	These drugs inhibit Digoxin absorption.
Atropine	Atropine decreases GI motility, this gives more time for the absorption of the complex, large structure of Digoxin. So more Digoxin absorption occurs.
Metoclopramide	Metoclopramide increases the GI motility, this gives less time for Digoxin absorption. Thus less Digoxin absorption occurs.
Tetracycline	Tetracycline kills part of the normal bacterial flora which plays a role in Digoxin metabolism. So this results in less Digoxin break down Digoxin lvls ↑ in serum

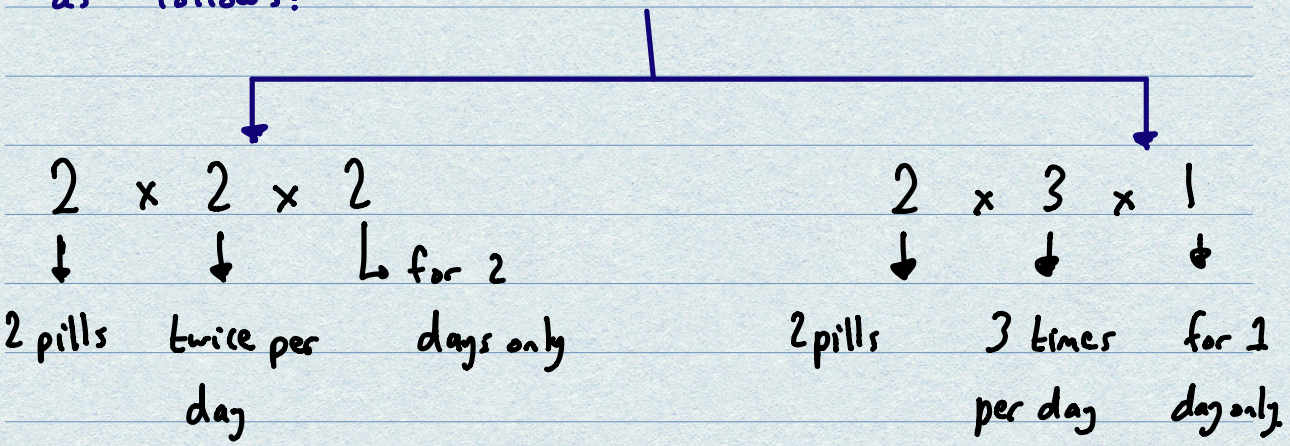
Drug	How does the drug interact with Digoxin?
Quindine	Quindine decreases renal clearance of Digoxin, which increases serum lvls of Digoxin.
Loop diuretics Thiazide diuretics	We usually need to give diuretics along with Digoxin for congestive heart failure pts. However, those drugs would cause Hypokalemia which would increase the risk of Digitalis toxicity. Solution? keep monitoring the lvls of K^+ in the pt's serum. Also advise the pt to eat foods rich with K^+ ions like bananas.

Digoxin dosage + administration.

Note that Digoxin is one of the cumulative drugs; meaning that their clearance is not that easy and they can accumulate in the body.
-Thus, to prevent that, the dose of Digoxin given should be low. That is, "one pill is given per day with 2 days off per week."

-Each pill contains as low as 0.25 mg of Digoxin.

- However, if the pt presents with **severe** heart failure, and you want your patient's condition to improve as fast as possible; then loading doses of Digoxin can be used as follows:



then after this loading dose, the pt can continue on the normal maintenance dose of 1 pill per day with 2 days off per weak.

→ How to know if your pt is improving and responding well to Digoxin therapy?

After 1 week, if the pt improved, he'd tell you that his edema / tachypnea / dyspepsea /... are gone.

Or, you can check the serum lvls of Digoxin, if they're between 1-2 ng/ml of blood, then excellent.

The pt is ← <1 not benefiting from the therapy

>2, → Digitalis toxicity.

Digitalis toxicity

→ **Predisposing factors include the following:**

a) - Old age → renal function decreases with old age, thus renal clearance of Digoxin decreases thus [Digoxin] increases serum.
- Renal failure; same reason as above.

b) Hypokalemia: Digoxin is more likely to bind to Na^+/K^+ ATPase when lvls of K^+ in the serum are low. Thus more Digoxin effect → More toxicity.

c) Hypercalcemia, → More Ca^{++} ions would enter through the Ca^{++} channels that opened due to Digoxin; thus causing more effects. etc...

- Manifestations of digitalis toxicity

- Cardiac effects
- Extracardiac effects

- Bradychardia
- AV heart block
- Arrhythmias like Bigeminy / trigeminy, ...
- Atrial tachycardia

since Digoxin increases interatrial conduction.

→ the most common cardiac manifestation occuring alongside any degree of AV block.

Explained below.

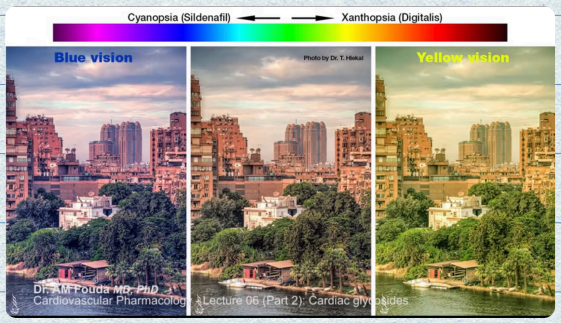
→ Extra-cardiac side effects of Digitalis toxicity:

1) The first symptom would be anorexia ; which can also be accompanied by diarrhea.

2) Pt feels fatigued; on the other hand if Digoxin was working well, the pt would otherwise feel less tired upon exercise and exertion.

3) Visual disturbances that include "Xanthopsia" where the pt sees everything (more) yellow in colour.

↓ this might be due to ↑ intracellular Na^+, Ca^{++} ions in the retina and visual centers of the brain.



Xanthopsia associated with Digitalis toxicity.

4) CNS effects: Due to the inflow of Ca^{++}, Na^+ ions into the neural cells, epilepsy-like symptoms would be seen; including convulsions, coma, and seizure.

5) Since Digoxin has a steroid-like structure; it'd compete with Testosterone rendering it inactive thus causing gynecomastia in male pts.

.....

→ Treatment of digitalis toxicity

a) Immediately stop Digoxin administration.

b) Since hypokalemia favors digitalis toxicity progression; then make sure to stabalize the lvls of K^+ by giving

K+ supplements; either oral / IV.

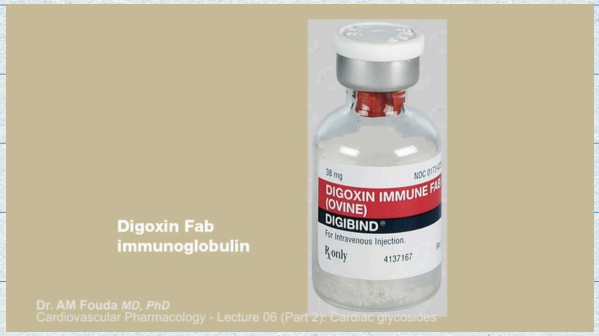
c) Give antiarrhythmic medications to correct for the arrhythmia that results from digitalis toxicity.

i) Lidocaine (100mg, IV) ⟶ for ventricular arrhythmia

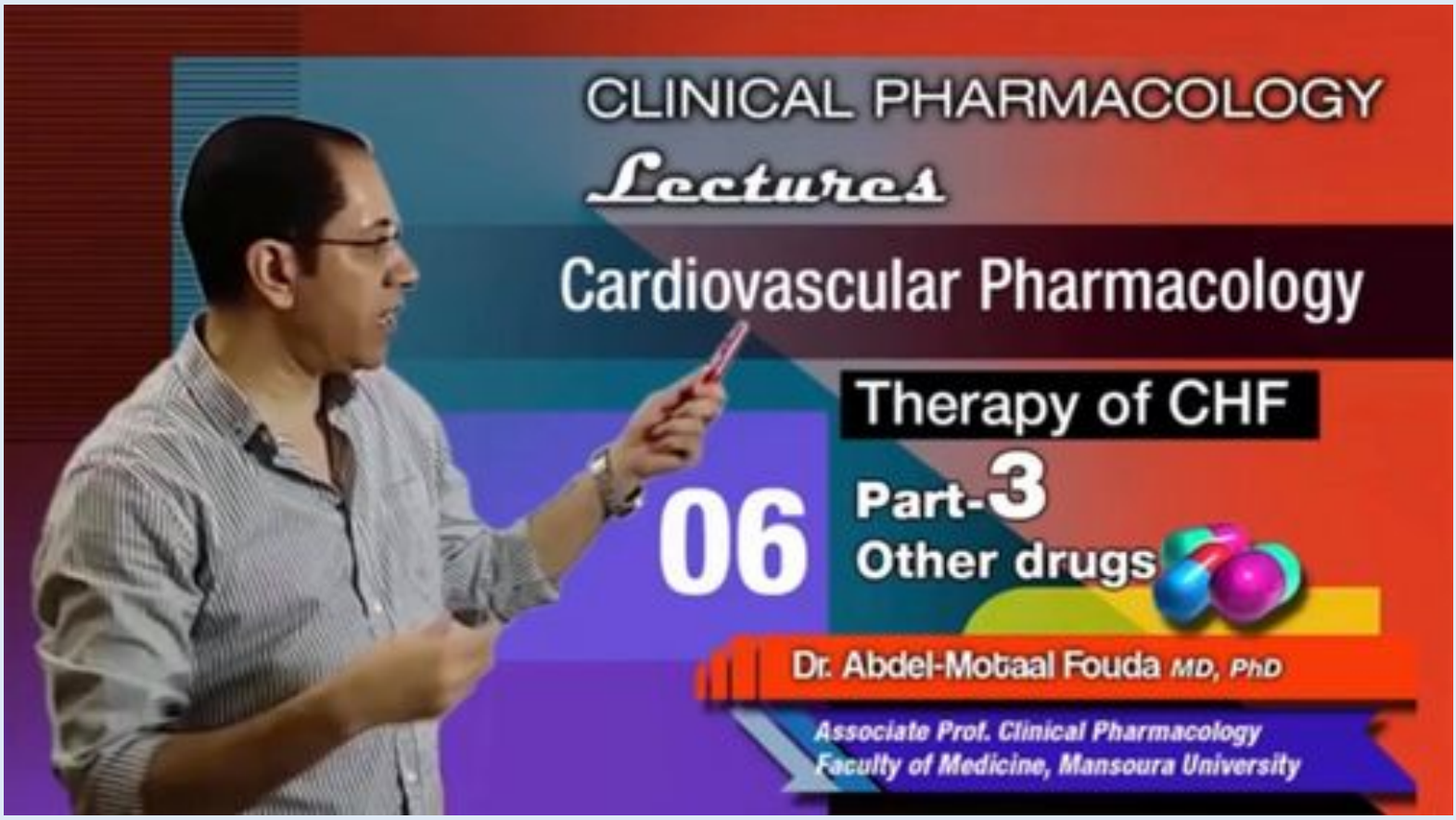
ii) Phenytoin ⟶ Arrhythmia associated with heart block

iii) Atropine ⟶ for txt of severe bradycharolia

d) The most specific txt of all for digitalis toxicity is giving the fractionated antibodies which bind to Digoxin ; this fab is called Digibind. Digibind / Digoxin complex will then get excreted in the kidneys.



Digibind, the most specific txt for Digitalis toxicity.



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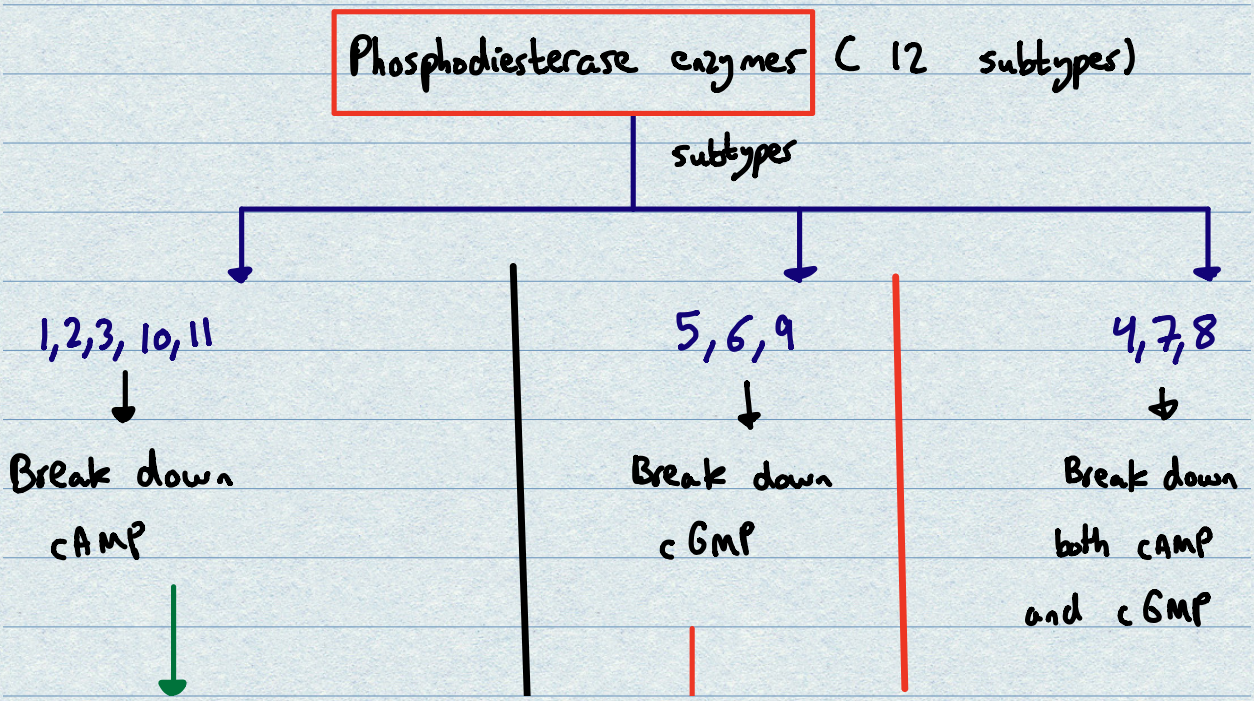
→ Other drugs used in the treatment of Congestive heart failure

- Concerning +ve inotropic agents, scientists wished to discover alternatives to Digoxin given that Digoxin has a very small therapeutic index. (which means that a small deviation from the normal therapeutic dose of 1-2 ng/mL would cause digitalis toxicity).

* Thus, scientists started considering a group of drugs which are **phosphodiesterase inhibitors.**



Inhibitors of PDE 1/2/3/10/11 would cause cAMP lvls to rise. cAMP has different effects depending on the target cell.

So if we give drugs that inhibit PDE 5/6/9, cGMP lvls would rise. cGMP increases the lvl of NO, which causes relaxation of smooth muscle cells at any smooth muscle cell.

-Example: Sildenafil specifically inhibits PDE-5 which is specifically present in the corpus cavernosum, this causes relaxation there with more blood flow treating erectile dysfunction.

cAMP: 1) In cardiac myocytes: cAMP increases lvls of PKA which ↑ intracellular $[Ca^{2+}]$ which increase cardiac contractility

2) In smooth muscle cells: of the GI tract, vascular smooth muscle cells, bronchi → Relaxation

3) Platelets: Decreases platelet aggregation.

.... cAMP has a lot of different functions in other body cells; but those are the most important.

∴ **PDE-3** is the most common subtype present within the cardiac myocytes. Thus giving an inhibitor to PDE-3 would result in an increase in cAMP in cardiac myocytes increasing its contractility.

∴ Also, the effects of this drug can also be extended by causing relaxation of vascular smooth muscle cells (vasodilation), and ↓ Platelet aggregation ! (PDE-3 is <u>not</u> only found in cardiac myocytes; yet it's the most common subtype of cardiac myocytes).

So theoretically, PDE-3 inhibitors seem to be very promising drugs. However; they're shown to be quite problematic ...

→ PDE-3 inhibitors unfortunately increase AV conduction! And this is indeed a <u>taboo</u> in pts with heart failure, who already have tachycardia because of the sympathetic reflex initiated by the brain as discussed earlier. → So the pt would get a **serious ventricular arrhythmia** due to this ↑ AV conduction → some patients would even get **sudden cardiac death**.

Also, PDEIs can not be given for more than 48 hours; as this would lead to the serious ventricular arrhythmia!

↳ ∴ So we can only use PDEIs in an acute setting (in a pt with acute heart failure) as IV infusion; ONLY if the pt can't take/ doesn't respond to Digoxin.

So concerning +ve inotropic agents, Digoxin is the best one.
PDEIs are only used if : 1) Pt can't tolerate Digoxin.
2) Pt has acute heart failure (< 48 hrs IV infusion).

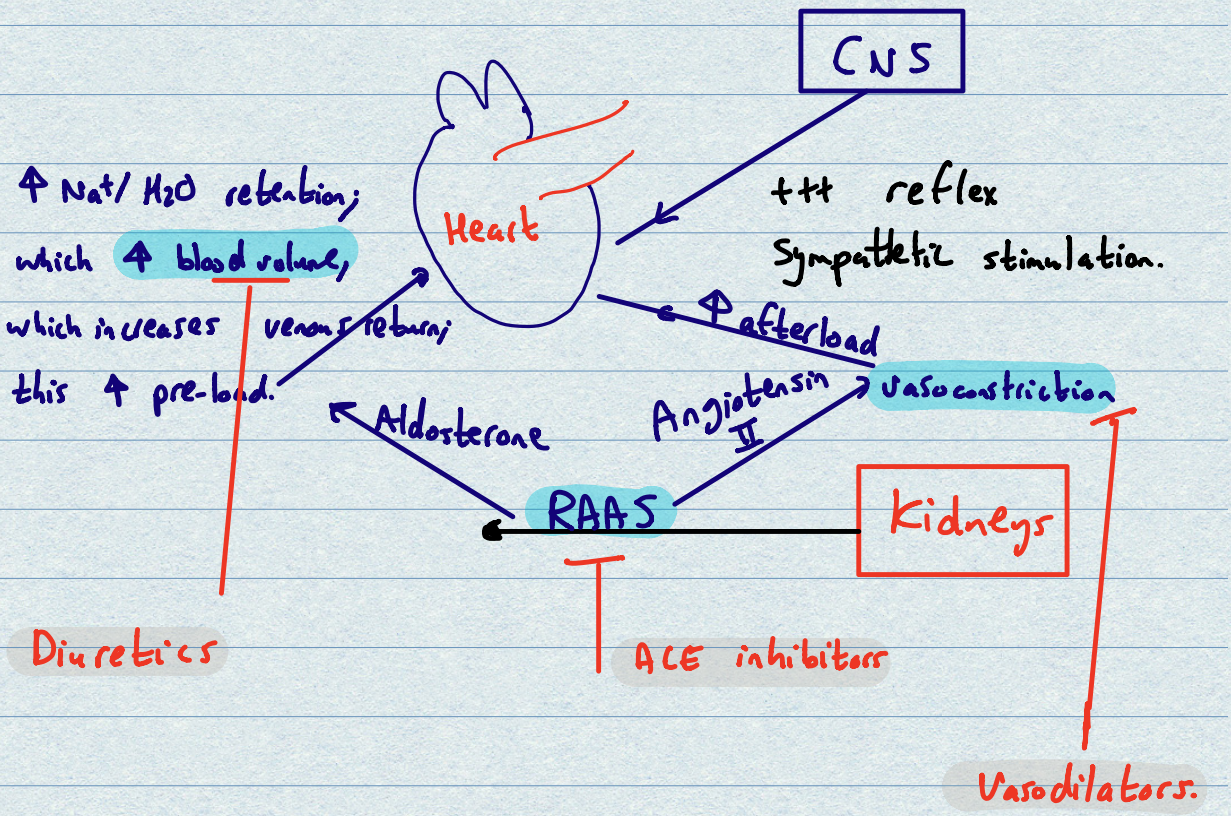
→ PDEIs are also hepatotoxic and also cause thrombocytopenia ↳ ↑ risk of bleeding.

-Examples on such drugs: a) Amrinone (Highly toxic; so it's no longer used and an isomer of it is developed; this isomer is called b) Inamrinone

c) Milrinone (أخف شوي بس لسا صحيحة)

- We previously discussed +ve inotropic drugs in details, and we made sure that they should never be given before reducing both the preload and the afterload; (we don't want the heart to increase its contraction against high resistance; which could further worsen the heart's condition !)

- Let's revise the vicious cycle that's getting the heart's condition to progressively worsen and deteriorate; and locate certain areas within this cycle which can be blocked to potentially stop it.



a) We can start by giving the patient ACE inhibitors (C-pril)

① Those drugs would decrease the lvl of Angiotensin II, which is itself a potent vasoconstrictor, so decreasing its lvl would decrease total peripheral resistance, thus decreasing the afterload.

② They'd also decrease aldosterone lvls, which eventually means that less sodium + H_2O retention occurs → blood volume is decreased so preload is decreased.

③ ACE inhibitors also reduce the rate of degeneration of tissues, by reducing tissue remodelling. This is important as ACE inhibitors would prevent the deterioration of myocardial function over time, so the heart failure won't progress into more dangerous levels.

(يعني بتحافظ على مستوى الضرر الحالي بدون ما يتفاقم لحالة أكثر سوءًا).

b) We can also give the patient diuretics; which have numerous benefits:

i) Diuretics would get rid from the excessive amount of water accumulated in the body. This is of immense significance because as we stated previously, CHF patients suffer from edema all over their body (neck+legs+,...) as well as Pulmonary edema! This pulmonary edema was the cause behind the orthopnia and Paroxysmal nocturnal dyspnea that this patient suffered from. The pt also used to suffer from "cough with expectoration" (المريض كان دائما يكح مع بلغم ، و ما كان يعرف ينام على وسادة و اطلية (orthopnia) و كان يصحى بالليل من ألم شديد في منطقة الصدر التي سميناها Paroxysmal nocturnal dyspnea)

So being able to reduce pulmonary congestion and improving the oxygenation; as well as getting rid of the edema in the legs and elsewhere is a big advantage to diuretic use.

ii) Diuretics also lower the blood volume, thus decreasing the venous return, which results in decreased preload.

iii) Also, one specially useful diuretic is Spironolactone which is a K^+ sparing diuretic.

a) It was shown and proven through clinical trials that giving Spironolactone to patients with advanced heart failure (class 3/4 HF) would improve the contractility and the function of the heart and reduce mortality in such patients. But as we previously know, Spironolactone is a weak diuretic. So this means that this effect of Spironolactone on the prevention of heart failure progression is not due to its diuretic ability; but rather due to an unknown mechanism of action.

b) Spironolactone also antagonizes Aldosterone, this gives it further credit as decreasing aldosterone lvls results in less water/Na^+ retention with a subsequent decrease in preload.

These 2 benefits of Spironolactone resulted in a change in heart-failure guidelines in 2012 as follows:

" Please prescribe Spironolactone along with the other drugs to heart failure patients."

However, there are some considerations related to the use of diuretics :

1) If blood volume is decreased a lot, then cardiac output might also decrease. However, we only give diuretics at doses which help get rid of the extra fluid accumulating in the lungs, legs, etc... and not to a level that reaches hypovolemia, so this risk of ↓ CO can be prevented by giving the appropriate dose of the diuretic.

2) - Also, some diuretics like thiazides + loop diuretics can cause hypokalemia; others like Spironolactone (K^+ sparing) can cause Hyperkalemia

- Also, some drugs like Spironolactone can cause acidosis, and others like loop-diuretics can cause alkalosis. And this acid-base imbalance is very dangerous in heart failure pts, as it can predispose them to arrhythmias!

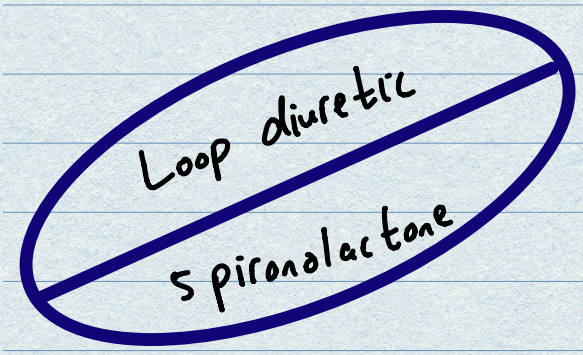
→ So, how to solve this problem?

You can simply give a tablet that contains 50 % loop diuretic and 50 % spironolactone !

↓ 50 % loop diuretic
- Hypokalemia
- Alkalosis

↓ 50 % spironolactone
- Hyperkalemia
- Acidosis

So those 2 drugs would antagonize one another, thus there would be no change in $[K^+]$; which could be problematic if the pt takes Digoxin (since Digitalis toxicity increases with hypokalemia), and no change in the acid/base balance.



ع called Lasilactone, given as 50 mg dose twice per day. The pt should stop taking the drug 2 days a week to prevent hypovolemia with subsequent decrease in cardiac output.

→ Lasilactone : ☺ الراحي الرسمي لـ Heart failure بكل الدول

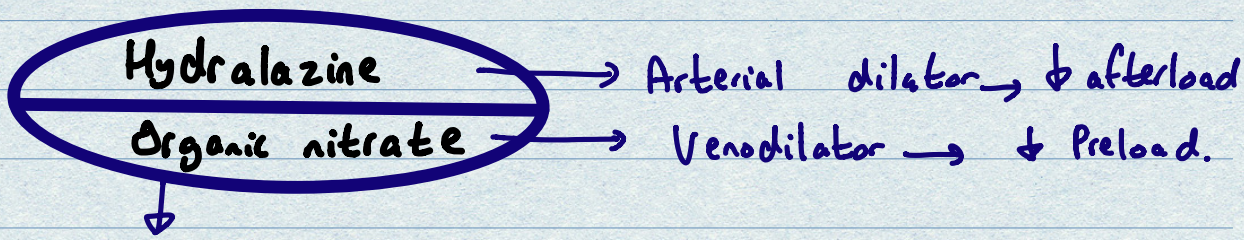
c) Is giving ACE inhibitors and diuretics enough?

No, we need drugs that **specifically** dilate the vessels. Vasodilators should be used alongside the ACE inhibitors and Diuretics.

Vasodilators that can be used include:

- Arterial dilators
  - These reduce the systemic vascular resistance thus decrease the **afterload** on the heart.
    - **Hydralazine**
- Venodilators
  - These cause venodilation thus decreased venous pressure thus less venous return thus decreases the **preload** on the heart
    - **Organic nitrates**

Thus, the latest guidelines advise the use of a fixed-ratio combination of an (arterial dilator) and a (venodilator) to reduce both afterload and preload at the same time.



This combination decreases the mortality in heart failure, so this combination should be given to such pts even if they take ACE inhibitors.

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d) Finally, we'd like to discuss Beta-blockers use in heart failure.

In fact, there are 2 opposing views concerning β-blocker use in heart failure pts:

One view is against the use of Beta-blockers in HF pts

Another view is with the use of β-blockers in heart failure pts.

→ Both views have reasons to support their claims as follows

View	Reasons supporting their claims
With	1) Beta blockers reduce the sympathetic overflow from the brain to the heart causing less Tachycardia. This means that the strain on the heart is now decreased as well! 2) Beta-blockers block the renin β_1-receptors in the Juxtaglomerular cells of the kidneys of the pt. This is very beneficial and ameliorates the effect of ACE inhibitors in this sense.
Against	- Beta-blockers are -ve inotropic agents thus can cause cardiac decompensation (تدهور في عمل عضلة القلب)

So, whom should we listen to? Should we use beta-blockers or not in heart failure patients?

→ Based on clinical trial results; (evidence-based medicine), Beta-blockers were shown to decrease mortality in heart failure patients.

(عملوا clinical trials و تبين معهم إنه نسبة الوفيات في المرضى اللي استخدموا Beta-blockers كانت أقل من المرضى اللي لم يستعملوا ال Beta-blockers. فبالدليل القاطع، (evidence-based medicine) ينصح باستخدام ال Beta-blockers لكن بشروط معينة.)

- Beta-blockers can be used to treat heart failure if the following criteria was followed:

i). Beta-blockers should be given in small doses to prevent cardiac decompensation.

ii) Beta-blockers should never be given to pts with acute heart failure

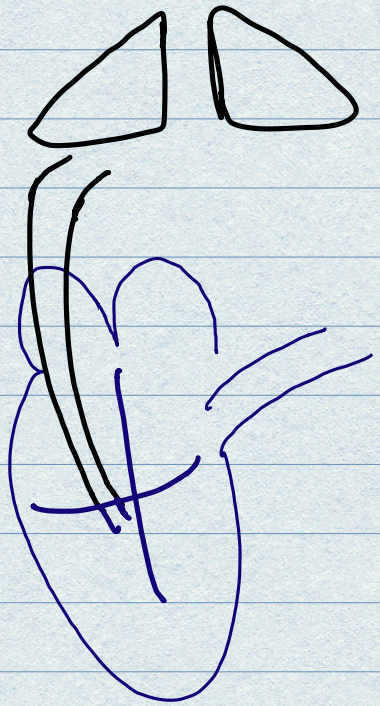
iii) Also, based on clinical trial data, the best 3 Beta-blockers to be used in heart failure are stated as follows (in descending order).

1) Bisoprolol: The best
2) Metoprolol
3) Carvedilol

Those are the 3 beta-blockers بدع الموصى based on (evidence-based medicine). (They're the ones that decreased mortality rate more than other beta-blockers; they're superior to other beta-blockers.

→ Now we'll discuss one important and common complication of (left-sided heart failure) is

Acute cardiogenic pulmonary edema

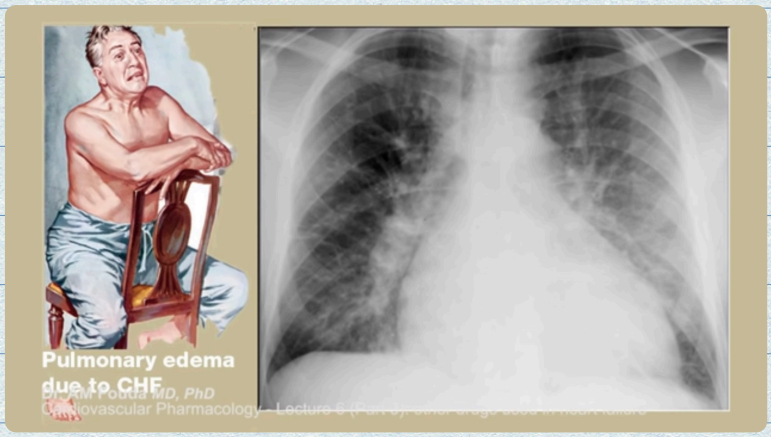


Under normal conditions, the volume of blood pumped by the right ventricle into the lungs should be equal to that which enters the left ventricle from the lungs. However, if the patient has left-sided HF, or the efficacy of the left ventricle is less than that of the right ventricle; this means the normal/healthy right ventricle would pump the SV to the lungs, but this amount of blood can't be pumped efficiently by the left ventricle, so some blood would accumulate in the diseased left

ventricle with time. (The RV is normal and healthy thus pumps blood normally to the lungs, but the LV won't be able to deal with all this blood volume so pumps part of it and the remainder accumulates within the left ventricle)

↳ With time, this blood would flow in a retrograde fashion from the left ventricle into the lungs. This causes blood to accumulate in the lungs ; so the intrapulmonary hydrostatic pressure (aka pulmonary-wedge pressure) would rise. And this causes the pulmonary capillaries to leak water into the alveoli decreasing the oxygenation of the blood.

↳ This is specially problematic during sleep. As we said earlier, if the pt sleeps in a supine position or on his left side, this would put more strain on the left ventricles causing more fluid accumulation in the lungs. Thus if the patient shifts from the 45° position to the supine position during sleep, this causes further fluid accumulation in the lungs. The patient would wake up from severe chest pain and dyspnea, with expectoration related to cough. This is all related to this acute cardiogenic pulmonary edema. (+cyanosis)



Plain X-ray showing diffuse haziness on the lung fields due to pulmonary edema associated with Left-sided heart failure.

- This is indeed a medical emergency. How to deal with it ?

1. Hospitalization is mandatory. The patient should enter the hospital in a sitting / semi-sitting position on a chair and **NEVER** on a trolley. Why? If the patient lies down on the trolley in the supine position, this would cause further accumulation of fluids within the patient's lungs worsening his condition as previously discussed.

2 Oxygen under pressure is mandatory

↳ to allow O_2 to enter the alveoli which are already filled with fluids!

Giving this oxygen would help decrease the hypoxia that affects all the body tissues. Also, hypoxia can induce vasoconstriction in the pulmonary vessels further increasing the intrapulmonary hydrostatic pressure which further worsens his condition. So reducing this hypoxia prevents the onset of hypoxia-induced vasoconstriction in the lungs thus ameliorating the patient's condition.

③ Furosemide : A loop diuretic that should be given IV in a dose ranging from 20 mg-80 mg.

Can we use another diuretic?

No. It should be a loop diuretic, furosemide in specific given IV in the maximum 80 mg dose.

- Furosemide produces its effects within 5 minutes while thiazides would need 30-60 mins to produce their effects.

→ **what's so special about Furosemide?**

i) It reduces the intrapulmonary hydrostatic pressure even before diuresis occurs!

ii) Loop diuretics are the strongest diuretics which help a lot in reducing pulmonary edema.

iii) Loop diuretics were shown to cause venodilation decreasing the preload on the heart.

iv) Furosemide produces its effects within 5 minutes while thiazides would need 30-60 mins to produce their effects.

④ Morphine : i) A strong narcotic analgesic which reduces the severe pain suffered by the patient. This is important to reduce the stress experienced by this patient which could possibly increase the sympathetic flow to the heart due to this stress deteriorating his condition.

ii) Morphine also causes venodilation → ↓ venous return → ↓ Preload → Less blood reaches the lungs. so less Pulmonary congestion.

iii) Morphine would "calm" the respiratory center, which is induced by hypoxia in this patient. The pt is exhausted with tachypnea because of the overstimulated respiratory center due to hypoxia, so Morphine can "calm" down the respiratory center reducing this tachypnea and subsequent exhaustion.

⑤ Organic nitrates: Sublingual nitroglycerine would cause vasodilation which ↓ preload with subsequent ↓ pulmonary congestion.

CNG can also cause arterial dilation → ↓ afterload).

∴ 1) The patient enters the hospital in a sitting position / semi-setting position.

2) Oxygen -under pressure- is given to the patient.

3) Furosemide (The first drug to be given.)

4) Morphine

5) Nitroglycerine.

→ Those 3 drugs are hypotensive drugs, so you should make sure that those drugs are given in appropriate doses not to cause Hypotension.

↳ Because this hypotension would induce reflex tachycardia further worsening the heart failure!

So, you must make sure to maintain systolic blood pressure not to fall below 100 mmHg (aka Hemodynamic support).

However, if unfortunately, you failed to maintain hemodynamic support and systolic blood pressure falled below 100 mm Hg. What to do in this case? Give the pt Dopamine or Dobutamine which increase the cardiac output preventing S.B.P from falling below 100 mm Hg.

What's the role of Digoxin in acute pulmonary edema?

It has no rule whatsoever, because our goal is to reduce preload and afterload not to increase

contractibility!

- Digoxin can be used in one case only.

↳ If the patient has pulmonary edema due to heart failure associated with atrial flutter or atrial fibrillation. otherwise, do not use Digoxin for acute pulmonary edema.

(No AF? Do not use Digoxin).