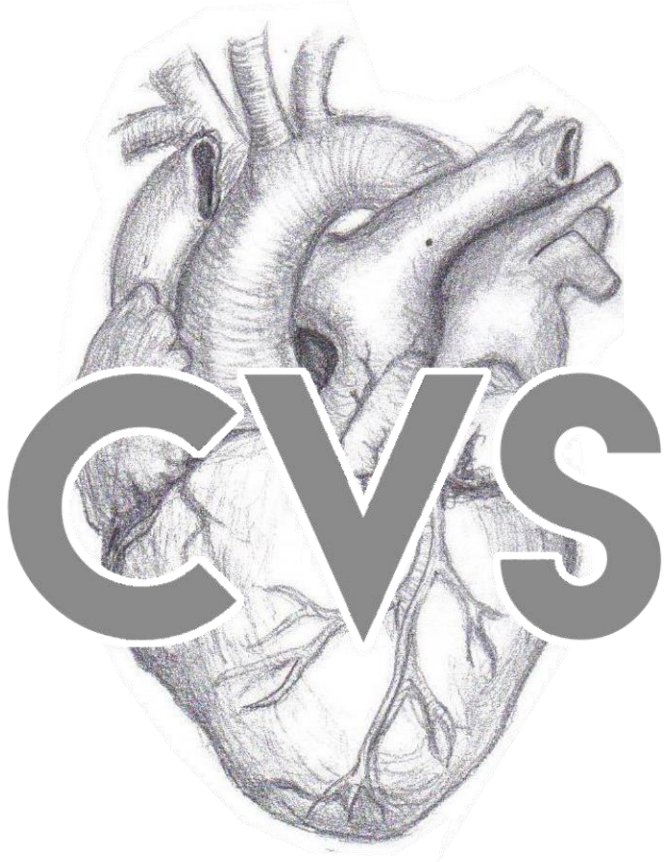

CVS

PHARMACOLOGY

✓Sheet ○Slide ○Handout

Number

7

Subject

Tx of Heart Failure #2

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Date: **14/11/2016**

Price:

CVS Pharmacology. Treatment of heart failure- 2nd lec.

If you remember; we ended the previous lecture saying that: whatever the cause of HF is (except high-output failure), *first line treatment is diuretics and vasodilators a few seconds later*

Which diuretics?
- Strong (High ceiling) diuretics like (**furosemide-** a loop diuretic) intravenously,
- **Spironolactone**. Aldosterone antagonist; because it ↓remodeling of the heart and it is K^+ sparing.

Which Vasodilators?
ACEIs or ARBs.
If contraindicated then give a combination of **hydralazine and nitrates**.

Too much of a good thing is a bad thing..
One of the compensatory mechanisms that the body uses in heart failure is sympathetic stimulation, the purpose of which is to improve cardiac functions. However, when it increases too much it causes damage to the heart and worsens the situation because of vasoconstriction, increased afterload and activation of the rennin angiotensin aldosterone system which causes water retention as well as remodeling of the heart (by the actions of both catecholamines and aldosterone). So scientists thought of using β adrenergic blockers for the treatment of heart failure. The problem of beta blockers: they exacerbate heart failure! So how are we going to use them? (1)**Never in acute HF**, but they might be started with **small doses after stabilization**, then the dose is tittered to make sure the patient is tolerating the dose. (2)Not any beta blocker can be used. But ONLY: **Metoprolol, bisprolol, carvedilol, Nebivelol**. If you selected the right dose in chronic failure you will reduce mortality and increase survival by the use of these drugs.

HOW DOES HYDRALAZINE+NITRATES DO THE WORK OF ACEI/ARBs ??! (extra)

Remember that ACEIs, ARBs block the action of angiotensinII which basically does two things:

1. Vasoconstriction; of which blocking **↓afterload.**
2. Fluid retention through aldosterone; of which blocking **↓preload**

If we compared that to the action of hydralazine and nitrates we'd find that:
-Hydralazine ↓TPR; **↓afterload**
- nitrates venodilate; **↓preload**

Conclusion*: Everything makes sense and pharmacology is fun. Enjoy it* ☺

In a Nutshell
↓remodeling of cardiac muscle and therefore improve survival: ACEI, ARBs, spironolactone, beta blockers.
Whereas +ve inotropes do not improve survival

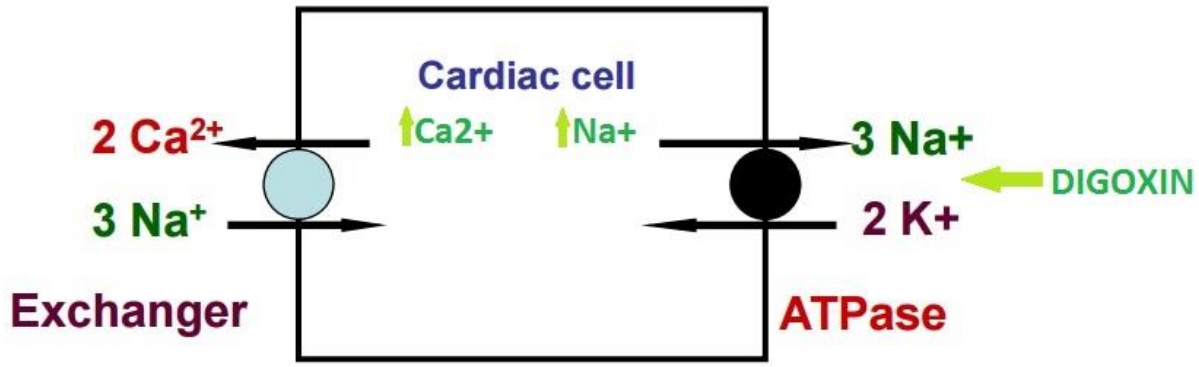
Suggested MOA:

1. Attenuation of the adverse effects of high concentrations of catecholamines (catecholamines increase the preload and afterload and cause remodeling of the heart) So you at least you stop the damage.
2. Up-regulation of β-receptors: More beta receptors= more contractility.
3. Reduction of excessive heart rate (excessive HR decreases the filling time and decreases perfusion to the myocardium- remember that the coronary arteries receive blood in the diastole mainly)
4. Reduction of remodeling through inhibition of the mitogenic activity of catecholamines.

*Must be administered very cautiously and at low doses- under observation.
Several months of therapy before improvement starts.

Positive Inotropes:
Remember that these do not improve survival but could be used in systolic dysfunction to increase contractility of the heart.

Cardiac glycosides- digitalis; **Digoxin** and digitoxin
contains a steroid nucleus, lactone ring attached to it sugars.
They stimulate contractility of the heart.
Digoxin is more commonly used.
Very Important: Not the first drug and never the only drug used in treatment of heart failure.



Na^+/K^+ ATPase is responsible for maintaining the homeostasis in the cell. It moves 3 sodium ions to the outside for every two potassium ions getting into the cell.
There is also Na^+/Ca^{2+} exchanger that will move one calcium ion in exchange of 3 sodium ions (it's written in the slides –pic above- two Ca^{+2} ions, which is wrong). Net result: the three sodium ions that got in will be out and 2 potassium ions are exchanged for one calcium ion.

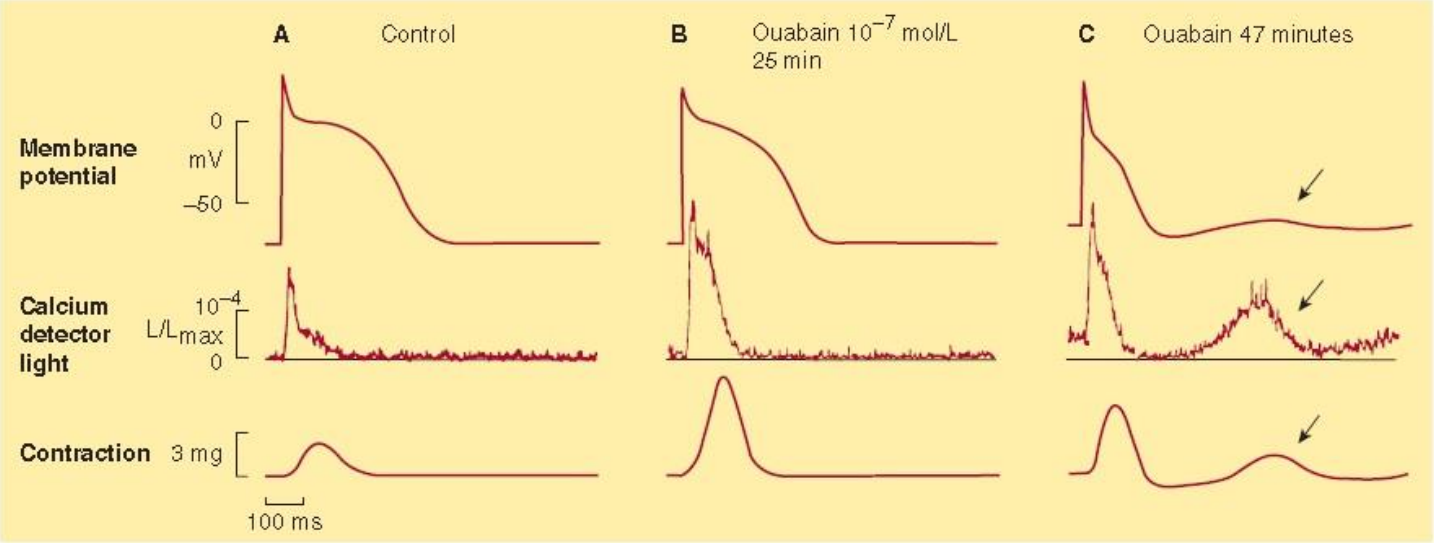
Digoxin inhibits the Na^+ -K^+ ATPase
and actually this action is not selective to the cardiac muscle but rather it will happen in every cell that has this ATPase on its surface.

>>Effects caused by inhibition of *cardiac* ATPase:
- ↑intracellular Na^+; and therefore
- ↑intracellular Ca^+ (as a result of decreased Na^+/ Ca^+ exchange) and so more calcium is available for contractile process b/w actin and myosin. →
-↑actin and myosin interaction
- ↑ contractile force (positive inotropy) as an end result for overload in intracellular calcium.

Note: Additional functions of Na+ /K+ -ATPase have been postulated, involving apoptosis, cell growth, and differentiation immunity and carbohydrate metabolism differentiation, immunity, and carbohydrate metabolism. (Not important but the Doc mentioned it for us to see how things are actually more complicated than we think.)

We also have the calcium channels (which CCB block) and we also have the SR
Increase of intracellular calcium is not only coming from outside the cell but also there is the SR which has a sarcoplasmic endoplasmic reticulum Ca 2+ -ATPase (SERCA). This calcium ATPase causes the storage of calcium in the SR for subsequent contractions.

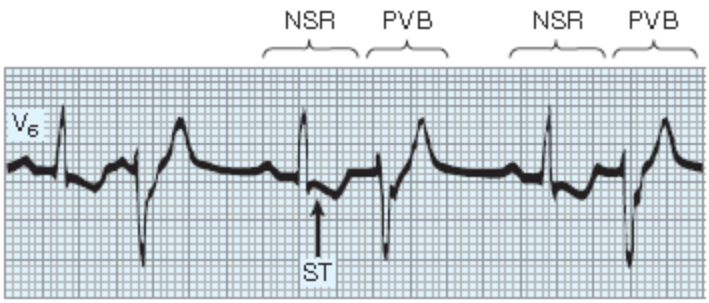
So digitalis: ↑intracellular Na^+, ↑intracellular Ca^+, ↓intracellular potassium. Would these changes affect the electrical activity of the heart? The answer is yes! The AP is largely dependent on electrolytes concentrations.



These AP are of cardiac muscles and not the Purkinje system and we can say that because of the absence of spontaneous depolarization in phase4. Be aware that this experiment was done on cardiac muscle cells and not on the heart. The calcium detector to be accurate doesn't detect calcium itself but another thing which signal is proportional to free intracellular calcium concentrations. The last tracing detects contractions. A is the normal control

When digitalis is given In therapeutic concentrations (B)
(Ouabain is a digitalis similar to digoxin and digitoxin with a shorter half-life making it suitable for labs). So when ouabain was given the calcium signal increased and the contractility increased as well. The duration of the action potential is less than the control even though there is no big deference.

If overdosed (C)
The duration of AP is so low → ↓refractory period → ↑excitability, and so you can notice a depolarization (see the arrow) If this depolarization wave reached the threshold it will fire an action potential. Now look at the second trace (Calcium detector) you will notice that the calcium signal is different than this on A or B in that it is present on phase4 and this will result in a cardiac beat. Meaning: If this was a patient and you did an ECG for him/her you will see 2 complexes one is normal and the other is ectopic. Normal, ectopic, normal, ectopic, normal, ectopic, etc. This is called **bigeminy** on the ECG.



NSR= normal sinus rhythm
PVB= premature ventricular beat (the abnormal beat)

Bigeminy might cause ventricular tachycardia and that is no good because it will decrease the filling time. It might also transform into ventricular fibrillation. This is a **digitalis induced arrhythmia**.

This depolarization wave is called **DAD (delayed after depolarization)** delayed because it happened in the diastole (in the baseline of the action potential). (There's also Early after depolarization which is mentioned in lec#9)
If this depolarization reached the threshold it will fire an action potential and it will be manifested in the ECG or even in the heart auscultation.

>> Effects caused by inhibition of *neuronal* ATPase: (Autonomic functions)
- Parasympathetic stimulation at therapeutic doses; ↓HR
and this effect is caused at different levels starting from the baroreceptors (increase their sensitivity) also in the vagal nucleus in the brain stem and increase the sensitivity of muscarinic receptors (M2) on the heart which are present on the atria and the AV node, none in the ventricle, so effect on the ventricle is indirect through the SA and AV nodes.
-sympathetic stimulation at toxic doses.

**It is claimed that digitalis can cause virtually any arrhythmia*, even atrial fibrillation which we use digoxin to treat.

Other effects:
- **GIT: most common site of toxicity** out of the heart
Nausea, vomiting, etc. That is caused by inhibition of the Na^+ -K^+ ATPase in the GIT and also by stimulation of the chemoreceptor trigger zone in the CNS
chemoreceptor trigger zone: connected to the vomiting center, and it is not separated by blood brain barrier, meaning: it responds to any chemical circulating in the blood.
- CNS effects include vagal and chemoreceptor trigger zone stimulation, disorientation (not knowing the place, the time or the person), hallucination (false perceptions), **visual disturbances** (including color perception, problematic in driving)**.**
- Gynecomastia: in men.
Remember: The structure of digoxin contains a steroid nucleus → blocks androgens. This is dangerous because the patient now is in higher risk of getting any of the diseases that happens in the breast.
- In the kidney it causes diuresis by inhibition of the Na^+ -K^+ ATPase (not enough to depend on for the treatment of HF)

Interactions:
- **K^+:** Digoxin competes with potassium for binding to the ATPase and therefore *hypokalemia will enhance digoxin binding.* Mild hyperkalemia reduces the action of digitalis
Hyperkalemia cause cardiac arrest.

-Hypercalcemia increases digitalis toxicity

-Magnesium is like calcium and opposite to potassium- generally speaking our diet is deficient in magnesium. And therefore if I was to prescribe digitalis to a patient I should measure the electrolytes before giving the drug.

<u>Differences between digoxin and digitoxin are in the Pharmacokinetics and not in the Pharmacodynamics</u>.

Half life is different

Bioavailability is different

Lipid solubility for digitoxin is high

Volume of distribution for digitoxin is less even though lipid availability is high because its plasma protein binding percentage is high. Meaning: It is lipid soluble but it is highly bound to plasma proteins and the small free percentage of the drug is what diffuses to the tissues.

	Digoxin	Digitoxin
Lipid solubility	**Medium**	**High**
Bioavailibility	**65-80%**	**> 95%**
Half-life (hours)	**36-40**	**168**
Plasma protein binding(%)	**20-40**	**>90**
% metabolized	**< 40**	**> 80**
Vd (L/Kg)	**6.3**	**0.6**

10% of the population their bacterial flora metabolizes digoxin decreasing its bioavailability and therefore if you give antibiotics→ no metabolism→ toxicity