Doctor.021
no.

CVS
PHARMACOLOGY

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a small introduction for the lecture:-

- **Heart failure is a complex and progressive disorder in which the heart can't pump sufficient blood for the body.**
- **There are 3 main symptoms for heart failure:Dyspnea,fatigue, and fluid retention(edema)**
- **Most of the time the heart failure is systolic, it can be diastolic but that's more rare.(LVEF is below 35 or 40)**

***the doctor didn't mention this but LVEF (left ventricular ejection fraction) is the stroke volume(volume of blood pumped from LV),divided by the end diastolic volume (volume of blood in LV at the end of the diastole)*(not required)**

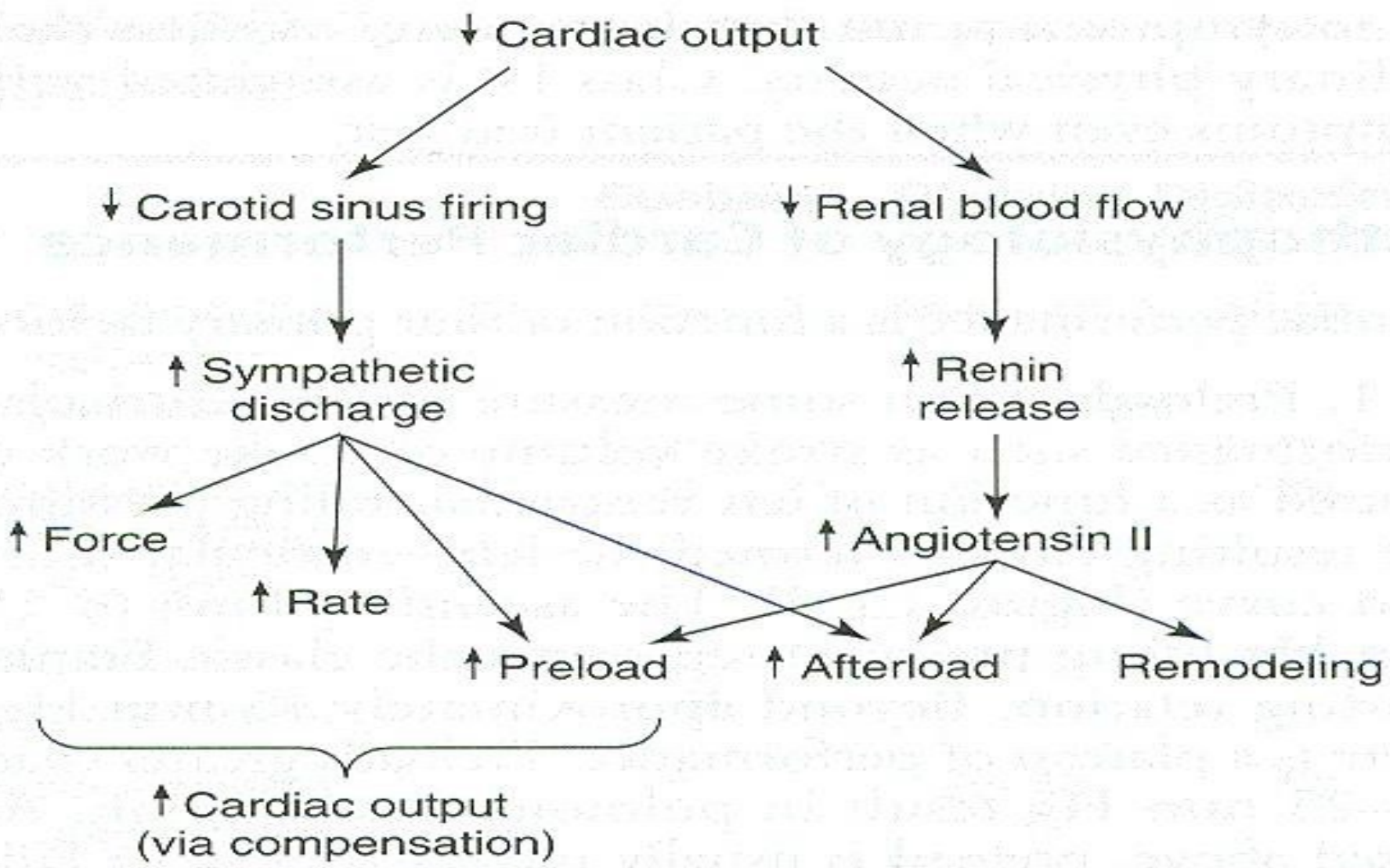


Figure 13–2. Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.

Notes on the previous slide:-

When the cardiac output decreases, the body compensates via 2 mechanisms:-

1-increased sympathetic activity:-↑ rate , ↑force, ↑preload and increased afterload.

2-increased renin release :- would result in the following:

- **↑ sodium and water retention (due to more angiotensin II and aldosterone) , vasoconstriction , which would increase both afterload and preload.**
- **And most importantly the very high levels of angiotensin II and aldosterone , cause increased remodeling (myocyte death and fibrosis) as well as hypertrophy.**

VERY important note:the more hypertrophy we have the worse the heart failure , worse ejection, less cardiac output.

Physiological responses in HF

- **Myocardial hypertrophy, here the heart increases in size and its chamber dilate, initially this will lead to a stronger contraction.**

  However, excessive elongation of fibers will result in weaker contraction, and the ejection of the blood will be diminished, producing systolic failure.

Treating HF

- **The main aims being**
- **(1) decrease the symptoms.(diuretics,loop diuretics** ,dixogin)
- **(2) slow disease progression(if managed correctly they can also improve survival, examples are ACEI, ARBS, B blockers.**
- **(3) improve survival.**

Six Classes of drugs have been shown to be effective

(1) ACE inhibitors,

(2) β-adrenergic blocking agents,

(3) (3)diuretics,

(4) inotropic agents,

(5) direct vasodilators, and

(6) aldesterone antagonist.

We already know most of the drugs in this lecture, the doctor focused on the new ones

- **Depending on the severity of HF and individual patient factors, one or more of these classes of drugs are administrated.**

ACE Inhibitors

- **Decreases vascular resistance and so blood pressure, resulting in an increase in the cardiac output.**

ACEIs,ARBs are the drugs of choice in HF in symptomatic, and asymptomatic patients.
Because of the very high levels of angiotension II and aldosterone.

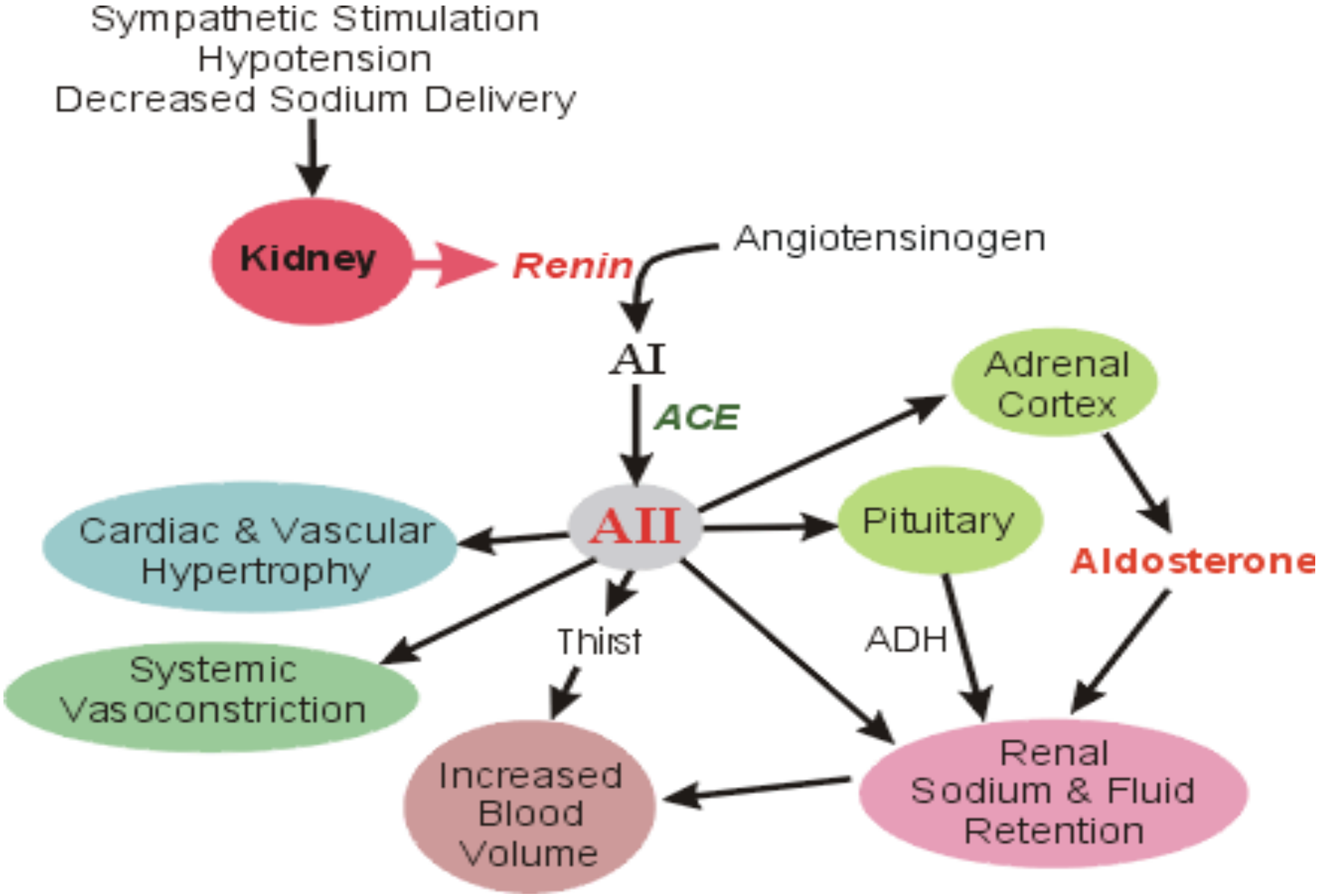
- **They also blunt (decrease) the usual angiogensin II-mediated increase in adrenaline and aldesterone seen in HF.**

- **These agents show a significant decrease in the mortality and morbidity.**

- **May be considered as a single-agent therapy in patients who have mild dyspnea on excursion, and do not have signs of volume overload.**

- **Early use of these ACE Inhibitors Indicated in patient with all stages of left ventricular failure, with or without symptoms.**

ACE Inhibitors for CCF



ACE Inhibitors

Adverse effects :

- Dry irritating persistent cough
- Hyperkalemia
- Angioedema
- Fetal toxicity

- Patients with heart failure due to left ventricular systolic dysfunction who are still symptomatic despite therapy with an angiotensin converting enzyme inhibitor and a beta blocker may benefit from the addition of candesartan, following specialist advice.

β-adrenergic blocking agents

- Although it may seem illogical to administer drugs with negative inotropic activity to patients with HF.

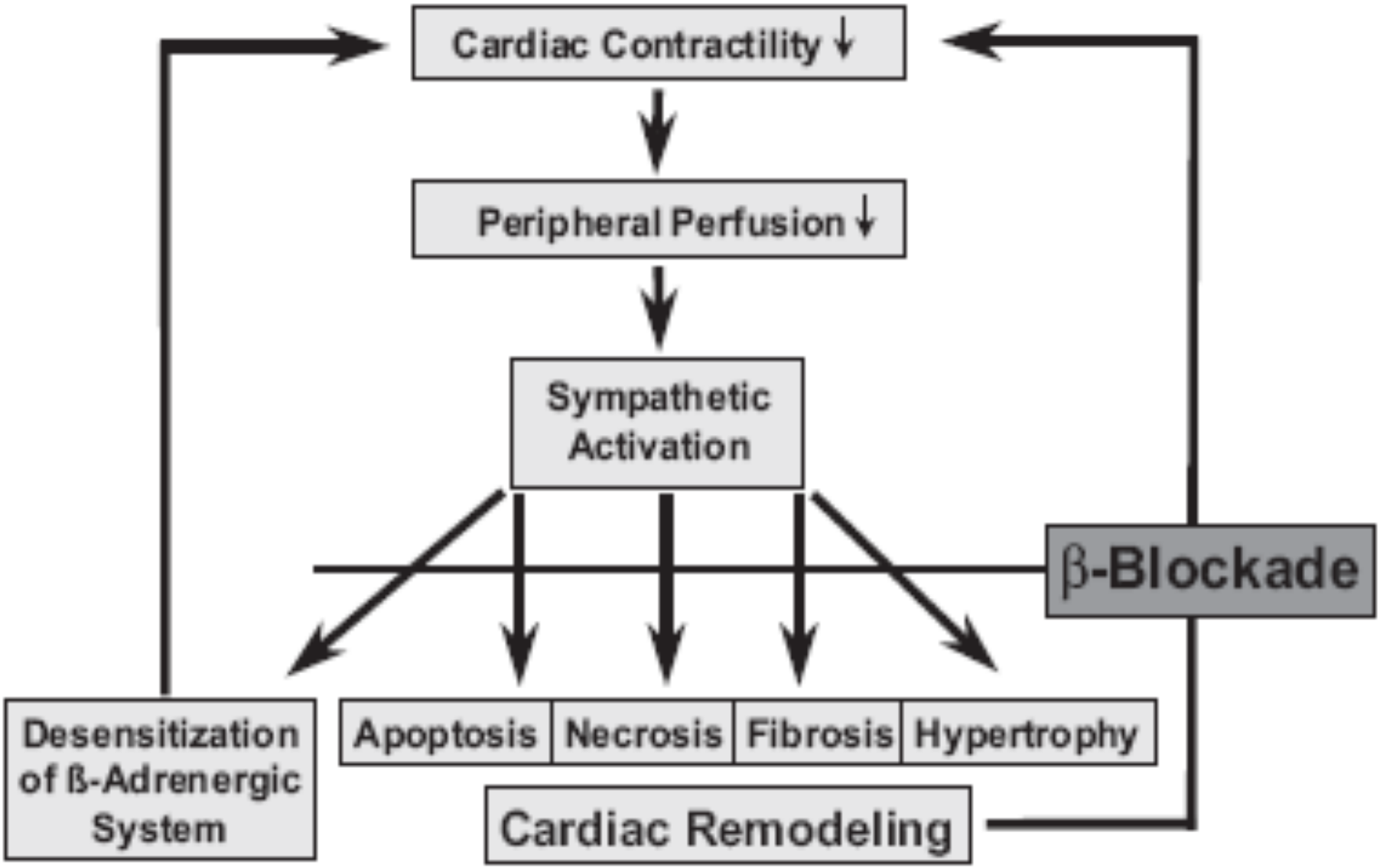
- Several clinical studies have clearly demonstrated improve systolic functioning and reverse cardiac remodeling in patients receiving β blocker

most importantly , we give low doses of b blockers because we have decreased cardiac output

- The benefit is attributed in part to their ability to prevent changes of the sympathetic system, resulting in decreasing the heart rate and inhibiting renin secretion.

- Bisoprolol (cardioseletive), carvedilol (non-selective) or nebivolol (increases NO) should be the beta blocker of first choice for the treatment of patients with chronic heart failure due to left ventricular systolic dysfunction.

Beta blockers in CCF



β-adrenergic blocking agents

- produce benefit in the medium to long term.
- In the short term they can produce decompensation with worsening of heart failure and hypotension.
- They should be initiated at low dose and only gradually increased with monitoring up to the target dose.
- contraindicated in patients with asthma, second or third degree atrioventricular heart block or symptomatic hypotension and should be used with caution in those with low initial blood pressure (ie systolic BP <90 mm Hg).

Diuretics

main use of diuretics here is the volume overload reduction, that is, to treat SYMPTOMPS.

These are useful in reducing the symptoms of volume overload by

- **decreasing the extra cellular volume**
- **decreasing the venous return**

- **Diuretic therapy should be considered for heart failure patients with dyspnoea or Oedema**

- **Loop diuretics like furosemide and bumetanide are the most effective and commonly used.**

- **Thiazides are effective in mild cases only.**

Diuretics

- The dose of diuretic should be individualised to reduce fluid retention without overtreating, which may produce dehydration or renal dysfunction. We cant give the same dose for all patients , **because we are afraid of hyponatremia and hypovolemia, since ACEIs,ARBs, also can cause hyponatremia, and diuretics are usually combined with them.**

- Loop diuretics and thiazides cause hypokalemia.**(remember that ACEIs, ARBs are combined with diuretics so the hyperkalemia effect that they induce is compensated by the hypokalemia from the diuretics)**

- Potassium sparing diuretics help in reducing the hypokalemia due to these diuretics.

Spironolactone

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

- Spironolactone is a direct antagonist of aldesterone, and so prevent sodium retention, myocardial hypertrophy, and hypokalemia. **spironolactone →aldosterone antagonist→decreased potassium secretion, decreased sodium and water reabsorption , so it causes hyperkalemia , hyponatremia**

also combined with diuretics to prevent the hyperkalemia

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

Spironolactone

- 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 (how? Spironolactone increases estrogen levels through several mechanisms)

10% of patients taking spironolactone

Patients are usually started on spironolactone, whether they are men or women , but if gynecomastia develops in men we switch eplerenone, although in Jordan we start with Eplerenone anyway.

Note: we didn't use spironolactones for diuresis for the edema, their main use is to prevent salt and water retention, prevent hypokalemia, and blunt myocardial hypertrophy and remodeling.

Stage C Therapy
(Reduced LVEF with Symptoms)

Aldosterone Antagonists

Addition of an aldosterone antagonist is recommended in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration. Creatinine should be less than or equal to 2.5 mg/dL in men or less than or equal to 2.0 mg/dL in women and potassium should be less than 5.0 mEq/L. Under circumstances where monitoring for hyperkalemia or renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits of aldosterone antagonists.

Routine combined use of an ACEI, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF.
(remember from previous lectures , they're rarely ever combined together)

Inotropic drugs (Digitalis)

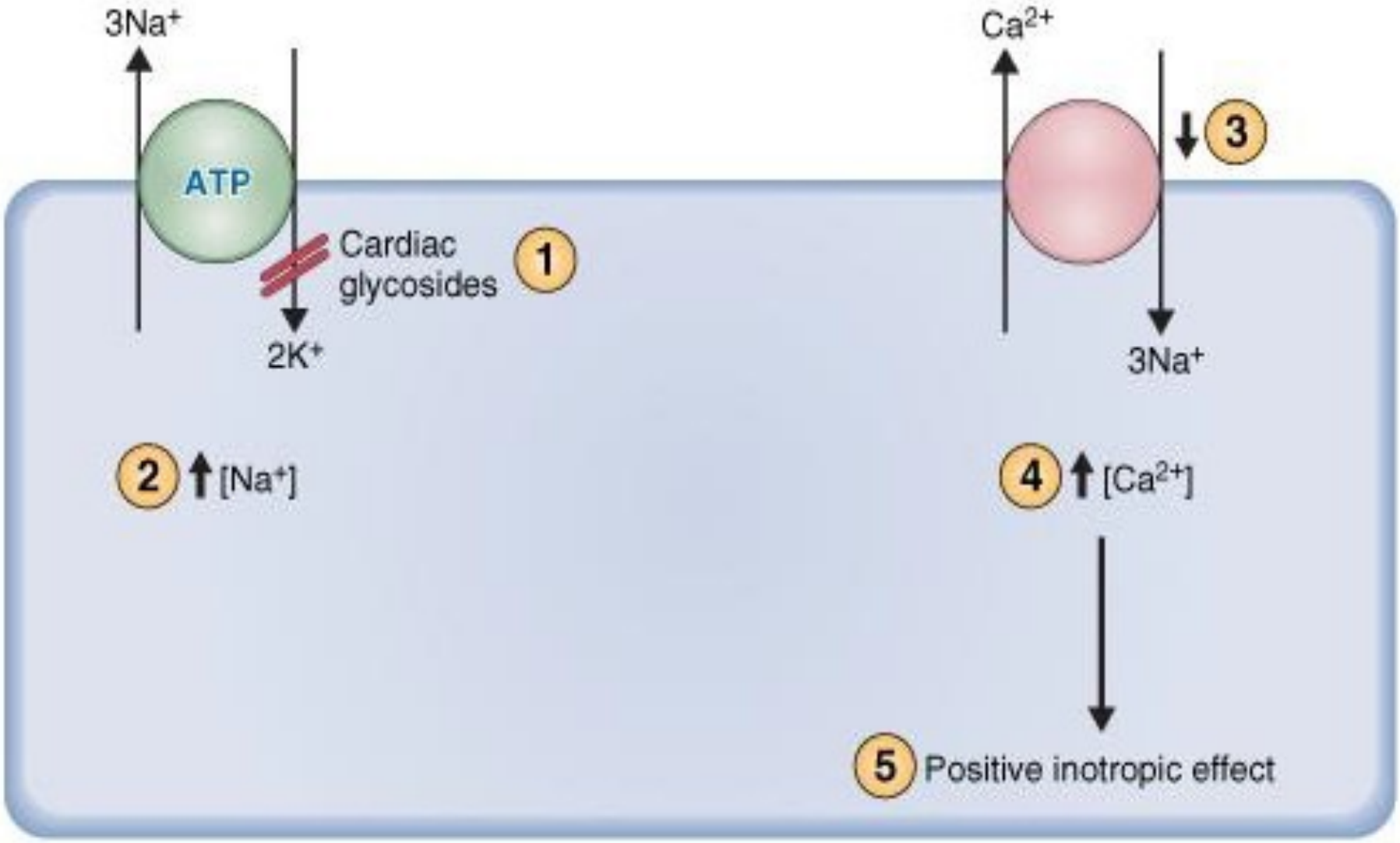
- **Increase the contractibility of heart muscles, and therefore are widely used in treatments of HF, causing the cardiac output to more closely resemble that of the normal heart. (The most widely used is digoxin).**

↑inotropic,↓chronotropic

- **Influence the sodium and calcium ions flows in cardiac muscle, thereby increasing contraction of the atrial and ventricular myocardium (positive inotropic action).**

- **The digitalis glycoside show only a small difference between a therapeutically effective dose and doses that are toxic or fetal. So these agents have a low therapeutic index or window.** very low dose , 0.25-0.5 mg daily , could reach 1 mg

POSITIVE INOTROPIC EFFECT OF CARDIAC GLYCOSIDES



Notes on the previous slide:

The mechanism of action of digoxin:-

By inhibiting the Na+/K+- (ATPase) enzyme(competitive with potassium on the enzyme), digoxin reduces the ability of the myocyte to actively pump Na+ from the cell .This decreases the Na+ concentration gradient and, consequently, the ability of the Na+/ Ca2+-exchanger to move calcium out of the cell. Further, the higher cellular Na+ is exchanged for extracellular Ca2+ by the Na+/Ca2+-exchanger (it can work both ways but depending on the gradient of the two different cations), increasing intracellular Ca2+, thereby increasing cardiac contractility.(↑inotropic).

How does it decrease the rate of pumping?(↓chronotropic)

the drug also increases the vagus activity, and increases the acytelcholine action on the m2 receptors on the heart , thus resulting in the negative chronotropic activity.

Digoxin

Another drug of the digitalis family is called digitoxin, but its not frequently used in Jordan

- **Digoxin is indicated with severe left-ventricular systolic failure after initiation of ACE inhibitors, diuretics, and β Blocker.**
- **Patient with mild to moderate HF will usually respond to ACE inhibitors and diuretics, and do not need digoxin.**
- **No good oral inotropic agents exist other than digoxin.**
- **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.**

Digoxin

- **Adverse effects:**

  digoxin have a low margin of safety (narrow therapeutic index) and intoxication from excess of both drug is common.

  intoxication is frequently precipitated by depletion of serum K^+ due to diuretic therapy. (lower potassium levels means there is decreased competition for the digoxin on the ATPase, which increases its potency, thus increasing the chances of intoxication)

  It also may happen because of the accumulation over a long period of time. It is lipid soluble , and with time it might be released from the adipose tissue while dosing , and the level of digoxin might increase.

  as the signs of systemic intoxication appear, the therapy must be discontinued.

Digoxin

Theres an antidote for digoxin its called DigiFAB, its an antibody fragment that binds digoxin and facilitates it's clearance. and digibind

these signs includes:

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

Digoxin interaction:

Quinidine, varapamil, and amiodarone can cause digoxin intoxication, both by replacing digoxin from tissue protein binding sites, and by competing with digoxin for renal secretion.

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

the microbiota are responsible for some part of the metabolism of digoxin, giving antibiotics could thereby increase digoxin concentration.

Mainly in acute HF

β-adrenergic agonist and Amrinone

- Dobutamine is a B1 adrenergic agonist that has positive inotropic effect and is the most used inotropc agent after digoxin.

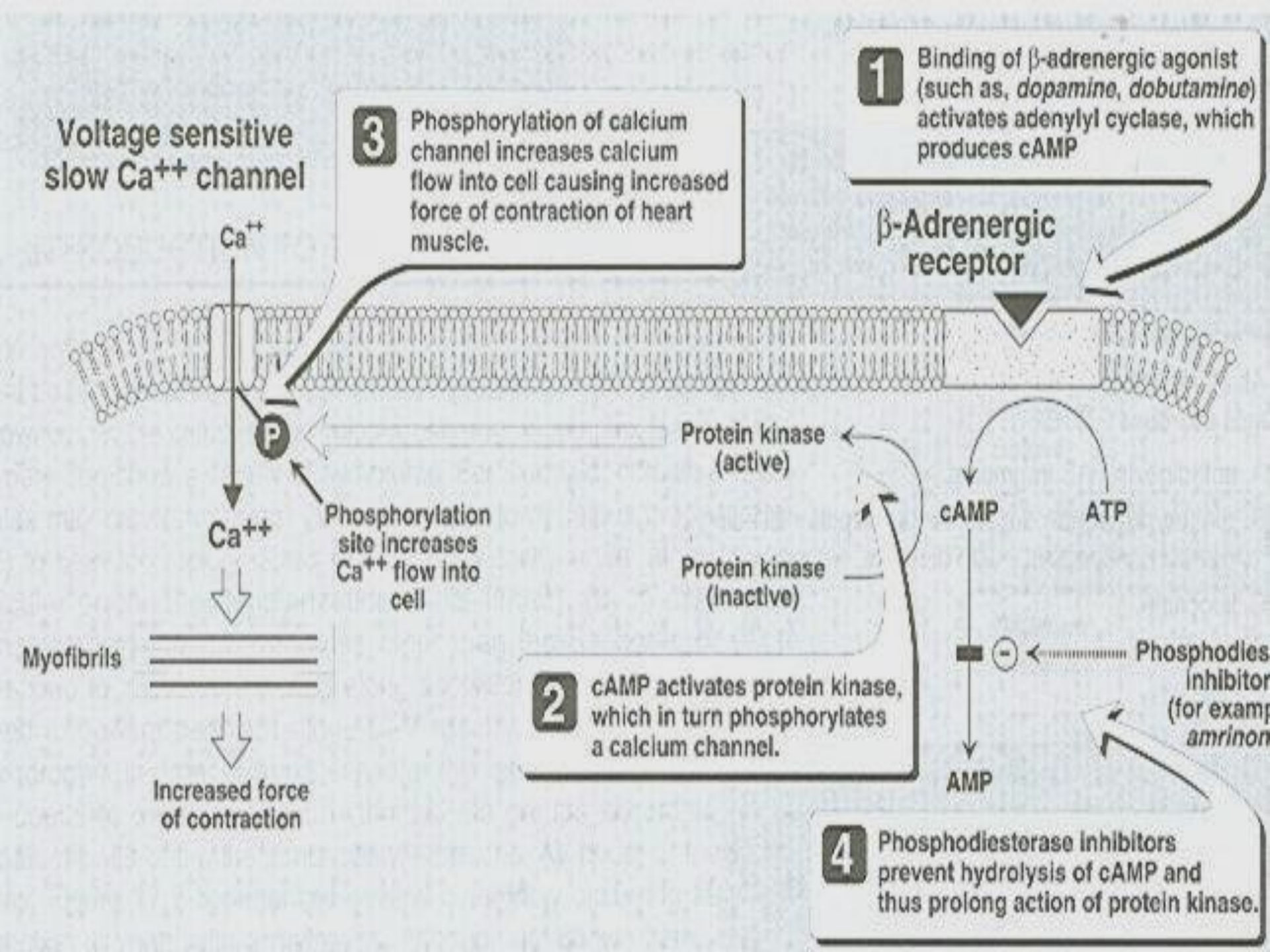
Adrenaline is stronger than dobutamine , but it might kill the patient because of how strong and nonselective it is.

Dobutamine doesn't have an effect on mortality, although some say it increases mortality.

- As mentioned, must be given by intravenous infusion and is used in the treatment of acute HF in a hospital setting.

- Amrinone Have a positive inotropic effect and increase systemic vasodilation.(not required for exam)
- Amrinone used in short term therapy of HF that is refractory to other agents.

When we are infusing a b agonist IV , it loses the selectivity, meaning it will affect the B2 receptors, which will cause vasodilation and thus hypotension, so we need to monitor the blood pressure , if we see any decrease in the blood pressure we give low dose noradrenaline.


Voltage sensitive slow Ca++ channel
Ca++
3 Phosphorylation of calcium channel increases calcium flow into cell causing increased force of contraction of heart muscle.
1 Binding of β-adrenergic agonist (such as, dopamine, dobutamine) activates adenylyl cyclase, which produces cAMP
β-Adrenergic receptor
P
Protein kinase (active)
Protein kinase (inactive)
cAMP
ATP
Ca++
Phosphorylation site increases Ca++ flow into cell
Myofibrils
2 cAMP activates protein kinase, which in turn phosphorylates a calcium channel.
Phosphodies
inhibitor
(for examp
amrinon
AMP
Increased force of contraction
4 Phosphodiesterase inhibitors prevent hydrolysis of cAMP and thus prolong action of protein kinase.

Stage C Therapy
(Reduced LVEF with Symptoms)

Hydralazine and Isosorbide Dinitrate

Lets say we reached the 10th year of treatment ,and the patient still has symptoms , we could decrease the preload and the afterload , via a combination of nitrates and hydralazine , called BIDIL,in addition to the standard therapy ,we increased cardiac perfusion , decrease the work load , decreased the oxygen demand, but be careful when using all those drugs to not induce severe hypotension.

The addition of a combination of hydralazine and a nitrate is reasonable for patients with reduced LVEF who are already taking an ACEI and beta-blocker for symptomatic HF and who have persistent symptoms.

A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency.

- **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.**

Charles Cullen

- admitted in 2003 to killing as many as 40 hospital patients with overdoses of heart medication—usually digoxin—at hospitals in New Jersey and Pennsylvania over his 16-year career as a nurse.

- On March 10, 2006 he was sentenced to 18 consecutive life sentences and is not eligible for parole.

v2:added a sentence on the macrlodies contraindication with digoxin,and some other small notes in green

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