CVS
PHARMACOLOGY

Modified NO:

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Before you start, you have to know these two concepts:

Inotropic: change in force of contraction قوة

Chronotropic: change in Heart Rate عدد

See this short video to minute 3 https://youtu.be/Kof18V2JyLI?si=hu-NztCPgs-Gff9A

- If these changes are positive or increased that will make the heart work harder.

Color code

- Slides
- Doctor
- Additional info
- Important

We will talk about Congestive Heart failure = systolic Heart failure= LF ventricular HF

Congestive/Systolic Heart Failure

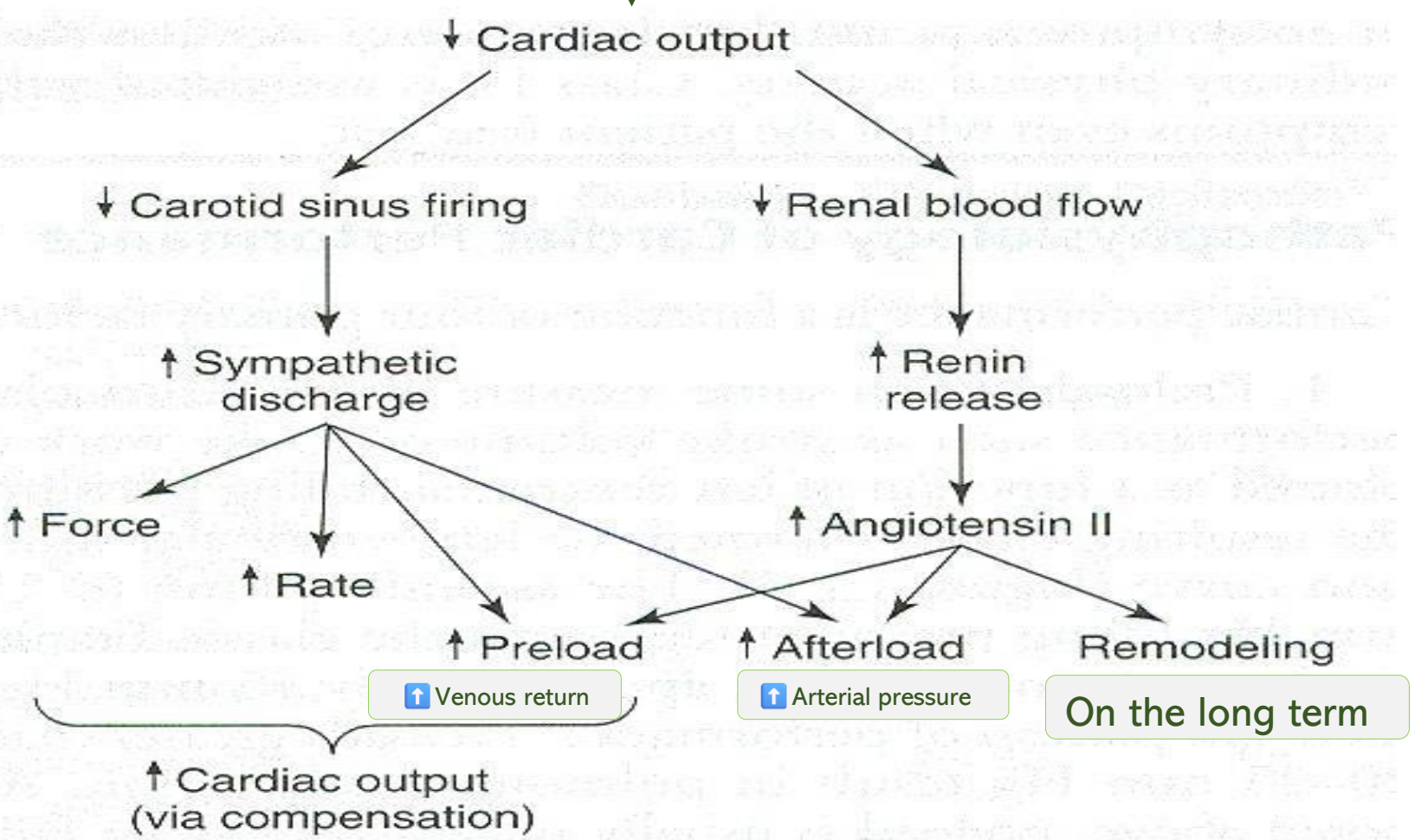


Figure 13–2. Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.

How do our bodies work?
Our body recognises heart failure as a Hypotension condition, so it gives a compensatory reaction that puts the heart in a worse situation.

Why?
Because the compensatory mechanism increase the workload on the heart by increasing the inotropic and chronotropic activity.

حُمِّل فوق قدرته...

Therefore, the most important process of HF treatment is How to reduce the compensatory mechanism that composed of two pathways:

- Renin or angiotensin pathway and
- Sympathetic pathway.

So, every single patient with heart failure except African Americans(who start with them with vasodilations(, we start with **ACEIs or ARBs or both in advanced cases + B-blockers ➡️ reduce the compensatory mechanism ➡️ reduce or stop the Deterioration = heart function or role.**

- Beta blocker is important to reduce myocardial necrosis over time so we increase the heart life.

+

During this pharmacological strategy, if we notice any edema/swelling/water retention we will give the patient **Diuretics**

والأعمار بيد الله عزَّ وجل.....

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.

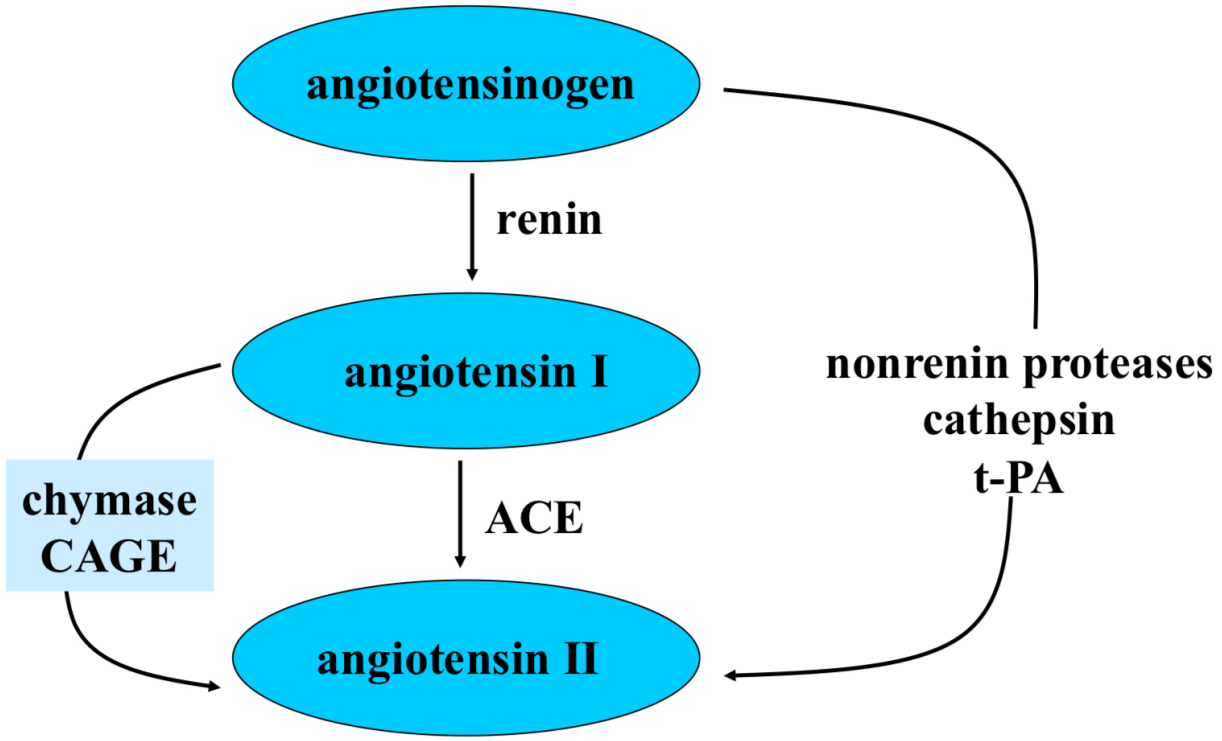
Imp note:
Congestive heart failure is a complex disease because of the continuous progression so, the patient needs to change the doses or even the drugs over the time.

When we talked about African Americans with HF, we give them vasodilation + B blocker of course to reduce the sympathetic compensation and stop the reflux tachycardia from vasodilators.

Treating HF

- **The main aims being**
- **(1) decrease the symptoms.**
- **(2) slow disease progression,**
- **(3) improve survival.**

This image is included with the final material.



We talked in previous slides that we can combine ACEI and ARB, but is it contraindicated!?
A: It is relatively contraindicated because there are other pathways to produce angiotensin II and to stop or decrease any angiotensin response we combine the (we need this in end stages of HF).

What about severe hyperkalemia?
We will use loop diuretic as we know.

This image explained three pathways their end result is angiotensin II:

- Renin pathway

Depend on ACE, affected by ACEI and ARB

- Nonrenin protease pathway
- Chymase pathway

Do not depend on ACE ,
These are shunts for the renin pathway, affected only by ARB

Six Classes of drugs have been shown to be effective

First option you have to think about it for HF patient except for African american

(1) ACE inhibitors,

(2) β-adrenergic blocking agents,

(3)diuretics,

(4) inotropic agents,

(5) direct vasodilators, and

(6) aldesterone antagonist.

We use loop diuretics because we have excess fluids and edema

If the patient reaches to severe HF with almost completely loss of function, now we need to stimulate it by inotropic agents as:

- Digoxin
- Bobutamin
- Ivabradine

They will be explained in online lecture

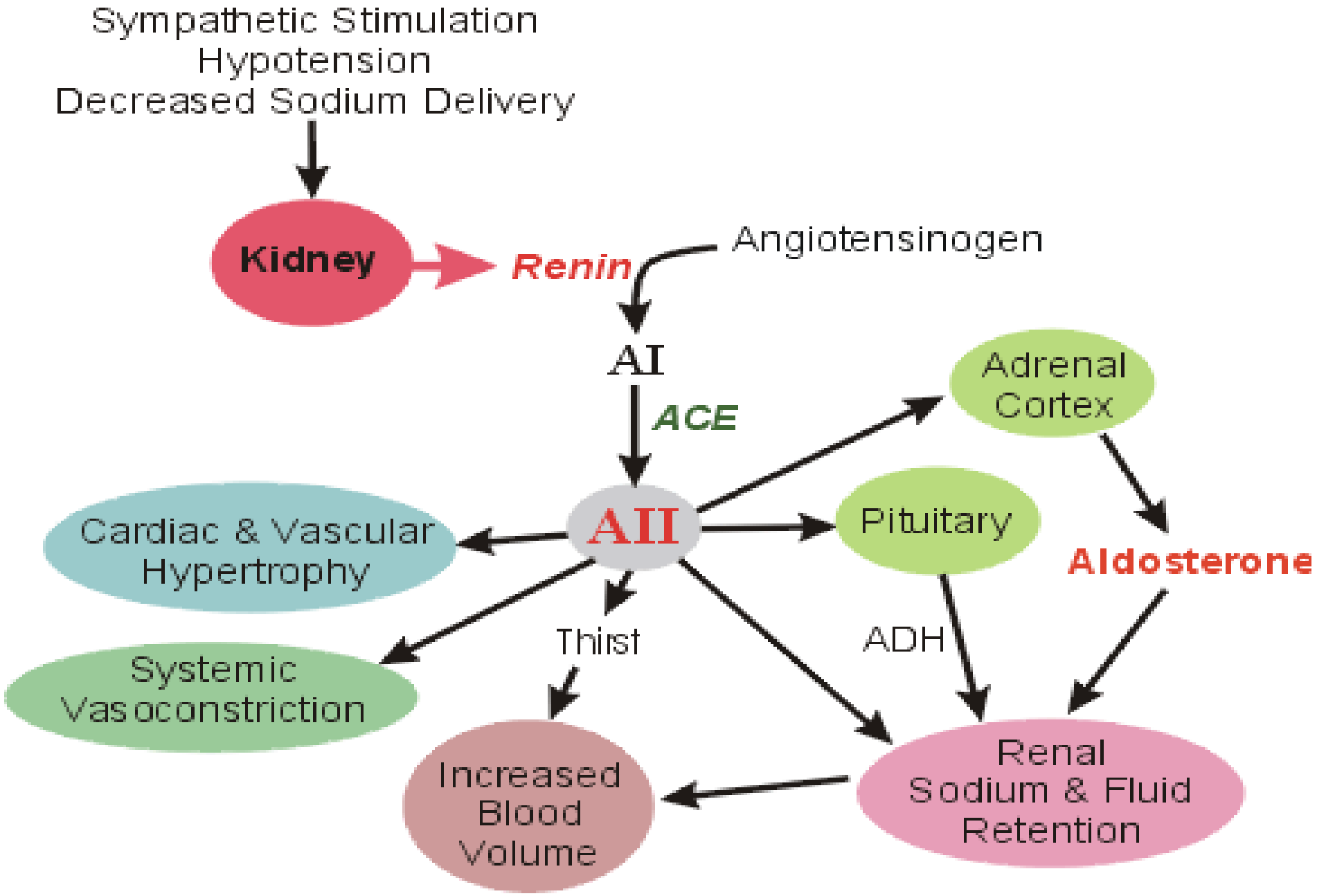
- We don't need to stop or reduce the compensatiry mechanism anymore (late stages).

- **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.**
- **They also blunt 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 :

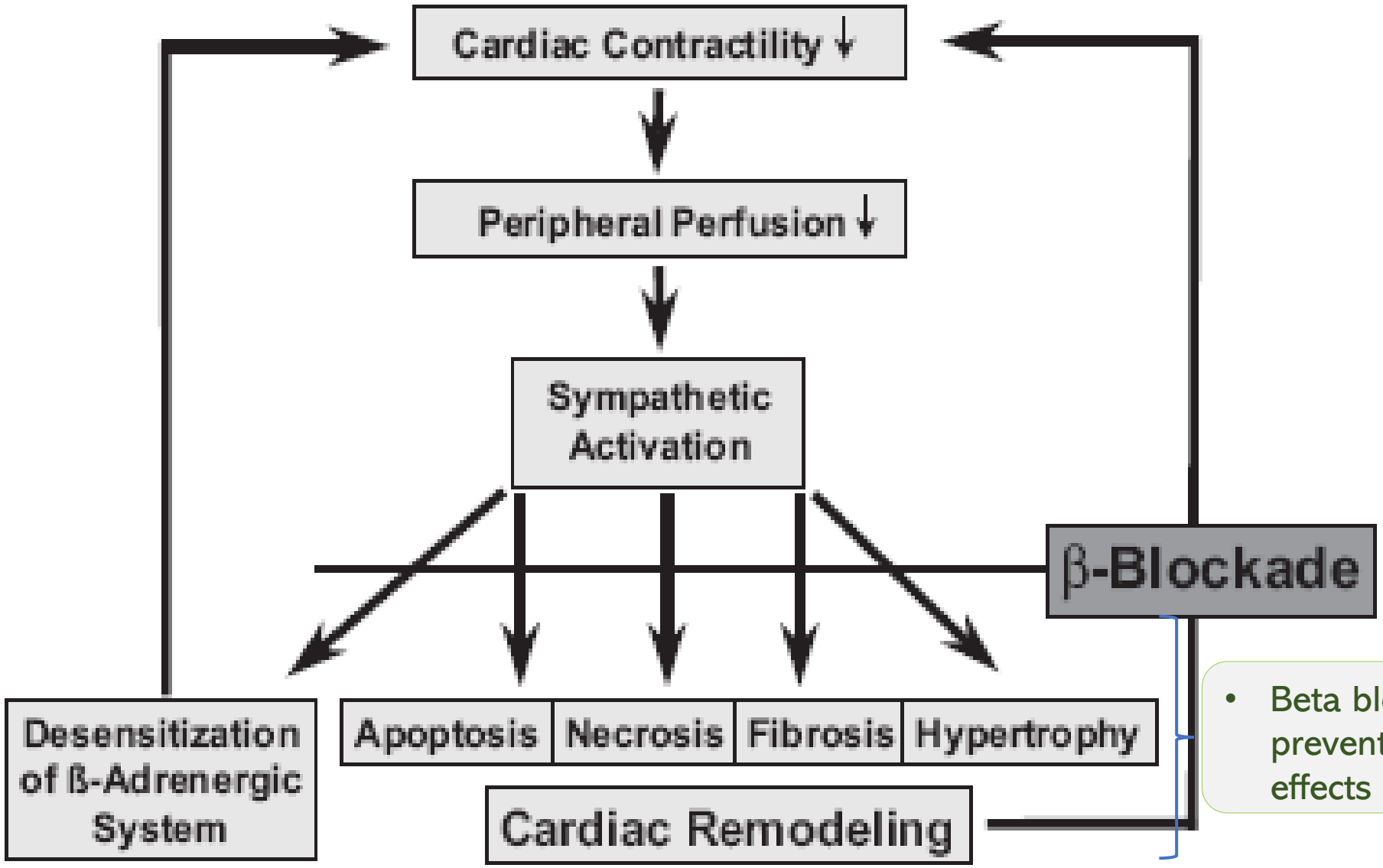
- Dry irritating persistent cough
- Hyperkalemia — Another reason on combine diuretics with ACEIs in HF
- Angioedema
- Fetal toxicity

- 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 in logical to administer drugs with negative inotropic activity to patient with HF.
- Several clinical studies have clearly demonstrated improve systolic functioning and reverse cardiac remodeling in patients receiving β blocker
- The benefit is attributed in part to their ability to prevent changes of the sympathetic system, include decreasing the heart rate and inhibiting renin secretion.
- Bisoprolol, carvedilol or nebivolol 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



- Beta blockers prevent all of these effects

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

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.

- Loop diuretics and thiazides cause hypokalemia.

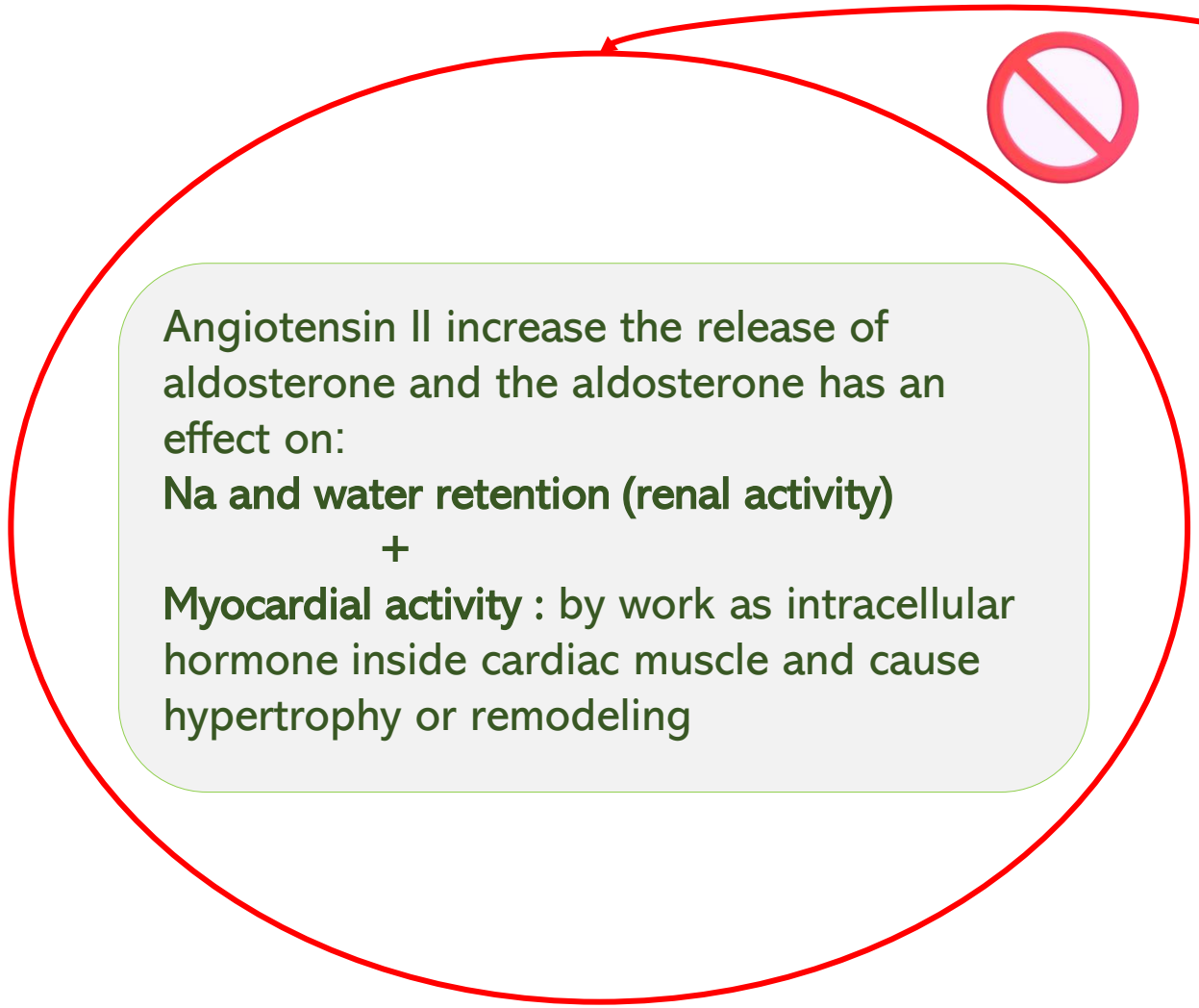
- Potassium sparing diuretics help in reducing the hypokalemia due to these diuretics.

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 should be preserved for the most advanced cases of HF.



Angiotensin II increase the release of aldosterone and the aldosterone has an effect on:

Na and water retention (renal activity)

+

Myocardial activity : by work as intracellular hormone inside cardiac muscle and cause hypertrophy or remodeling

- So we need **spironolactone to stop this activity of Aldosterone**
- Aldosterone doesn't have a diuretic effect only, it has also an effect toward myocardial cells of heart
- Remember this drug is used for advanced 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

Stage C Therapy
(Reduced LVEF with Symptoms)

Note:
Risk vs. benefits are not stasis, they are dynamic through age or the condition of the patient and so on.

It is a balance!

Abstract:
If you might not be able to monitor and control potassium levels in a patient; you shouldn't give aldosterone antagonists.

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.

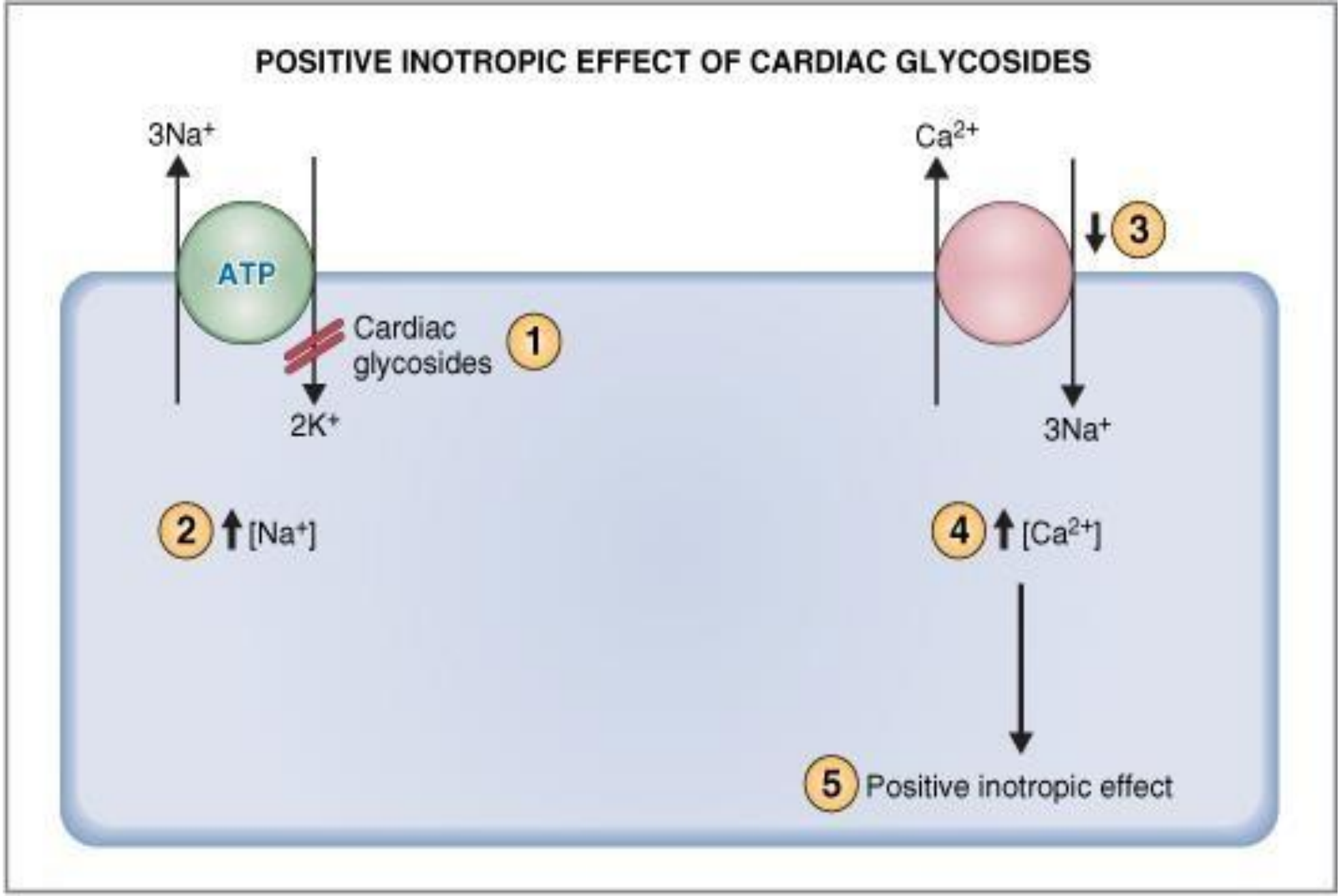
Routine combined use of an ACEI, ARB, and aldosterone antagonist is not recommended for patients with current or prior symptoms of HF and reduced LVEF. Although you have an access to ward monitoring K and renal function

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).**

- **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.**



- Digoxin, derived from the plant Digitalis, is a cardiac glycoside that binds to the sodium-potassium ATPase pump in myocardial cells. It competitively and reversibly inhibits potassium binding, preventing potassium entry into the cell.

- Inhibition of potassium entry prevents sodium from being pumped out of the cell, as the sodium-potassium pump relies on a gradient (moving ions from low to high concentration) and requires ATP. This results in an increased sodium concentration inside the cell.

- There is also a non-ATP-dependent sodium-calcium exchanger, which normally moves calcium out of the cell and sodium into the cell. When the intracellular sodium concentration increases, it inhibits the function of this exchanger, as it relies on the sodium gradient. This results in an accumulation of calcium inside the cell.

- Imagine a myocardial cell with a high concentration of calcium. Before calcium is released from the sarcoplasmic reticulum (SER), its contractility, ejection fraction, and cardiac output will return to normal, considering that we administer this drug to patients with myocardial infarction (MI).

- It can be dangerous. The cell becomes more positively charged (depolarized), which impairs its ability to repolarize properly. This makes it easier for the cell to become excited and fire an action potential. Because the sodium-potassium pump is inhibited, the sodium gradient across the membrane is diminished, preventing the cell from reaching the normal resting potential of -70 to -90 mV. As a result, the cell is more prone to spontaneous depolarization and abnormal action potentials, increasing the risk of arrhythmias.

- Arrhythmia may happen when you give digoxin.

- Digoxin has a unique effect on the vagus nerve. For reasons we don't fully understand, digoxin enhances the activity of the vagus nerve, increasing acetylcholine release. This acetylcholine binds to M2 receptors in the heart, leading to potassium efflux and hyperpolarization, which makes it harder to generate action potentials. This effect occurs primarily in the AV node.

- So, digoxin has 1- positive inotropic activity and 2- negative chronotropic activity. It increases contraction force and decreasing HR.

- Again, is it without consequences? By causing depolarization and making cardiac cells excessively positive, all of this increases the risk of arrhythmias.

- but isn't digoxin antiarrhythmic drug? yes, but it can cause arrhythmia.

- All antiarrhythmic drugs are proarrhythmic. Remember this, and we will talk about it next week

- DG Fab (also known as Digoxin-specific antibody fragments or Digoxin Immune Fab) is antidote for digoxin.

Digoxin

- **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.

  Imagine that your patient is taking thiazide or loop diuretics (which is very common). These drugs can cause hypokalemia, and as we mentioned earlier, digoxin competes with potassium. A decrease in potassium concentration will increase the risk of digoxin toxicity.

  It also may happened because of the accumulation over a long period of time.

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

Digoxin

Medicine is beautiful, Dr.Malik Zuhlif 🙂

these signs includes:

1. **Anorexia, nausea and vomiting and diarrhea.**
2. **<u>Vision changes (xanthopsia)</u>, fatigue and headache.**

From vagus nerve effect

3.cardiac effects that include: premature ventricular contraction, and ventricular tachycardia and fibrillation. Arrhythmia and atrial tachycardia. Even Torsade de Pointe could occur, because you are too close to threshold, any massage from around can cause firing.

From positive inotropic effect

Digoxin interaction:

Quinidine, varapamil (contraindicated, it has negative inotropic and chronotropic activity, we give it with digoxin only if the patient has arrhythmia) , and amiodarone can cause digoxin intoxication, both by replacing digoxin from tissue protein binding sites, and by competing with digoxin for renal secretion.

We always say in introductory courses not to give drugs with digoxin because:

Macrolide and tetracycline antibiotics should be avoided because they elevate digoxin serum concentration and enhance the risk for digoxin toxicity. Explanation in next slide

- Torsades de Pointes (TdP) is a specific type of polymorphic ventricular tachycardia, characterized by a distinctive twisting of the QRS complexes around the ECG baseline. The name comes from French, meaning "twisting of the points." It is a potentially life-threatening arrhythmia that can lead to ventricular fibrillation and sudden cardiac arrest.

- Vision changes (xanthopsia) <-- Yellow holes seen by the patient, especially as a side effect of digoxin. **Xanthopsia** refers to a **yellowish tint** or distortion in vision, which is a well-known side effect of **digoxin toxicity**. People experiencing xanthopsia see everything with a yellow or greenish hue, and it can be a **warning sign** of digoxin overdose or toxicity, especially if accompanied by other symptoms.

- Also, remember that the heart is not normal; it has congestive heart failure, and may have a myocardial infarction (MI), or angina, so the cells are very susceptible. So digoxin is a drug with the narrowest therapeutic index.

- We start with a dose of 0.25 mg for the patient, and we may increase it to 0.5 mg, 1mg is lethal.

- There is a microbiome in the GI tract, and if you are giving a broad-spectrum antibiotic, you are altering the microbiome. A small part of this microbiome is responsible for digoxin metabolism. Although it's a small part, digoxin levels in the body can increase, leading to toxicity. We care about digoxin because it is a narrow therapeutic index drug.

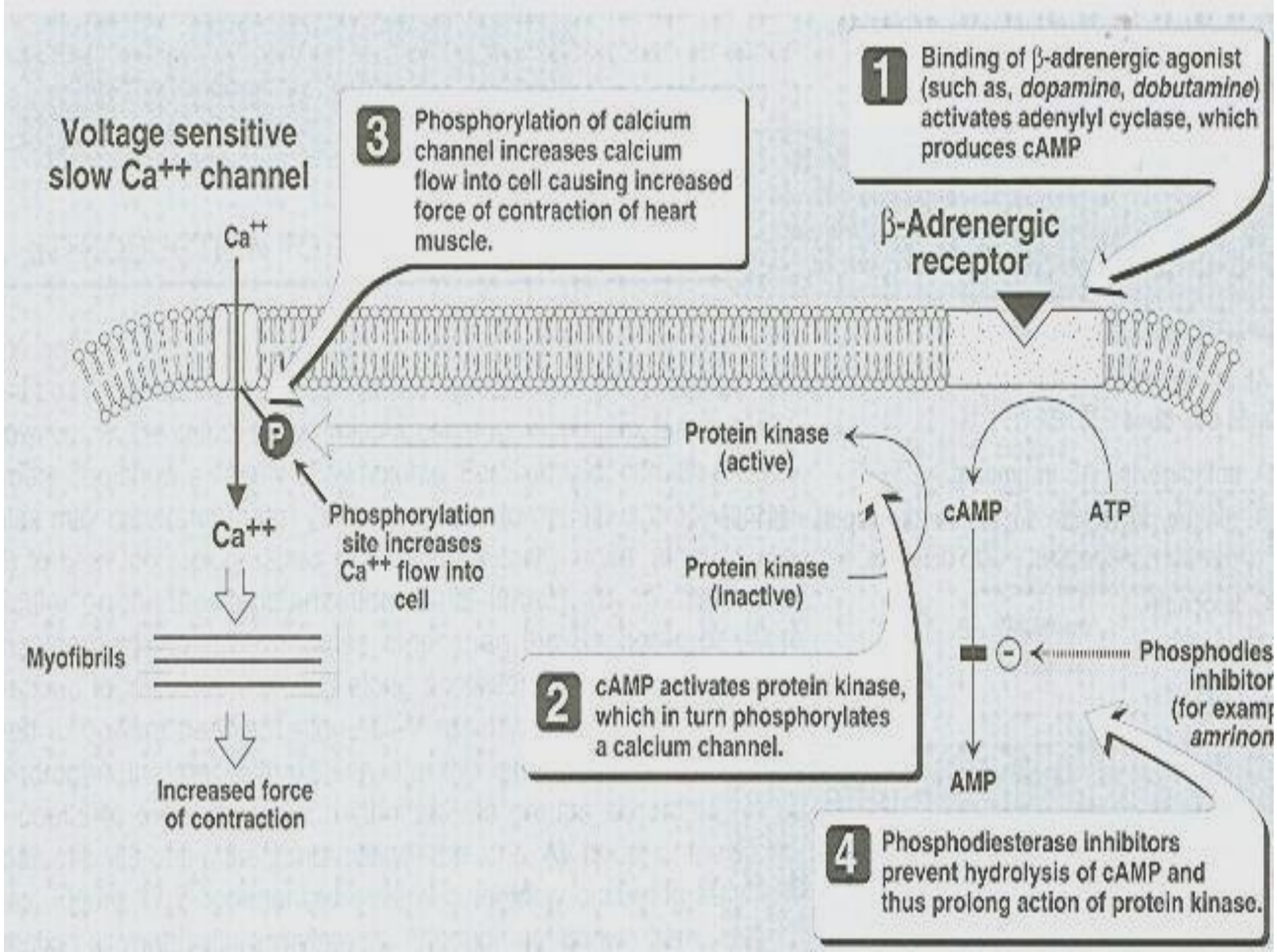
β-adrenergic agonist and Amrinone

Read it properly (not antagonist)

Dobutamine increases the rate of mortality, but we use it in one condition, if the ejection fraction is too low or cardiogenic shock (heart is very weak). So in this only case we give it.

- Dobutamine is a B1 adrenergic agonist that has positive inotropic effect and is the most used inotropc agent after digoxin.
- As mentioned, must be given by intravenous infusion (no oral) and is used in the treatment of acute HF in a hospital setting.
- Amrinone (not required because it increases death) Have a positive inotropic effect and increase systemic vasodilation.
- Amrinone used in short term therapy of HF that is refractory to other agents.

- Beta-1 receptors are found on the SA node, AV node, and myocardial cells, so stimulation of these receptors leads to a positive inotropic effect. Remember, beta-2 receptors are found on blood vessels; stimulating beta-2 receptors with an agonist can cause hypotension. Also, keep in mind the selectivity of the drug—it primarily acts on beta-1 receptors but can also affect beta-2 receptors, which may exacerbate strong hypotension in patient who takes beta-2 agonist and potentially lead to death in the patient.


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)
Phosphorylation site increases Ca++ flow into cell
Ca++
cAMP
ATP
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

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.

Main combination in African Americans: Hydralazine and Nitrate

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 <u>renal insufficiency.</u>

- Hydralazine --> reduction in afterload
- Nitrate --> reduction in preload

- We are talking about bilateral renal stenosis patient which can't be given ACEIs.
- محدش يجي يعمل استنتاج ويقول
  ACEIs are contraindicated in renal insufficiency.
  العلم دقيق 🤓

- **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.

أضاعت الجنَّةُ أمْ أُخبرتَ بعدم القبول
هوّن عليكَ فكلُّ ما دونَ الجنَّةِ دون

واعلموا أنَّ مهمتكم ليست ورقةً تنالونها
بل أمّةً تحيونها 🌿

Additional sources

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	4 18	Isotropic	Inotropic To stop this activity of aldosterone
V2→V3	2	Isotropic	Inotropic

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا!!