PHARMACOLOGY

بسم الله الرحمن الرحيم

MID | Lecture 7

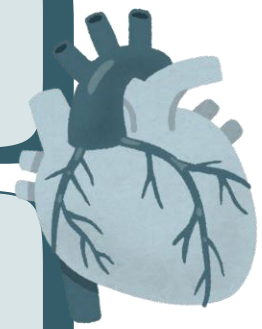
# Heart Failure Drugs

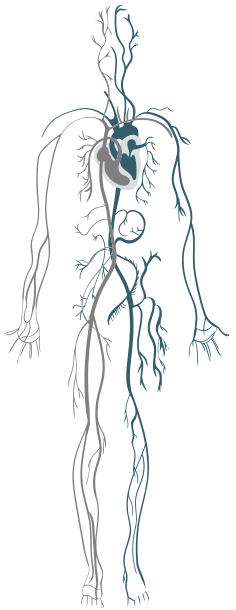
وَلَقَدْ خَلَقْنَا الْإِنسَانَ وَنَعْلَمُ مَا تُوَسْوِسُ بِهِ نَفْسُهُ ۖ وَنَحْنُ أَقْرَبُ إِلَيْهِ مِنْ حَبْلِ الْوَرِيدِ

اللهم إنّا نعوذ بك من شرور أنفسنا ومن سيئات أعمالنا


Written by: Aya Ghalayini
Roaa Maakoseh

Reviewed by: Sarah Mahasneh

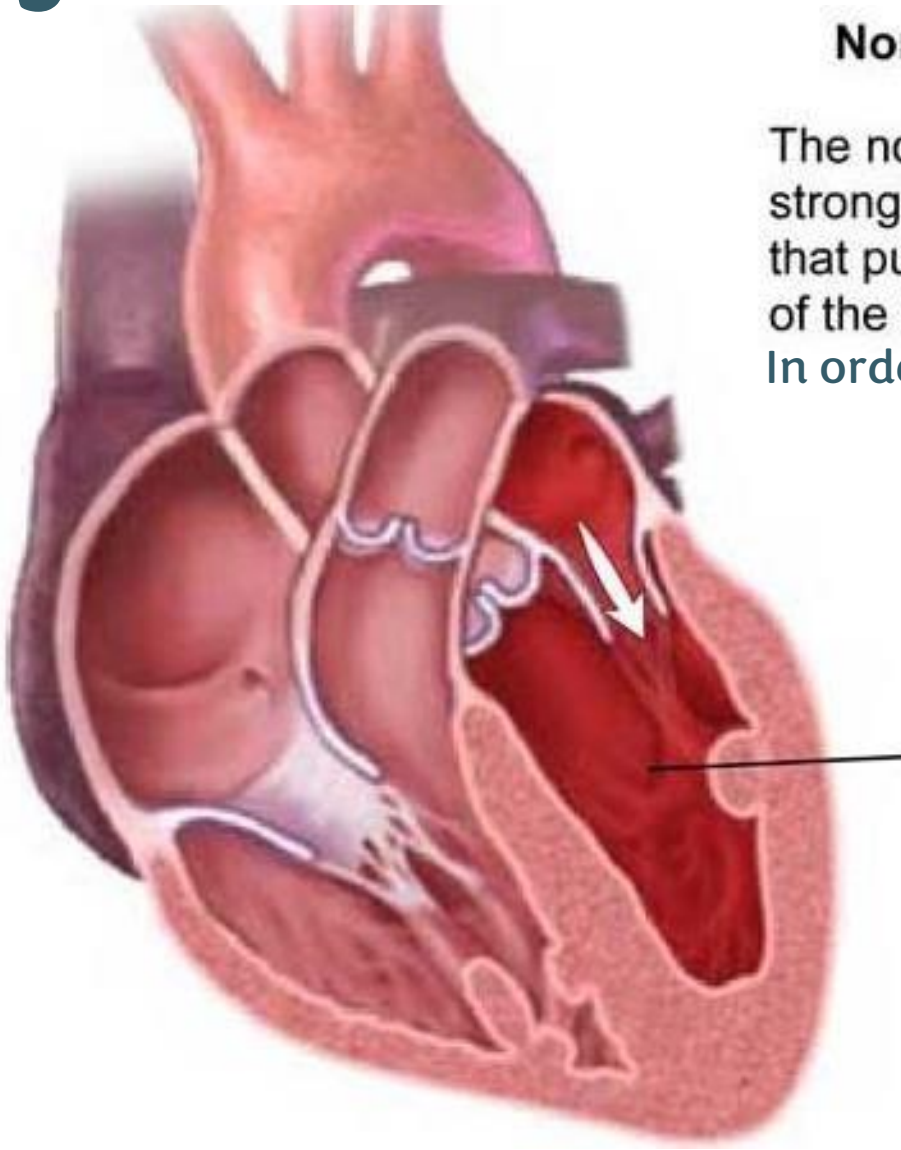



# Heart Failure

- **The heart is unable to pump sufficient blood to meet the body's needs. Its key symptoms are dyspnea, fatigue, and fluid retention.**
  - The impaired ability of the heart to adequately fill or eject blood
- **HF is due to an impaired ability of the heart to fill with or eject blood adequately.**
- **Underlying causes of HF include atherosclerotic heart disease, myocardial infarction, hypertension, and valvular heart disease.**
- **Left systolic dysfunction secondary to coronary artery disease is the most common cause, account to 70% of all cases.**

# Morphology of the Heart

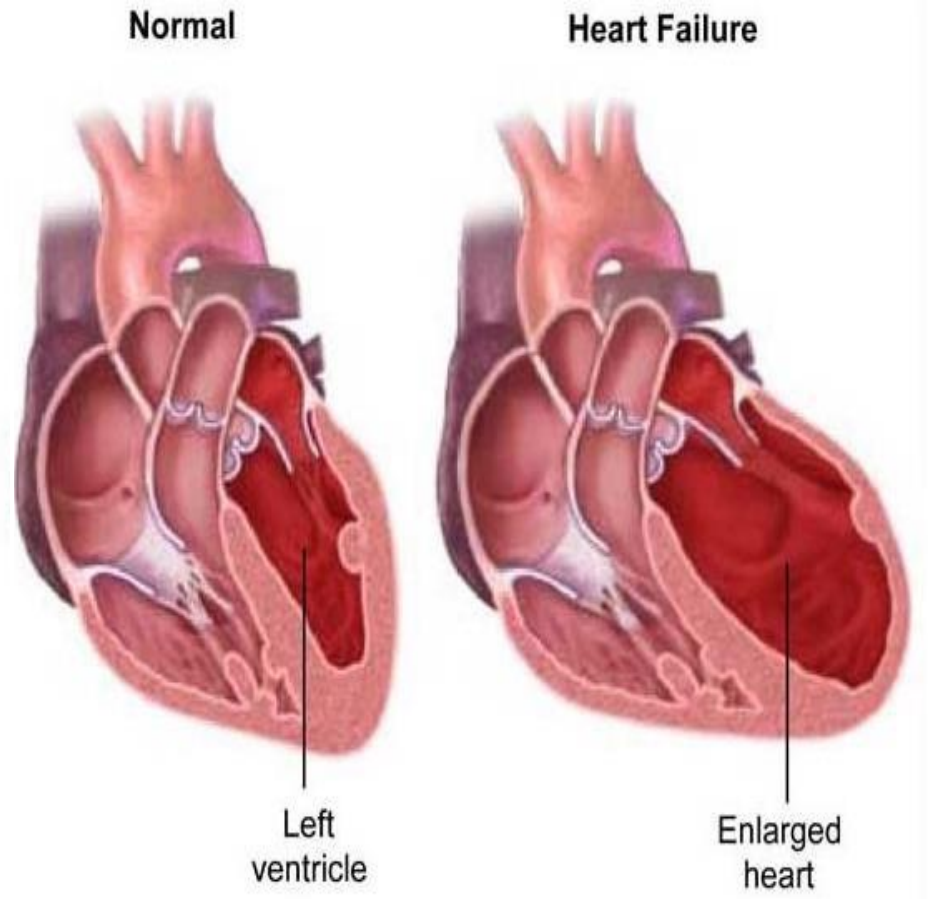


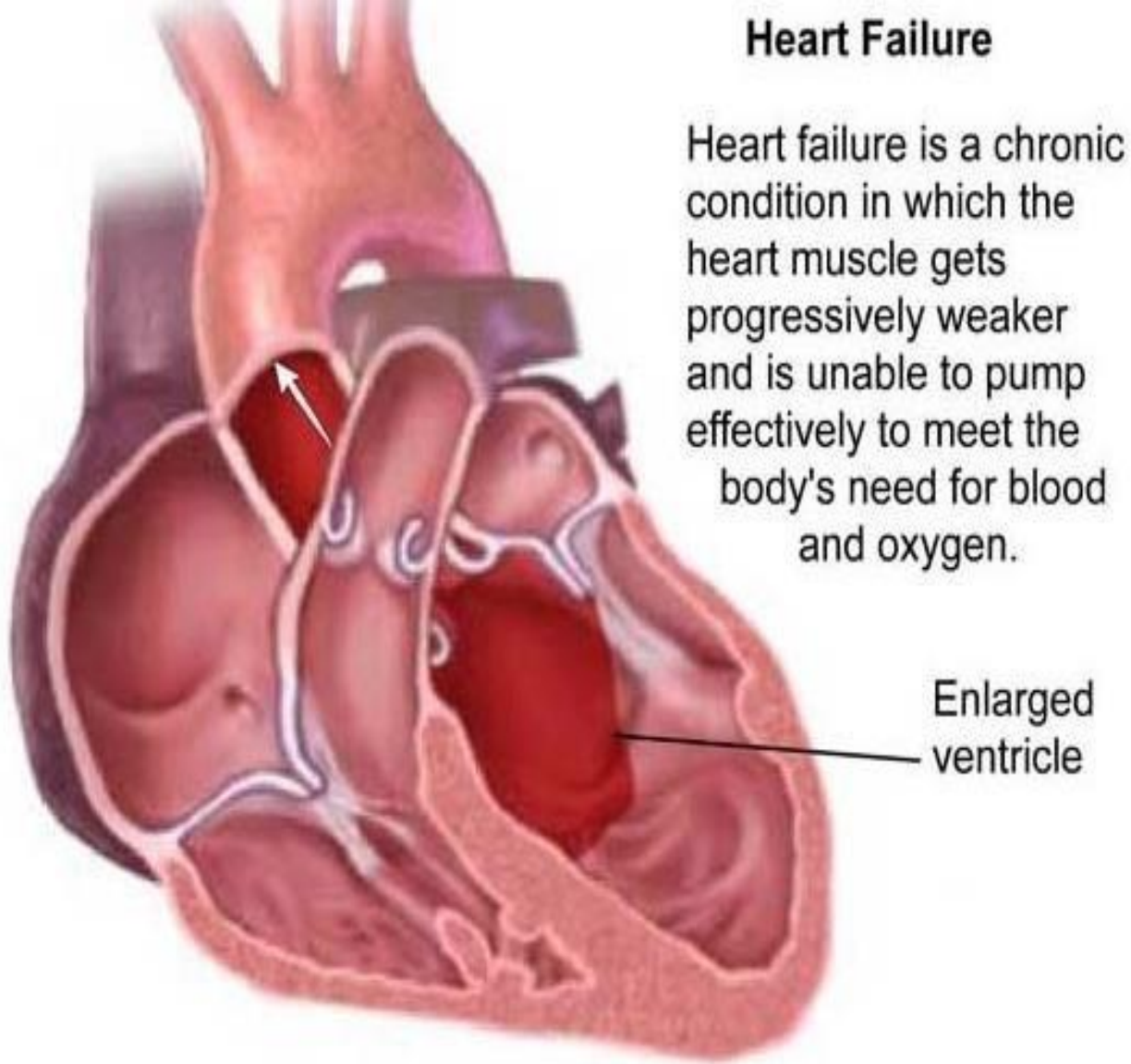
# Morphology of the heart

In heart failure,
The heart enlarges, and the chambers dilate and become more rounded (Rounded and spherical).

1. Initially, the body activates **compensatory mechanisms**, including stretching of the heart muscle. This stretch temporarily increases contraction strength and helps maintain cardiac output.

2. However, excessive stretching weakens the contractions, and progressive structural changes occur in the myocardium. At this point, the condition is referred to as **systolic heart failure**, characterized by reduced ventricular contractility and pumping ability.





## Heart Failure

Heart failure is a chronic condition in which the heart muscle gets progressively weaker and is unable to pump effectively to meet the body's need for blood and oxygen.

Enlarged ventricle

# Compensatory mechanisms in Congestive Heart Failure

When the heart begins to reduce its cardiac output, two major **compensatory systems** are stimulated to correct low perfusion, reduced blood flow, and decreased oxygen delivery. One of these two systems is the:

1) **Baroreceptor reflex** (sympathetic nervous system activation): A decrease in cardiac output leads to reduced stretch of the carotid sinus baroreceptors, resulting in ↓ baroreceptor firing and ↑ sympathetic outflow. This increases the release of **norepinephrine** and **epinephrine**, which bind to several adrenergic receptors throughout the body, including:

β1-adrenergic receptors (heart):
→ Increase heart rate (positive chronotropy), enhance myocardial contractility (positive inotropy), and increase the force of contraction, helping to support cardiac output.

A1-adrenergic receptors (blood vessels):
→ Cause vasoconstriction, which **raises afterload** and increases venous return (thereby **increasing preload**).

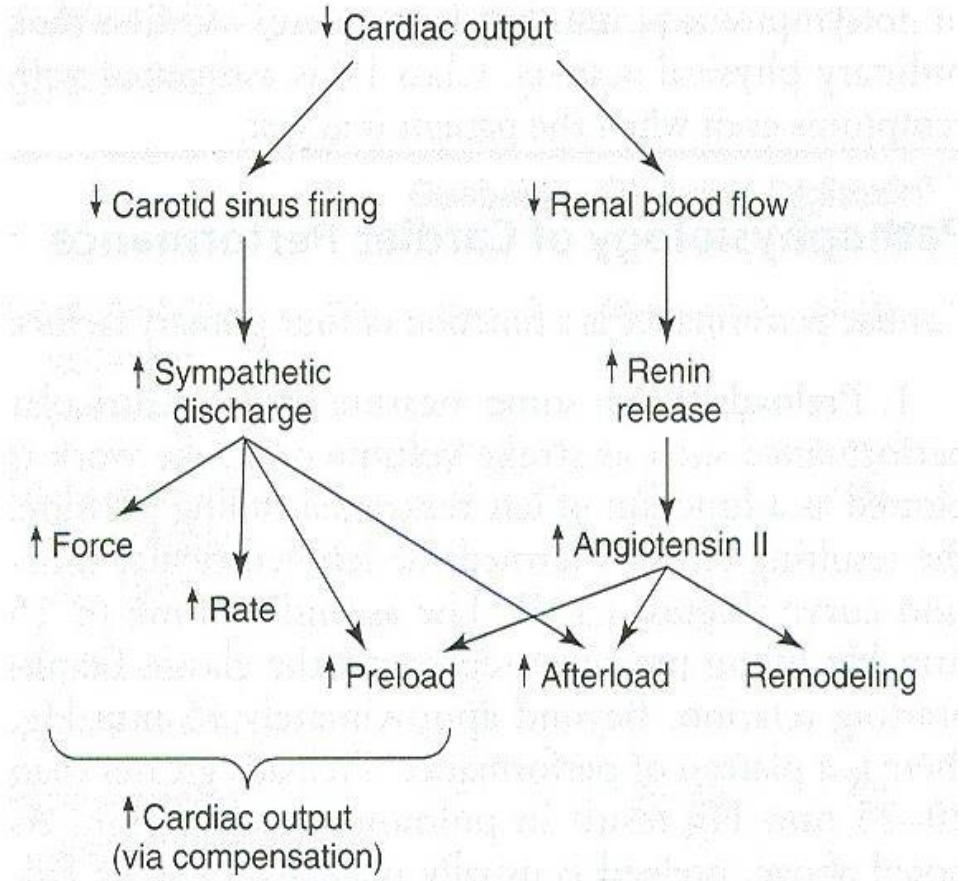



***Figure 13–2.*** Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.

# Compensatory mechanisms in Congestive Heart Failure Cont.

**2) Renin-Angiotensin-Aldosterone System (RAAS):**
Decreased cardiac output reduces renal blood flow, which stimulates the release of renin and leads to increased production of angiotensin II.

Angiotensin II binds to its receptors and causes vasoconstriction, which raises afterload and, through aldosterone-driven sodium and water retention, increases preload.

In addition, angiotensin II promotes **hypertrophy** and fibrosis in both the heart and vascular structures, resulting in remodelling of the cardiac muscle and vascular structures.
Note: structural remodelling causes thickening and stiffening of both heart muscles and vessels, reducing their ability to maintain proper circulation .

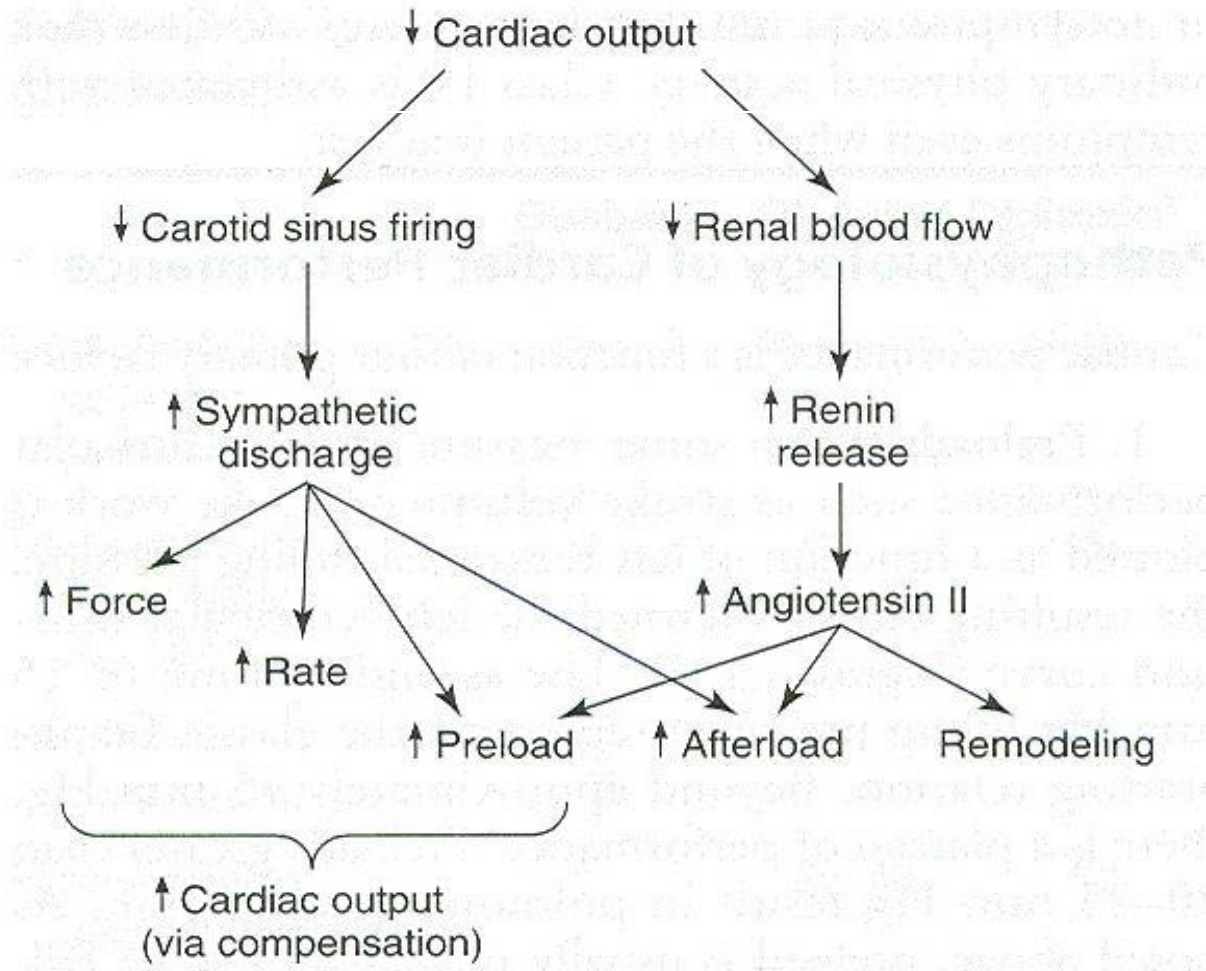



***Figure 13–2.*** Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.

# 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.**

- If the compensatory mechanisms restore cardiac output in a patient with heart failure, it is called **compensated heart failure**, meaning the body successfully adapts to maintain circulation.
- If these compensations increase the heart's workload but **fail** to improve organ perfusion, they may worsen heart function, and this is called **decompensated heart failure**.

# Treating HF

**The main therapeutic strategies for heart failure aim to:**

**(1)alleviate the symptoms.**

**(2)slow disease progression.**

**(3)improve survival.**

# Six Classes of drugs have been shown to be effective in treating HF

1)Inhibitors of RAAS include **ACE inhibitors**(primarily), **and ARBs can also be used.**

2)β-adrenergic blocking agents

3)diuretics

4)inotropic agents

5)direct vasodilators

6) Aldosterone antagonist

## Choosing a drug of choice :

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

ARBs: Angiotensin II receptor blockers

# RAAS activation in HF

As previously discussed, a decline in cardiac function activates compensatory mechanisms that increase renin release in an attempt to restore effective cardiac output.
This **rise in renin** occurs through two main pathways:

- **Reduced renal blood flow** decreases perfusion to the kidney, causing the juxtaglomerular (JG) cells in the afferent arteriole to release more renin.
- **Increased sympathetic nervous system** activity stimulates β1-adrenergic receptors on juxtaglomerular cells, further enhancing renin secretion.

The overall effect of increased renin is the production of **angiotensin II**, which has two major actions:

- Potent vasoconstriction, leading to increased (**PVR**) and elevated afterload.
- Stimulation of aldosterone release, which promotes salt and water retention. This increases preload, and over time contributes to fluid accumulation and **edema** in various organs—hence the term **congestive heart failure**.

➢ In **left ventricular heart failure**, the increased pressure in lungs often leads to **pulmonary edema.**

# ACE Inhibitors

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

# ACE Inhibitors for CCF

As previously mentioned, the **ACE** enzyme is necessary for the formation of **angiotensin II**, which activates the following pathways:

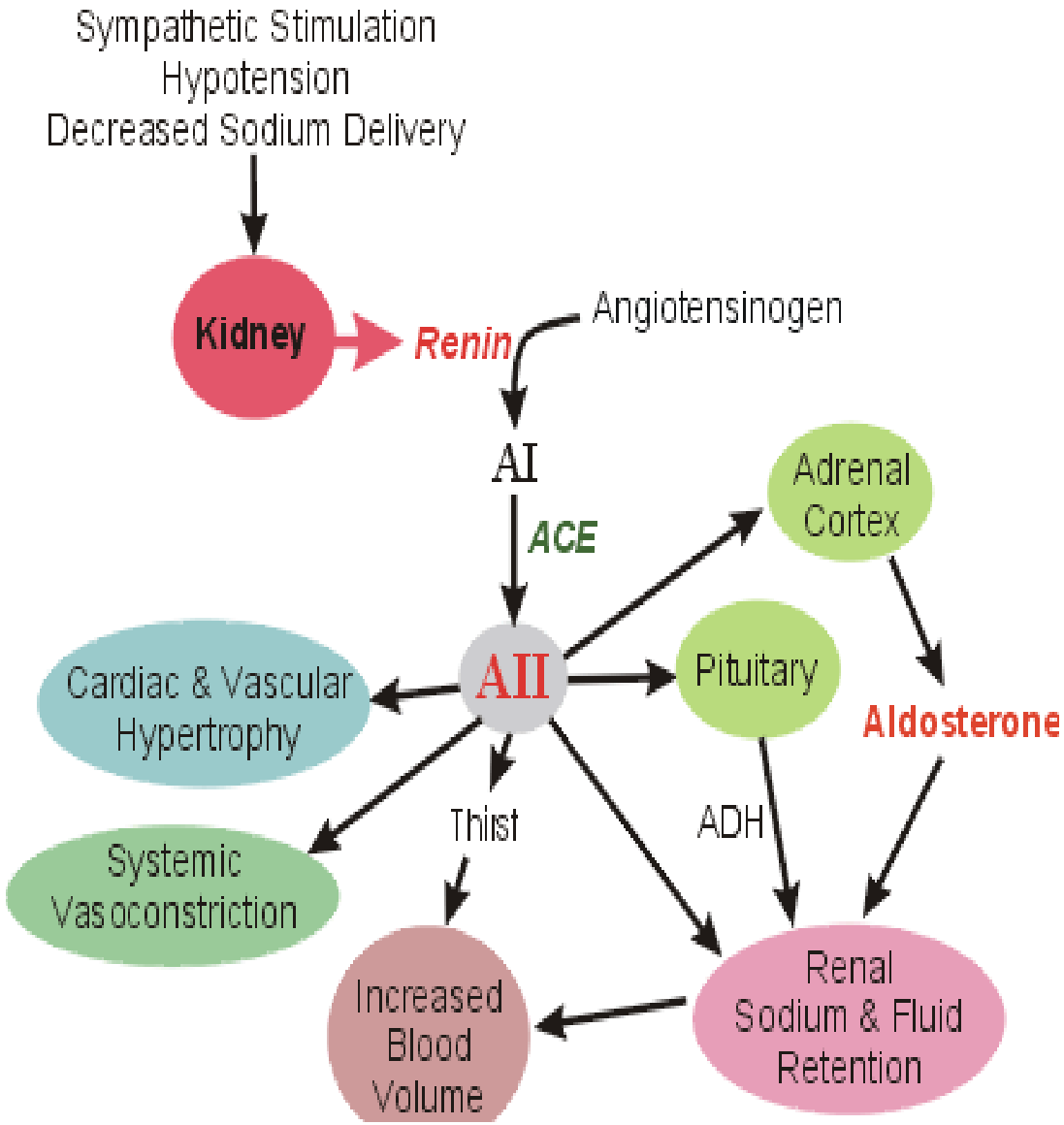
- Stimulation of the adrenal cortex to secrete **aldosterone** and the pituitary gland to secrete **ADH**. Both of these hormones cause renal sodium and fluid retention.

- Stimulation of the **thirst mechanism**, which increases blood volume.

- Angiotensin II also causes cardiac and vascular effects, which further **worsen** the condition.

This is **one of the main reasons** why ACE inhibitors are essential for the treatment of heart failure.

ACE inhibitor's main target in heart failure is to prevent cardiac and vascular hypertrophy or the remodeling that happens in the tissues as a response to the failing heart.




CCF: Congestive Cardiac Failure

# ACE Inhibitors

**Adverse effects:**

- Dry irritating persistent cough
- Hyperkalemia
- Angioedema
- Fetal toxicity(contraindicated in pregnancy)

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

# β-adrenergic blocking agents

- Although it may seem inlogical 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

- Bisoprolol, metoprolol, carvedilol, or nebivolol should be the beta blockers of **first choice** for the treatment of patients with chronic heart failure due to left ventricular systolic dysfunction.

# β-adrenergic blocking agents

- The effect of these beta-adrenergic blocking agents will not be seen immediately, so they would produce benefit in the medium to long term .

- In the short term they can produce decompensation with worsening of heart failure and hypotension. The use of a beta-blocker initially causes the body to sense a **decrease in sympathetic activity**, which triggers a compensatory mechanism involving **upregulation of β-receptors**—an increase in **both** the number of **receptors** and their **sensitivity**.

- **Therefore**, beta-blockers should be started at a low dose and gradually increased, with monitoring, until the target dose is reached. Over time, this improved receptor responsiveness leads to better clinical outcomes in heart failure patients.
- An additional benefit of beta-blockers is that they lower blood pressure, reducing both preload and afterload, which decreases cardiac workload and improves heart failure outcomes.

- 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**edema**
- By decreasing venous return, these drugs help relieve pulmonary congestion and peripheral edema. Reducing venous return lowers preload, which decreases cardiac workload and Oxygen demand.
- Additionally, diuretics can lower afterload by reducing plasma volume and blood pressure.

- **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 and are not recommended in patients with a creatinine clearance below 50 mL/min. In patients with excessive dialysis or significant renal insufficiency, loop diuretics are preferred. However, excessive doses of loop diuretics can cause profound hypovolemia, so careful monitoring is required.

# Diuretics

- Loop diuretics and thiazides cause **hypokalemia**.
- If a patient develops significant hypokalemia from these diuretics, switching to a potassium-sparing diuretic may help prevent further potassium loss and reduce the hypokalemia.

# **Spironolactone-** Potassium sparing diuretic

Used in Patients 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 prevents sodium retention, myocardial hypertrophy, and hypokalemia.

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

- Because spironolactone promotes potassium retention, patients should not take potassium supplements while using it.

# Spironolactone- side effects

- 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 lethargy, confusion, **endocrine abnormalities**: gynecomastia, decreased libido, menstrual irregularities, and impotence as well as **gastric disturbances** like peptic ulcer, gastritis .

- Eplerenone can be substituted for spironolactone in patients who develop gynecomastia, It helps in reducing the side effects of gynecomastia in male patients.

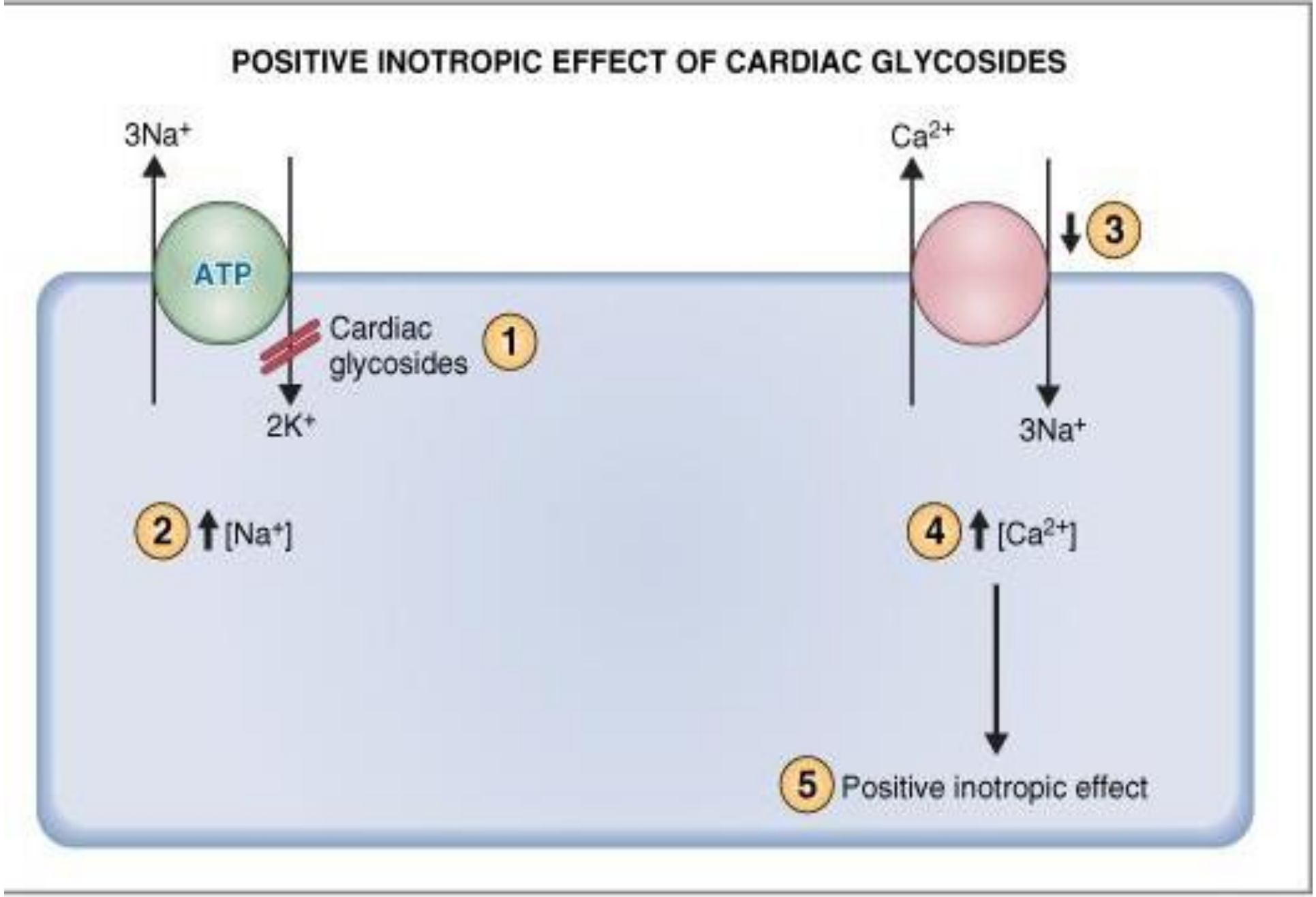
# Inotropic drugs (Digitalis)

- 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, which belongs to the class of cardiac glycosides, is one of the most commonly used medications for the treatment of heart failure.



# Mechanism of Action of Cardiac Glycosides

· Cardiac muscle contraction depends on the intracellular calcium concentration. Calcium levels inside cardiac muscle increase either through the opening of voltage-gated calcium channels or via release from the sarcoplasmic reticulum (SR). Calcium entry from outside the cell also triggers additional calcium release from the SR, a process known as (calcium-induced calcium release).

· To prevent continuous contraction, calcium is removed from the cytoplasm through reuptake into the SR and via the sodium-calcium exchanger (NCX), which normally extrudes one $Ca^{2+}$ ion in exchange for three $Na^{+}$ ions entering the cell.
To maintain the sodium gradient, the sodium-potassium ATPase pump moves three $Na^{+}$ ions out of the cell and two $K^{+}$ ions in.

· **Cardiac glycosides** inhibit the $Na^{+}/K^{+}$-ATPase pump. Inhibition of this pump increases intracellular sodium levels, reducing the transmembrane sodium gradient and consequently decreasing the driving force for the NCX. As a result, less calcium is extruded from the cell, leading to greater cytosolic calcium accumulation. This increase enhances calcium release from the SR, producing stronger cardiac muscle contraction and a positive inotropic effect.

# Digitalis Glycosides

**Actions :**

- **Positive Inotropic Effect.**
- **Vascular Muscle Contraction.**
- **Vagal Stimulation.**
- **Effects on Electrical Properties of Cardiac Tissues.**

· An increase in myocardial contractility enhances the efficiency of contraction and raises the ejection fraction by reducing end-systolic volume. As cardiac output improves, sympathetic activity decreases, leading to a lower heart rate and a reduction in myocardial oxygen demand.

# Digitalis Glycosides

**Therapeutic Benefits:**

- **Nowadays, useful in CHF with supraventricular arrhythmia**
- **Also indicated with severe left-ventricular systolic failure after initiation of ACE inhibitors, diuretics, and β Blockers.**
- **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.**
- **Dobutamine (another inotropic agent) can be given intravenously in hospitals.**

○ Because digoxin has a very narrow therapeutic window and a low therapeutic index, its risk of toxicity is **high**, and it is associated with multiple drug interactions.
Moreover, ACE inhibitors and β-blockers provide greater benefits in heart failure, as they reduce both mortality and morbidity, whereas digoxin does not reduce mortality.
Therefore, digoxin use has declined and is now reserved for patients who remain symptomatic despite optimal therapy with ACE inhibitors (or ARBs/ARNI), β-blockers, and diuretics.

# 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.**

# Adverse effects:

**digoxin have a low margin of safety (narrow therapeutic index) and intoxication from excess of both drug is common, (often caused by drug-drug interactions).**

**intoxication is frequently precipitated by depletion of serum K+ due to diuretic therapy.**

- Therefore, it is very important to monitor the patient's potassium levels. If the patient is taking a diuretic that causes potassium loss, it is necessary to supplement potassium or switch to a potassium-sparing diuretic to prevent 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.**

# Digitalis Toxicity

- **G.I.T.(Anorexia, nausea, intestinal cramping, diarrhea).**
- **Visual (Xanthopsia, abnormalities in color vision) This is due to long term therapy with digoxin.**

· **Xanthopsia** is a condition in which there is a predominance of yellow in the visual field, resulting in yellow-tinted vision. Result from yellowing of the optical media of the eye.

- **Neurologic (Malaise, confusion, depression, vertigo).**
- **Cardiac (bradycardia, Palpitations, syncope, arrhythmias, AV node block, ventricular tachycardia).**

**Toxic effects are greater in hypokalemic patients.**

- **K+-depleting diuretics are a major contributing factor to digoxin toxicity .**

# Digitalis Toxicity

**Treatment of Toxicity:**

- **Reduce or stop the drug.**
- **Cardiac pacemeker for heart block.**
- **Digitalis antibodies( Digoxin Immune Fab)**
- **Arrhythmias may be converted to normal sinus rhythm by $K^+$ when the plasma $K^+$ conc. is low or within the normal range.**
- **When the plasma $K^+$ conc is high, antiarrhythmic drugs, such as lidocaine, phenytoin, procainamide, or propranolol, can be used .**

# Drug interactions

**Digoxin interaction :**

**Quinidine, varapamil, and amiodarone can cause digoxin intoxication, both by replacing digoxin from tissue protein binding sites, thus Increasing its concentration in plasma, 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**

# Important

- **NSAID use can cause salt and water retention and so worsen the HF.**
- **Itraconazole (antifungal drug) may elevate digoxin level, so avoid combination.**
- **Ibuprofen and Indomethacin elevate digoxin level.**
- **Diazepam may increase digoxin level**

# Positive Inotropic Agents

## Cyclic AMP Dependent Agents:

### β-adrenergic Agonists:

- **NE**
- **Dopamine**
- **Dobutamine**

**Phosphodiesterase Inhibitors** (Affecting AMP levels by inhibiting its breakdown):

- **Amrinone**
- **Inamrinone**
- **Milrinone**
- **Vesanirone**
- **Sildenafil**

# Positive Inotropic Agents

## Cyclic AMP Dependent Agents:

## β-adrenergic Agonists:

***All increase myocardial oxygen consumption, so not helpful for chronic use, maybe used (IV) for short term or in acute heart failure.***

**NE:**

**Was used in cardiogenic shock, but caused severe vasospasm and gangrene**

**Ep:**

**Still used in cardiac arrest, by intracardiac injection.**

# Positive Inotropic Agents

**Dopamine:**

**Widely used in cardiogenic shock.**

**Low doses: stimulate $DA_1$ receptors leading to renal vasodilation and improved renal function.**

**Intermediate doses: work on $\beta_1$ receptors leading to positive inotropic actions.** (For the treatment of heart failure, it is better to use intermediate doses in an emergency situation).

**High doses: stimulate α receptors leading to vasoconstriction and elevation of blood pressure . Can cause arrhythmias and ischemic changes.**

**Dobutamine:** The drug of choice for the treatment of cardiogenic shock

**Selective $\beta_1$ agonist, used intermittently (IV) in CCHF. Produces mild vasodilation.**

**Has more inotropic than chronotropic actions.**

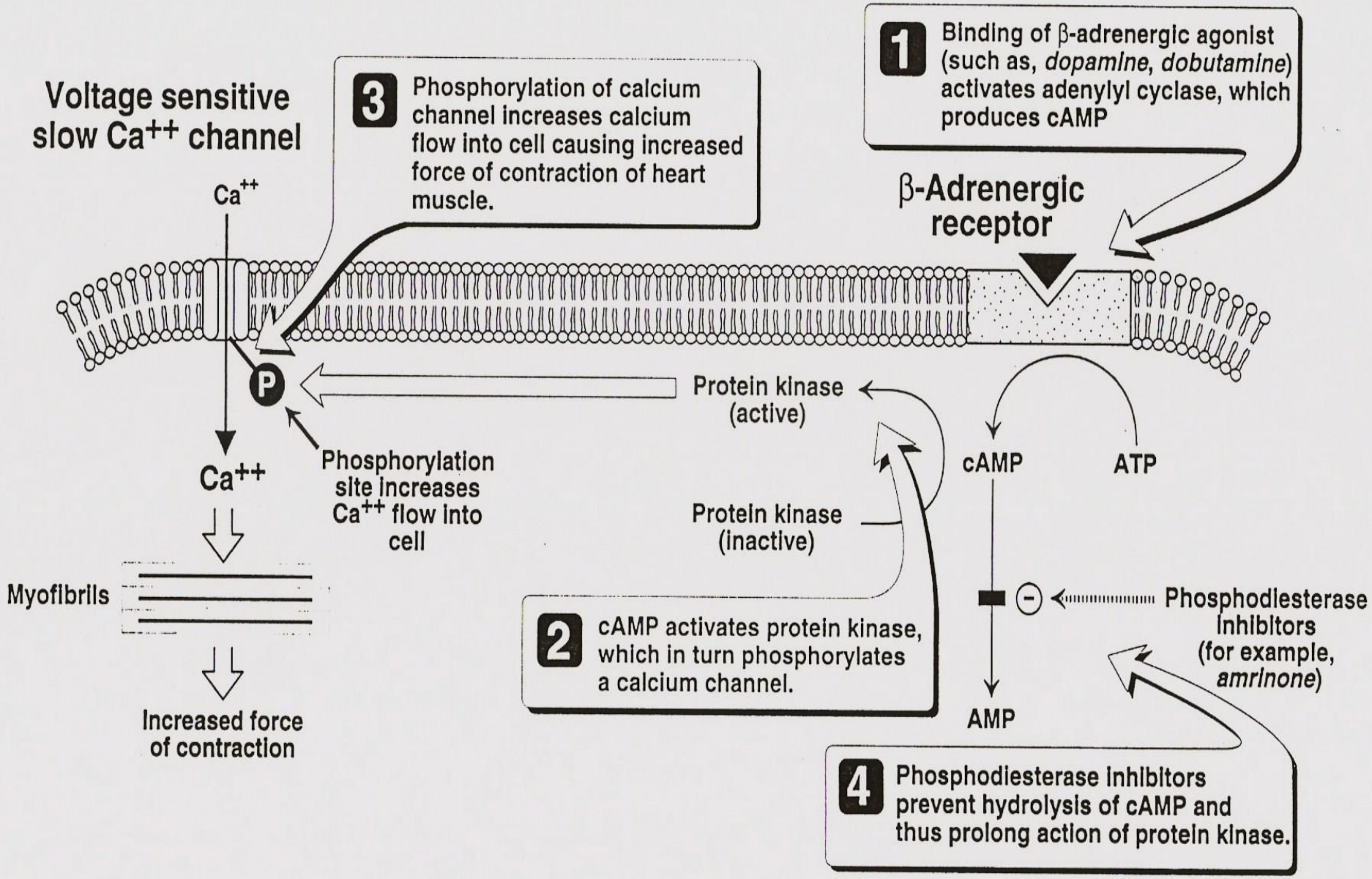



**Figure 16.11**
Sites of action of β-adrenergic agonists on heart muscle.

# The effects of beta-adrenergic receptor activation in heart muscle

- Agonists such as dopamine and dobutamine activate adenylyl cyclase, which increases intracellular cAMP. This activates protein kinase A (PKA), which phosphorylates various targets in the cardiac muscle, including L-type calcium channels, leading to an increase in intracellular calcium and stronger contraction.

- Another pathway involves phosphodiesterases, which normally break down cAMP. **Inhibition of phosphodiesterase** increases cAMP levels, causing further PKA activation, additional phosphorylation of calcium channels, and an enhanced force of contraction.

# Positive Inotropic Agents

## Phosphodiesterase Inhibitors:

PDE inhibition leads to accumulation of cAMP and cGMP leading to positive inotropic activity and peripheral vasodilation.

Toxic: arrhythmias, and thrombocytopenia.

Short acting, so reserved for parenteral therapy of acute heart failure.

Inamrinone (PDE-3)

Milrinone (PDE-3)

Vesanirone (PDE-3)

Sildenafil (PDE-5)

# Vasodilators

- Affect preload and/or afterload without directly affecting contractility.
- Consequently can decrease myocardial ischemia, enhance coronary blood flow and decrease MVO.2
- Can be used in acute heart failure and for short periods in CCHF.
- Hydralazine-Isosorbide dinitrate combination was found to decrease mortality, maybe by reducing remodeling of the heart.
- Can be combined with ACEI, Diuretics and digitalis.

# BNP-Niseritide

- Brain (B-type) natriuretic peptide (BNP) is secreted constitutively by ventricular myocytes in response to stretch.

- BNP binds to receptors in the vasculature, kidney, and other organs, producing potent vasodilation with rapid onset and offset of action by increasing levels of cGMP.

- Niseritide is a recombinant human BNP approved for treatment of acute decompensated CHF .

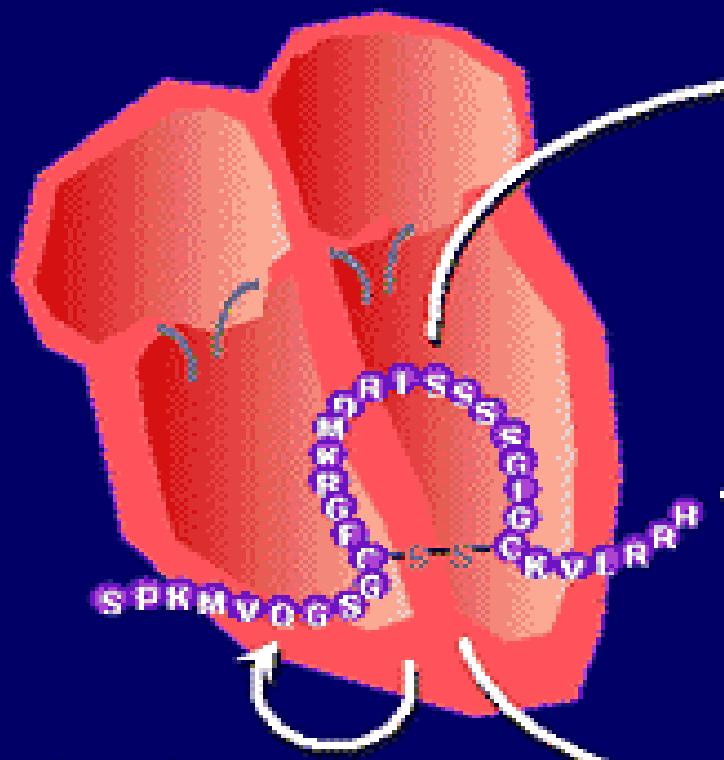
# BNP-Niseritide

- Reduces systemic and pulmonary vascular resistances, causing an indirect increase in cardiac output and diuresis .
- Effective in HF because of reduction in preload and afterload.
- Hypotension is the main side effect.

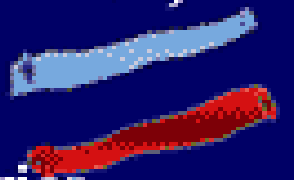
The treatment of heart failure depends on classifying patients into four stages (A–D) according to the severity of the condition.
**As the disease progresses, the need for combination therapy increases.**

- **Stage A** (high risk with no symptoms or structural disease):
Management includes patient education and treatment of predisposing conditions such as hypertension, diabetes, and dyslipidemia. Many patients are started on ACE inhibitors or angiotensin receptor blockers (ARBs) when clinically appropriate.
- **Stage B** (structural heart disease but no symptoms):
All patients should receive ACE inhibitors and beta blockers, which help slow disease progression.
- **Stage C** (structural heart disease with current or previous symptoms):
All patients are treated with ACE inhibitors and beta blockers, and additional therapy may include dietary sodium restriction, diuretics, and digoxin.
- **Stage D** (refractory end-stage heart failure):
Patients continue all appropriate treatments from Stages A, B, and C, but often require advanced non-pharmacological options, such as heart transplantation or ventricular assist devices (VADs).

# Pharmacologic Actions of Human BNP

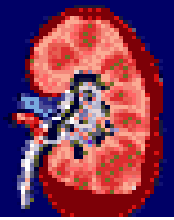



Hemodynamic
(balanced vasodilation)
- veins
- arteries
- coronary arteries



Neurohumoral
- ↓ aldosterone
- ↓ endothelin
- ↓ norepinephrine

Renal
- ↑ diuresis
- ↑ natriuresis



Cardiac
lusiotropic
anti-fibrotic
anti-remodeling

# Sacubitril

- **Neprilysin inhibitor used in combination with valsartan *(Entresto)* to reduce the risk of cardiovascular events in patients with chronic heart failure.**
- **Also breaks down angiotensin I and II, endothelin-1 and peptide amyloid beta-protein.**

# PHARMACOLOGY QUIZ LECTURE 7

# Scan the QR code or click it for FEEDBACK

Corrections from previous versions:

| Versions | Slide # and Place of Error | Before Correction | After Correction |
|---|---|---|---|
| V0 → V1 | | | |
| V1 → V2 | | | |