432

Pharmacology Team

Heart failure 1

Red	Important
Purple	Extra Notes
Orange	To differentiate
Black	From the slides

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Objectives

- Describe the different classes of drugs used for treatment of acute & chronic heart failure.
- Describe the mechanism of action , therapeutic uses , side effects & drug interactions of individual drugs used for the treatment of heart failure

Heart Failure:

It is a complex, progressive disorder in which the heart is unable to pump sufficient blood to meet the needs of the body.

Causes:

- Disorders of coronary arteries.
- High blood pressure
- Cardiomyopathy.
- Abnormal heart rhythm
- Heart valve disorder.

Factors affecting heart performance

Preload	Afterload	Contractility	Heart Rate

Heart Failure = ↓ Contractility + ↑ Preload + ↑ Afterload

1- Preload: Ventricular filling pressure and streching of the myofibrils during diastole.

Determined by:

A-Blood volume: (more venous return = high preload = heart can't handle this much volume = increases the probability of Heart failure)

How to avoid this problem?

- Diuretics
- Salt restriction (to reduce salt-water retention and reduce the volume) "restriction by avoiding salty food"

B- Venous tone (Constriction and relaxation of the veins): high constriction = high preload = increased probability of heart failure.

How to avoid this problem:

- Vasodilators

2- Afterload: Pressure that develops at the left ventricle at the beginning of systole.

Determined by:

A. Peripheral vascular resistance: (high PVR = high Afterload = increased probability of Heart failure)

How to avoid this problem?

- Arteriodilatiors

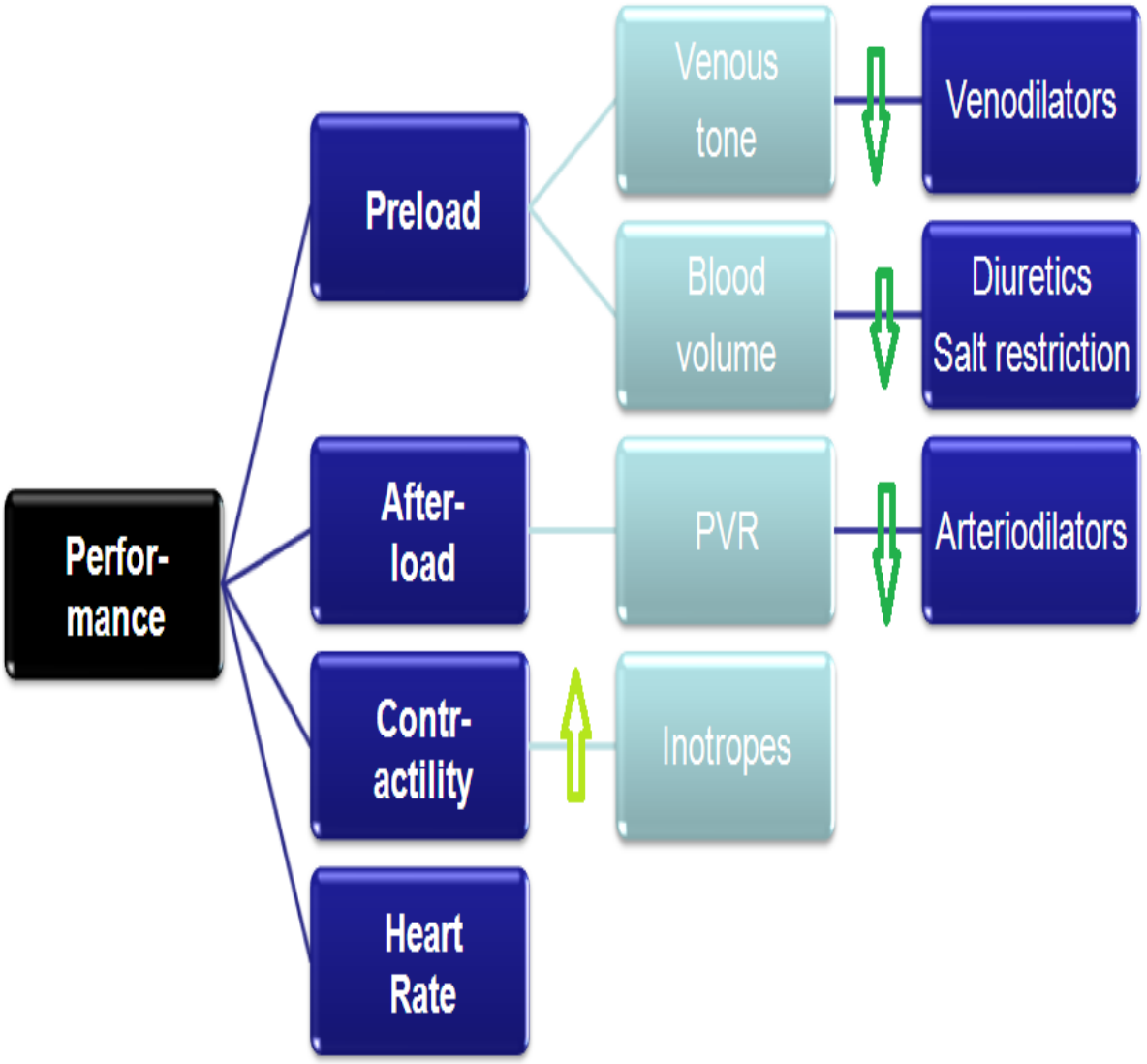
3- Contractility:

- Weaker contraction of the heart = higher chance of heart failure

- We use +ve inotropes to increase it

4- Heart rate:

⬆ Heart Rate = ⬆ Oxygen consumption ➡ may lead to ischemia ➡ Myocardial infarction ➡ Heart failure



Cardiac performance in heart failure:

When the Heart fails it leads to reduced cardiac output resulting in:

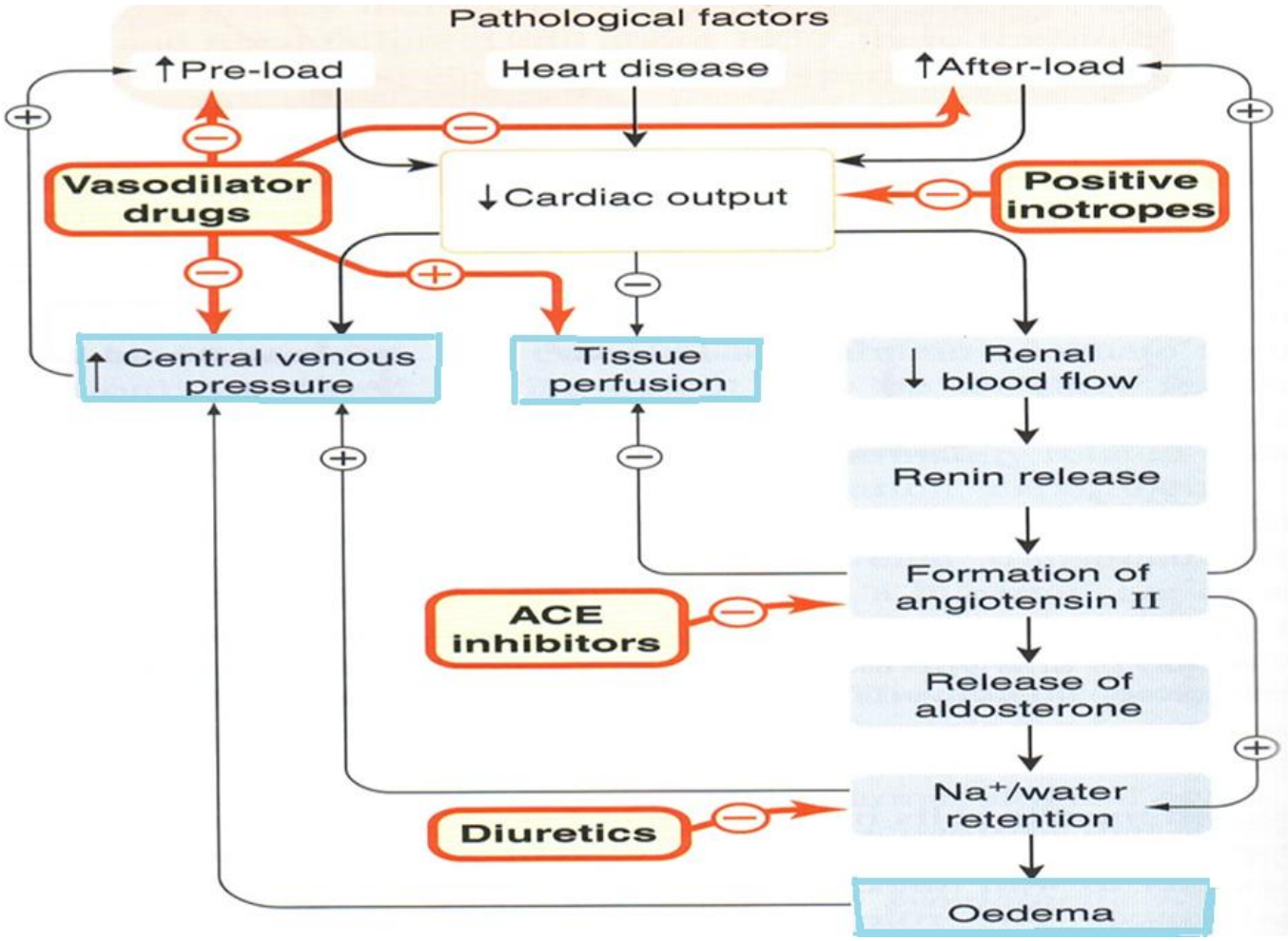
1- Activation of renin-angiotensin-Aldosterone system:

- Fall in cardiac output decreases blood flow to the kidney, and renin is released.
- Renin increases the formation of angiotensin II , which is a potent vasconstrictor.
- Vasoconstriction will lead to increasing in the velocity of the transmission of the blood to the tissues.
- Increased Aldosterone causes salt-water retention which increases preload.

2- Activation of sympathetic system:

- Baroreceptors sense a decrease in blood pressure, so it will activate the sympathetic nervous system.
- It will increase the heart rate and the contractility and the conduction velocity of the electrical impulses within the AV node.

Continuous activation of the sympathetic nervous system and the renin-angiotensin-aldosterone release, will lead to Remodeling of cardiac tissue (which is a biochemical changes in the myocardium cell by change it into connective tissue). This will interfere with its ability to efficiently function as a pump. Creating an abnormal cycle that, if left untreated, leads to death



1- ACE (Angiotensin Converting Enzyme) inhibitor:

Reduction in Angiotensin 2 by inhibiting its synthesis → Vasodilatation (due to bradykinin)→ reduced Afterload and increased blood perfusion to body.

2- Diuretics:

A. Reduces Salt-water retention → reduces the edema.
B. Reduces central venous pressure (accumulation of blood in the veins creates the central venous pressure)

3- +ve Inotropes:

Increase the contraction → Increases Cardiac Output.

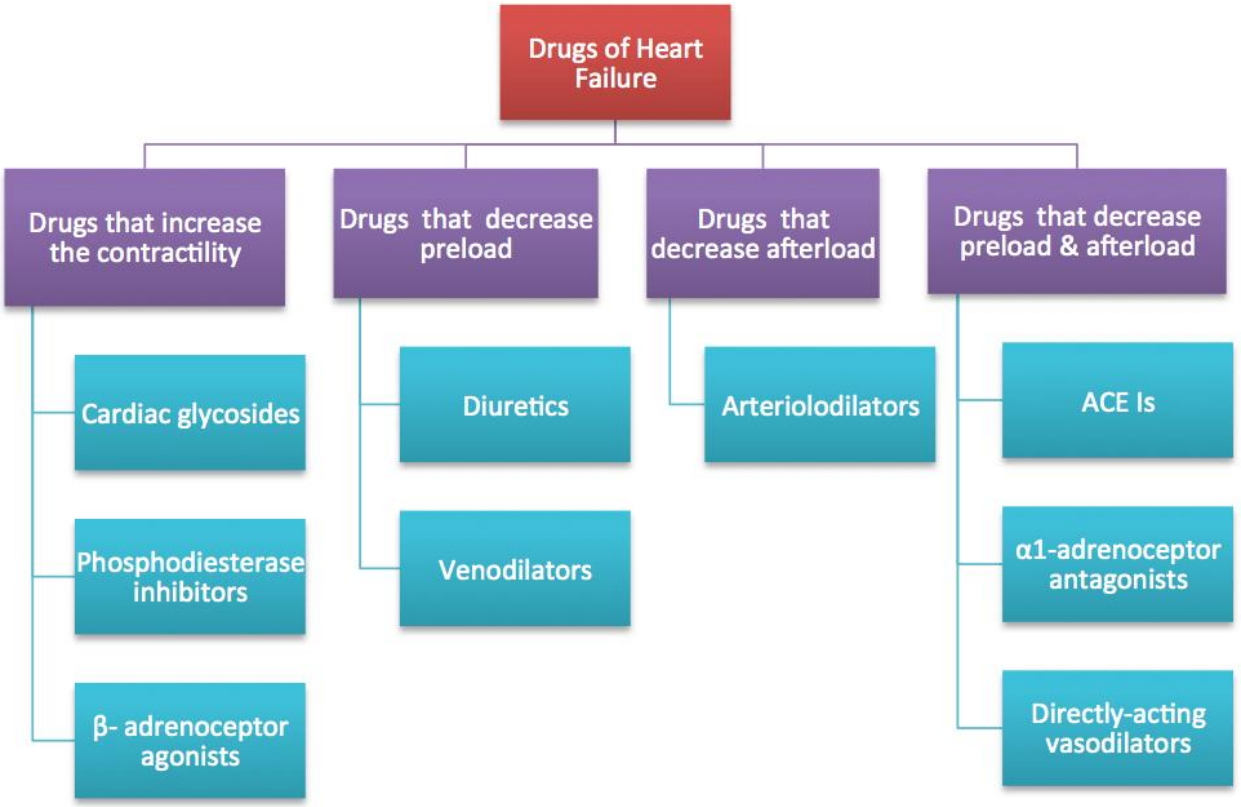
4- Vasodilators:

Reduces preload and afterload.

Symptoms of Heart Failure

Peripheral edema

Tachycardia | Rapid Fatigue | Dyspnea | Cardiomegaly



In this lecture we're going to cover Drugs that increase the contractility (cardiac glycosides and Beta Adrenoceptor agonists)

1-Cardiac Glycosides (digitalis drugs)

e.g Digoxin

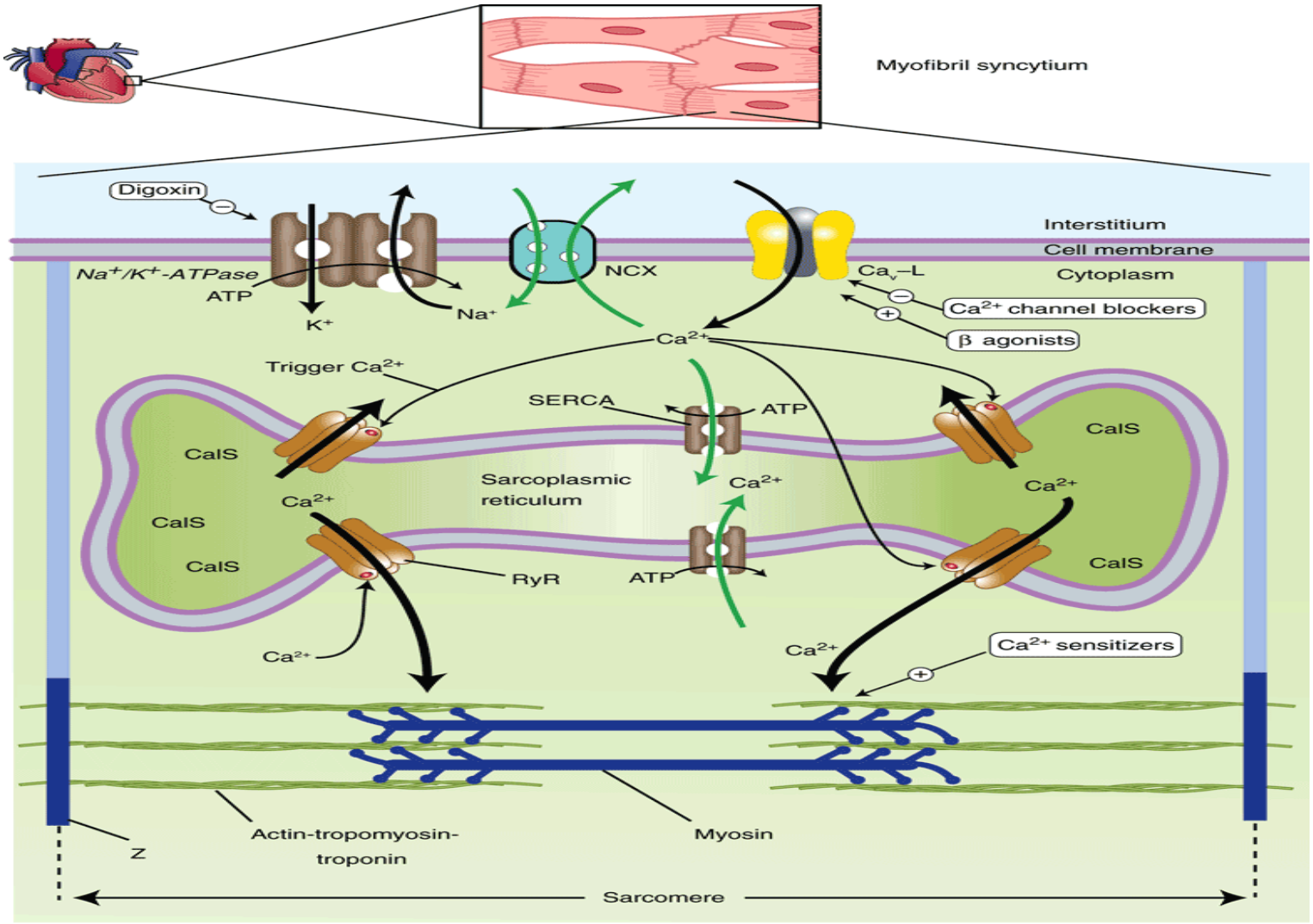
- Increase only the force of contraction+decrease the heart rate(by vagal nerve stimulation)(beta agnoists and phosphodiesterase inhibitors increase both force of contraction and the heart rate).
- Has Narrow theraputic range (last choice of treatment).
- Optained from a plant called Digitalis lanata (so it's a natural drug)
- Most commnly used for Heart failure , atrial flutter and atrial fibrillation.
- Has a long half life (40h) "Incase of emergency, we give a large dose inorder to reach the steady state faster".
- Mostly Excreted by Renal System (so incase of renal disease,Digoxin toxicity may occur).

Mechinism of Action:

- Normally, Sodium (Na) get's inside the cell inexchange of calcium (Ca) getting outside the cell.
- Digoxin inhibits Na-K pump → Accumulation of (Na) inside the cell → (Ca) excretion will be inhibited → Accumulation of (Ca) inside the cell "not enough to trigger contraction proteins"
  → Triggers more (Ca) from the sarcoplasmic reticulum
  → Stronger Contraction.

Drugs that increase the Contractility

- Stronger Contraction resulting improved circulation leads to reduced sympathetic activity & reduction in heart rate "the reduction in the heart rate has less effect than the stronger contractility, so the cardiac output will still increase"
- Reduced Sympathetic activity → Enhanced vagal tone "that's why we get reduced heart rate, and we can use this drug in arrhythmias because it inhibits AV node by the enhanced vagal tone".



Therapeutic uses:

1. Congestive Heart Failure "Because it increases the force of contraction which leads to an increased C.O, even if the heart rate is decreased due to enhanced vagal tone".
2. Atrial flutter / fibrillation and supraventricular tachycardia.

In case of atrial flutter/ fibrillation, not all impulses (i.e. 300 impulses) go to the ventricle. Because there is AV node delay, which means less impulses will go through (i.e. only 200 impulses). And Digoxin suppresses the AV node "by enhanced vagal tone" and the conduction velocity is reduced, so even less impulses will go through to the ventricle (i.e. 150 impulses).

SO WE ONLY USE IT IN ATRAL FLUTTER to Protect the ventricles from the high impulses of the atria, because the ventricles is more important so we don't care if the atria will become fibrillated we only focus in the suppressing activity at the AV node which protects the ventricles which is more involve in the Cardiac output.

Adverse effects:

1. **Digitalis-induced arrhythmias:**

   Can cause any type of arrhythmia, especially:

   - Extra systole, coupled beats "Normal Sinus rhythm followed by premature beat".
   - Ventricular tachycardia or fibrillation.
   - A.V node block, cardiac arrest.

2. **GIT** "earliest signs of toxicity":
   - (Anorexia, nausea, vomiting, diarrhea)
3. C.N.S:
   - (Headache, visual disturbances, Drowsiness).

Factors increase digitalis toxicity:

- Small Lean body mass(small mass of muscle which is reduced in old age people)
- Renal disease: "the drug won't excrete"
- Hypothyroidism: "the drug won't degrade"
- Hypokalemia
- Hypomagnesaemia
- Hypercalcemia

(Hypokalemia, Hypomagnesaemia, and Hypercalcemia): Increase the activity of the drug on Na+ / K+ ATPase enzyme, so they increase intracellular (Ca) hugely. HOW?

1-Hypokalemia: Digoxin inhibits (Na-K pump) by attaching to (K) side of the pump, so if we have high extracellular potassium (K), it will block the receptor from digoxin, therefore decreases therapeutic action and toxicity. If we have low extracellular potassium (K) "Hypokalemia" there is a high chance of toxicity "because there is less potassium to inhibit digoxin from binding".

2-Hypercalcemia: Over accumulation of (Ca) inside the cell will lead to toxicity and arrhythmia (digitalis-induced arrhythmia).

3- Hypomagnesaemia: Magnesium is a natural (Ca) blocker. So if we get low Mag, it will lead to Hypercalcemia and then toxicity.

Treatment of Adverse effects:

(One of the earliest signs of toxicity is GIT upset)

1. Stop Digoxin.
2. Give Diuretics, but it will also excrete potassium and we might get Hypokalemia (causes arrhythmia), so we give K supplement.
3. Give Atropine "to prevent cardiac arrest (AV block) caused by overstimulation of parasympathetic system, and atropine has anticholinergic effects"
4. Antiarrhythmics.
5. Fab antibodies in life-threating or severe cases.

Drug Interactions:

1. Diuretics: Cause hypokalemia (Arrhythmia).
2. Quinidine: increases plasma level of digitalis "BY: displacing digoxin from protein binding site or decreasing the renal excretion. So I have to reduce the dose of digoxin if I'm giving quinidine".

2-β-Adrenoceptor agonists

Drug	Pharmacological Actions	Therapeutic uses
Dopamine	α ,β1 and dopamine receptors	Acute L.H.F. mainly in patients with impaired renal blood flow. "Activation of dopamine receptors lead to vasodilatation in renal blood vessels, and that lead to improved renal function"
Dobutamine	Selective β1 agonist (better to use because it's more selective on β1)	Acute heart failure (Cardiogenic shock)

- Both given IV.
- Not used β-Adrenoceptor agonists in chronic HF, because:
    1. They increase heart rate (tachycardia) that may lead to angina pectoris.
    2. It has tachyphylaxis "Tolerance".

Qs:

Q1:Digitalis has profound effect on myocyte intracellular concentration of Na+,K+ and Ca2+. These effects are caused by digitalis inhibiting :

A.ca2+ Atpase of sarcoplasmic reticulum.

B.Na+/K+ Atpase of myocyte membrane.

C.Cardiac phosphodiesterase.

D.Cardiac B1 receptors.

E. Juxtaglomerular rennin release B

Q2:A 46 year old man is admitted to the emergency department. He has taken more than ninety digoxin tablets. Ingesting them about 3 hours before admission. His pulse is 50 to 60 beats per minute snd ECG shows third degree heart block.which one of the following is the most important therapy to initiate in this patient?

A. Digoxin immune fab
B. K salt
C. Lidocaine
D. Phenytoin
E. DC cardioversion. A

Third drug that increases Contractility "Phosphodiesterase inhibitor" is covered on Heart failure 2"