Heart Failure

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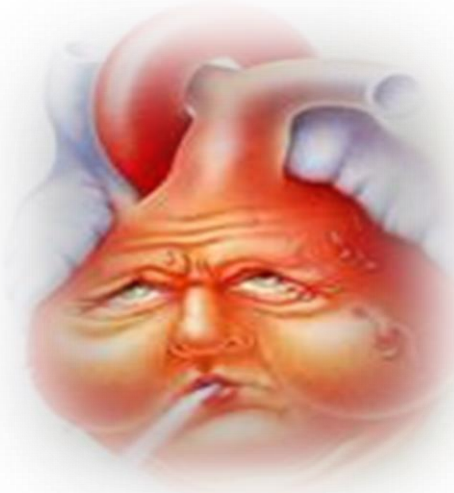


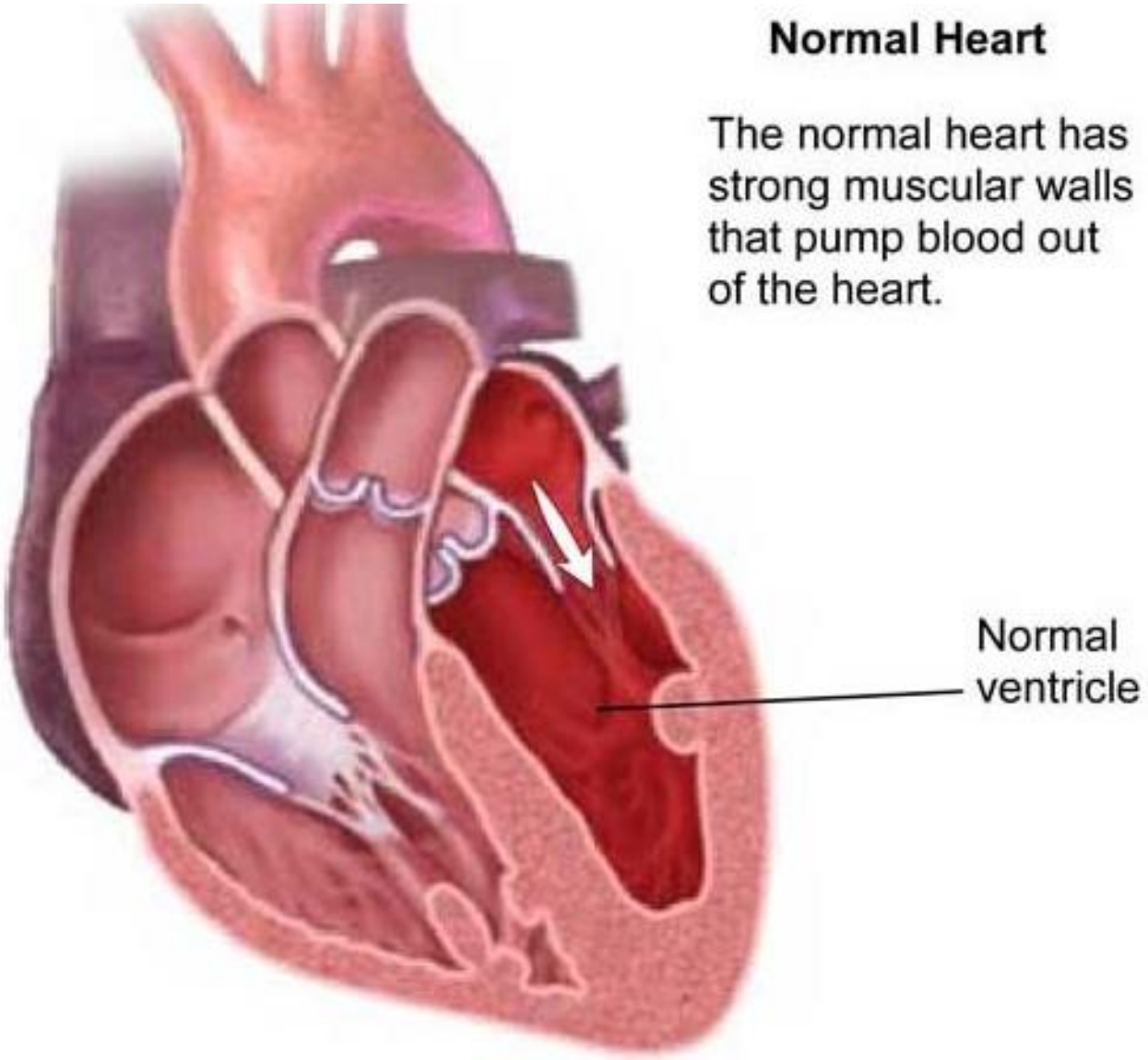
Heart Failure

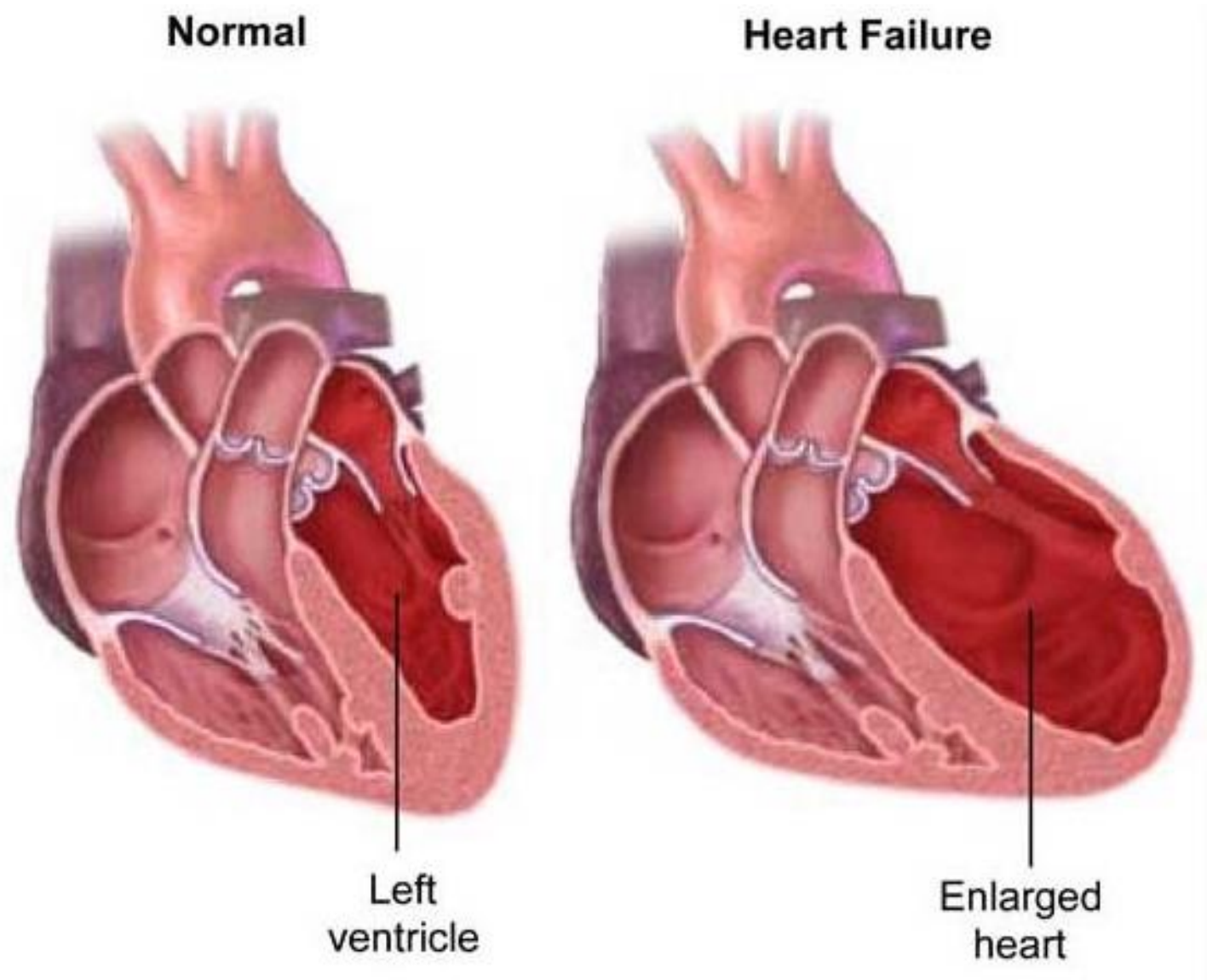
- **Heart is unable to pump sufficient blood to meet the needs of the body. It is key symptoms are dyspnea, fatigue, fluid retention.**

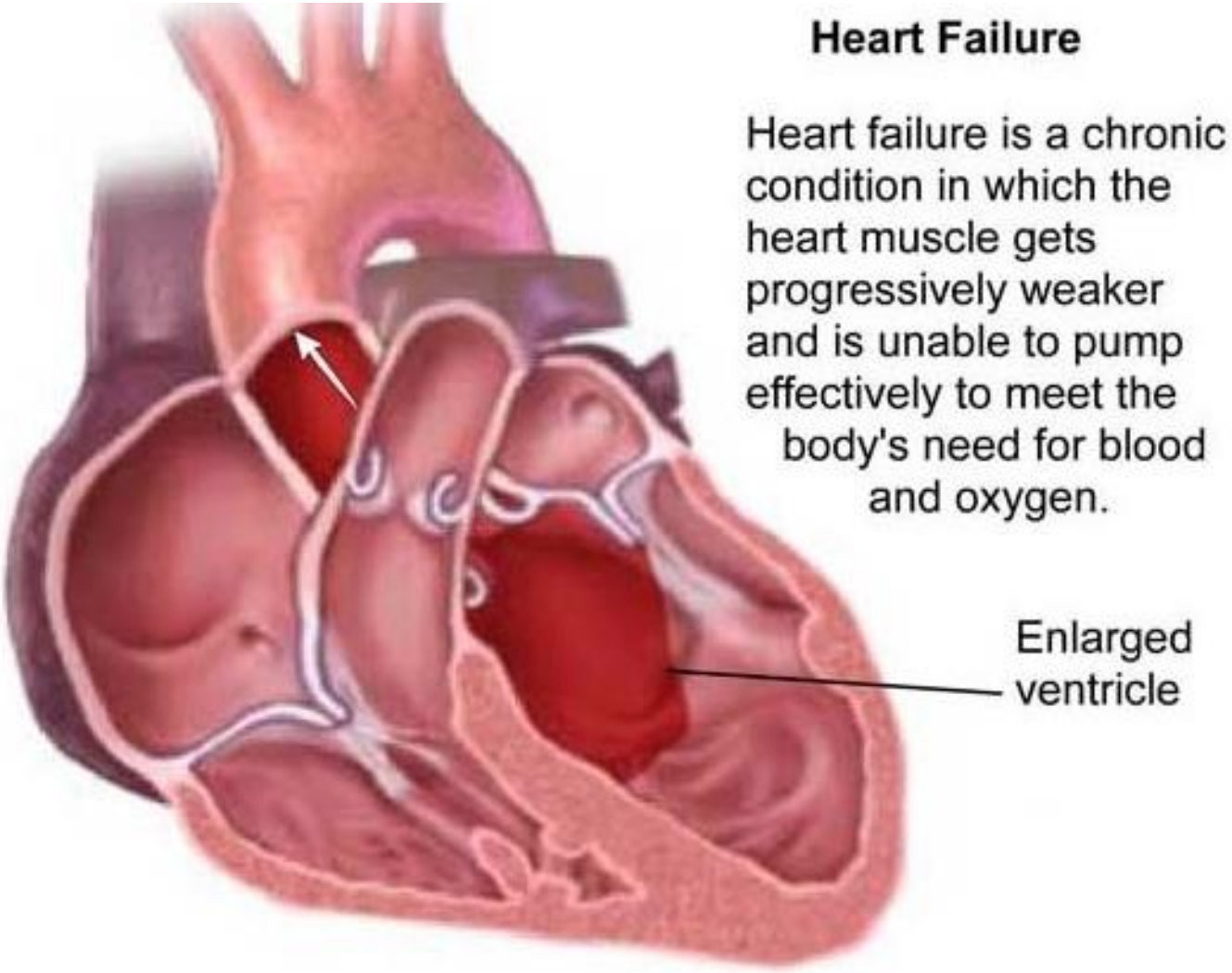
- **HF is due to an impaired ability of the heart to adequately fill with or eject blood.**

- **Underlying causes of HF include atherosclerosis heart disease, myocardial infarction, hypertension, valvular heart disease.**

- **Left systolic dysfunction secondary to coronary artery disease is the most common cause, account to 70% of all cases.**


Normal Heart
The normal heart has strong muscular walls that pump blood out of the heart.
Normal ventricle


Normal
Heart Failure
Left ventricle
Enlarged heart


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

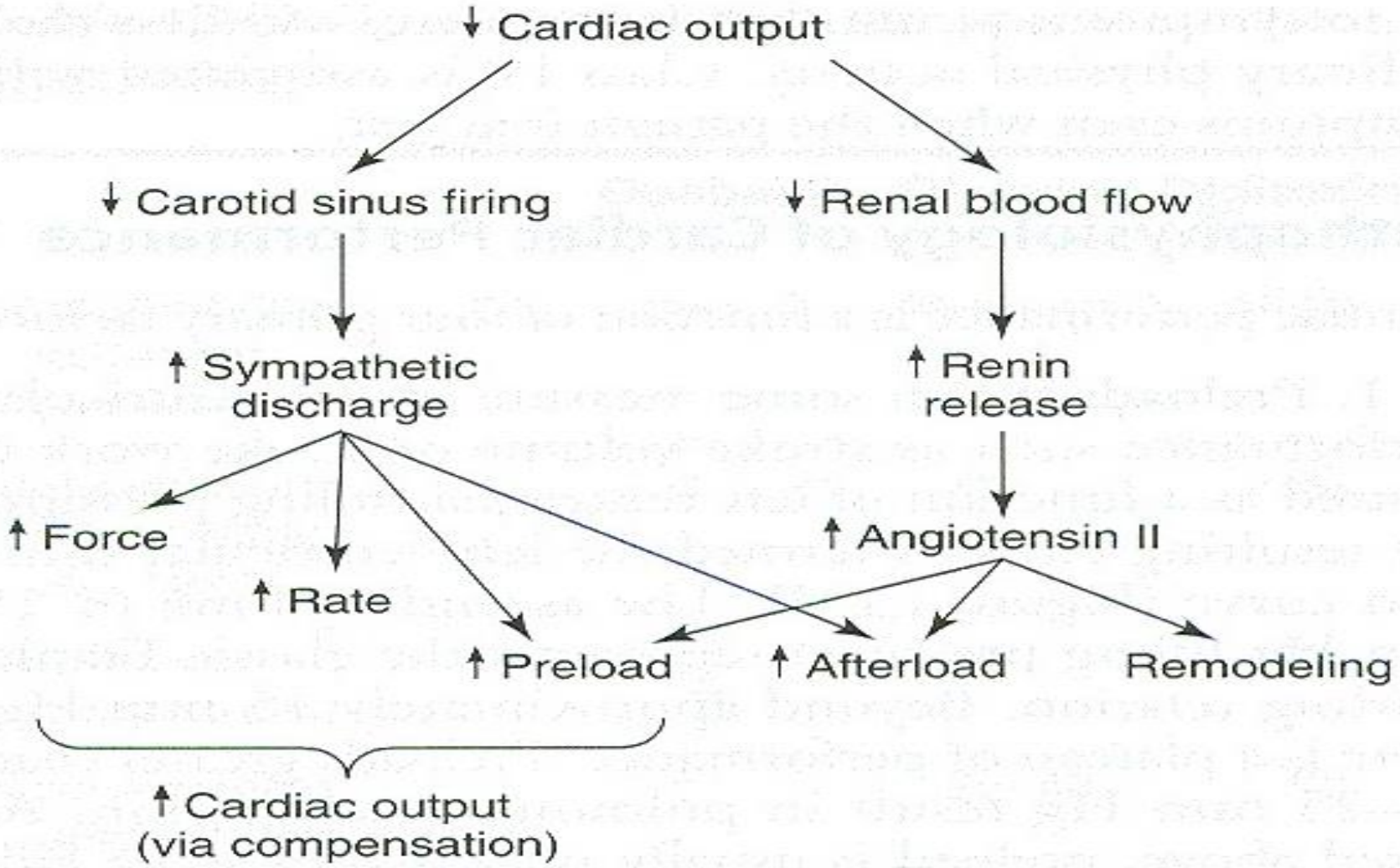


Figure 13–2. Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.

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.

Treating HF

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

Six Classes of drugs have been shown to be effective

(1)ACE inhibitors

(2)β-adrenergic blocking agents

(3)diuretics

(4)inotropic agents

(5)direct vasodilators

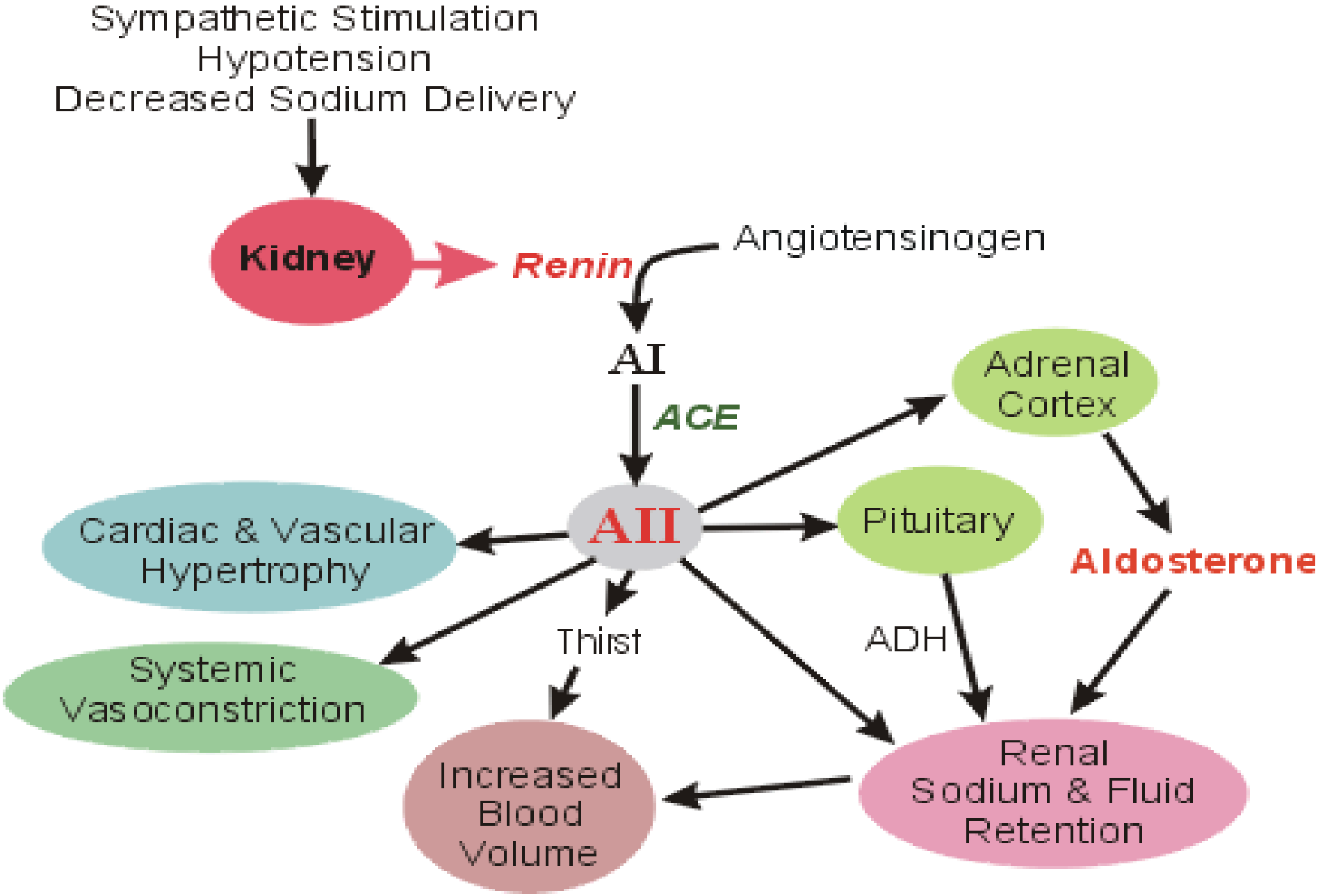
(6)aldosterone antagonist

- 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 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



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 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 ,misoprolol, 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.

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

- 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 .

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

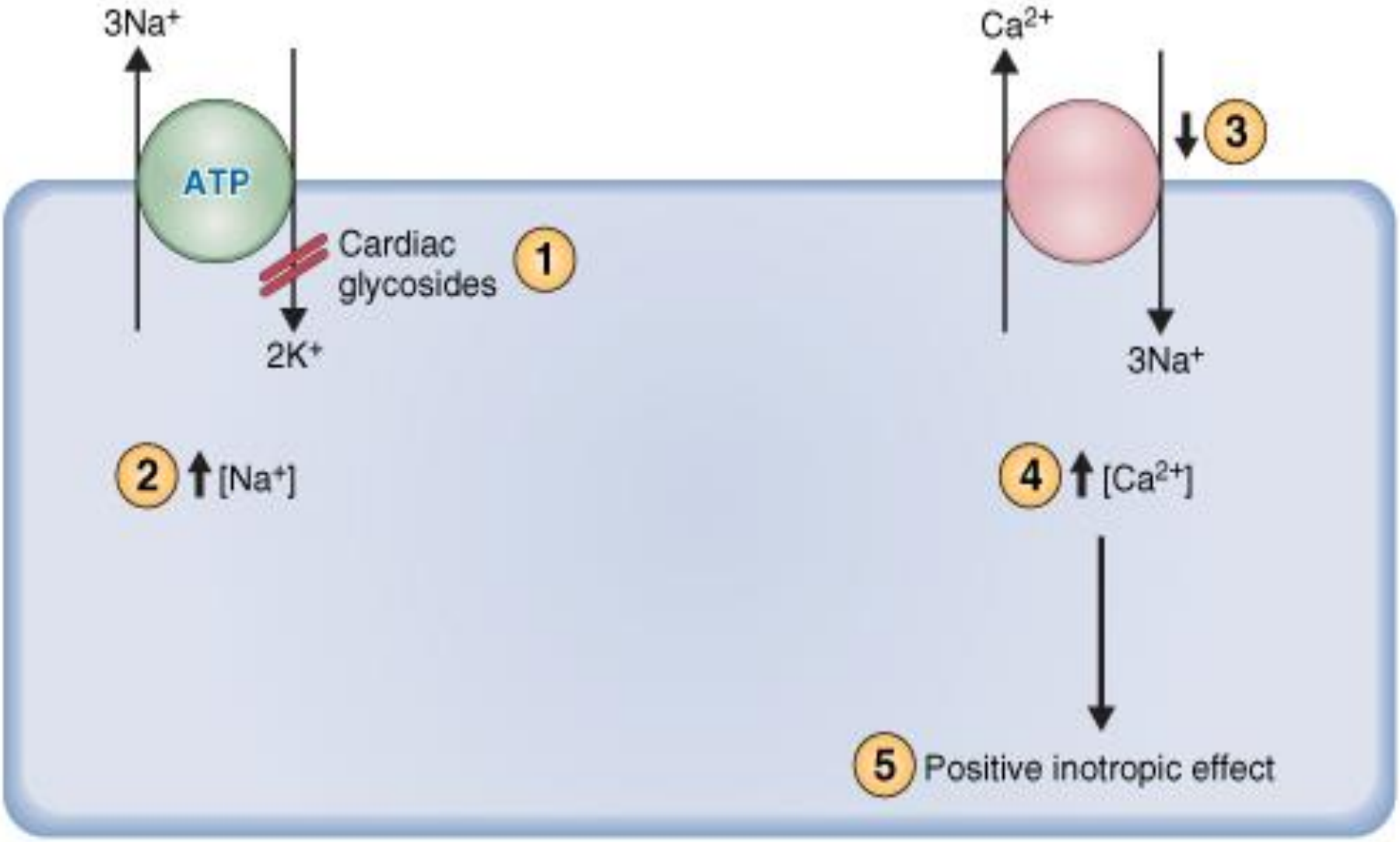
Inotropic drugs (Digitalis)

- **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.**

POSITIVE INOTROPIC EFFECT OF CARDIAC GLYCOSIDES



Digitalis Glycosides

Actions :

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

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 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.***
- ***Dobutamine (another inotropic agent) can be given intravenously in hospitals.***

Digitalis Toxicity

- G.I.T.(Anorexia, nausea, intestinal cramping, diarrhea)
- Visual (Xanthopsia,abnormalities in color vision)
- 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 .**

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.**

Drug interactions

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

Important

- **NSAID use can cause salt and water retention and so worsen the HF.**
- **Itraconazole 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:

®-adrenergic Agonists:

- NE
- Dopamine
- Dobutamine

Phosphodiesterase Inhibitors:

- Amrinone
- Inamrinone
- Milrinone
- Vesanirone
- Sildenafil

Positive Inotropic Agents

Cyclic AMP Dependent Agents:

®-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

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 β_1 receptors leading to positive inotropic actions.
- High doses: stimulate α receptors leading to vasoconstriction and elevation of blood pressure .
- Can cause arrhythmias and ischemic changes.

Dobutamine:

- Selective β_1 agonist, used intermittently (IV) in CCHF. Produces mild vasodilation.
- Has more inotropic than chronotropic actions.

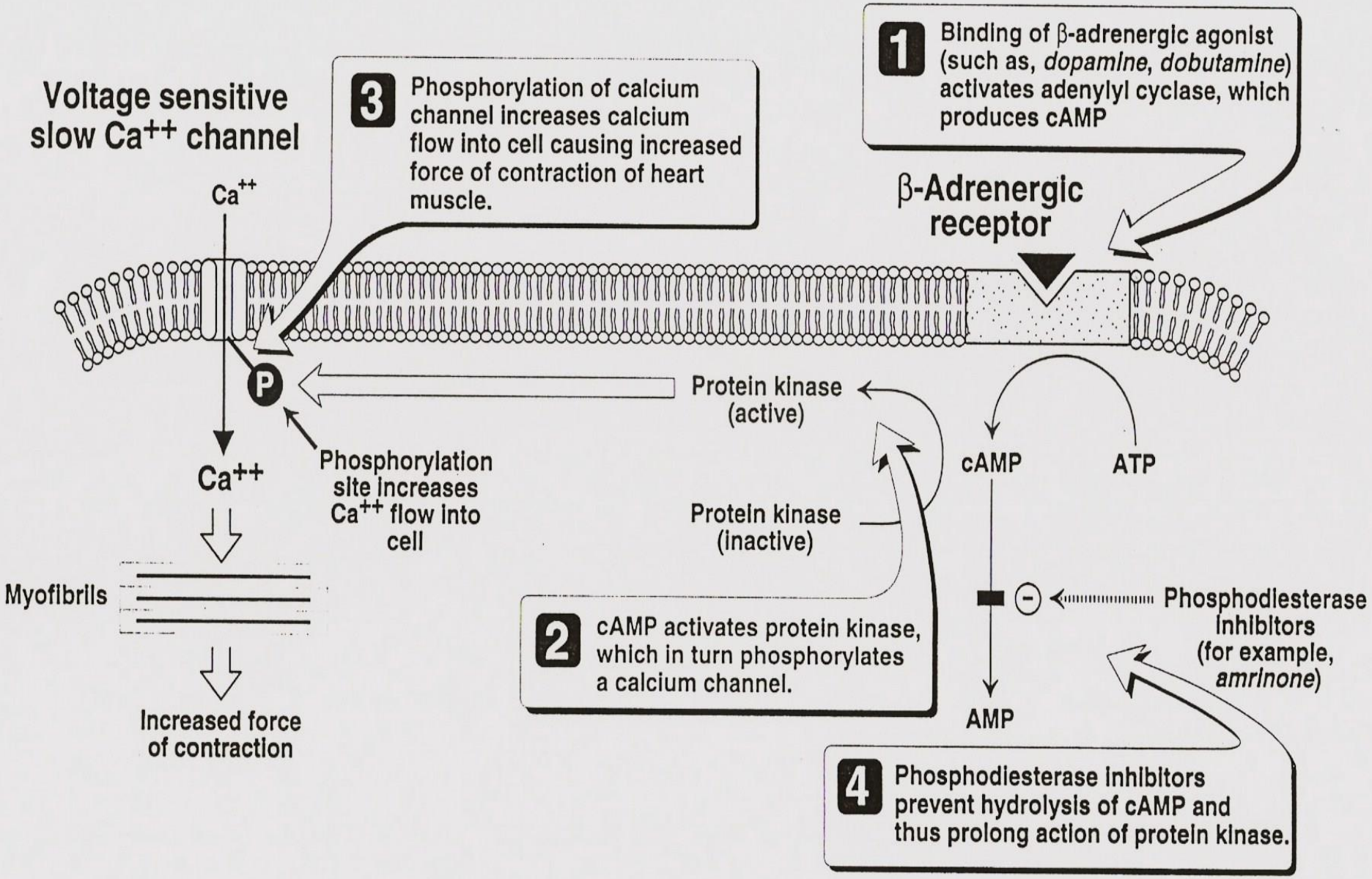


Figure 16.11
Sites of action of β-adrenergic agonists on heart muscle.

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 .

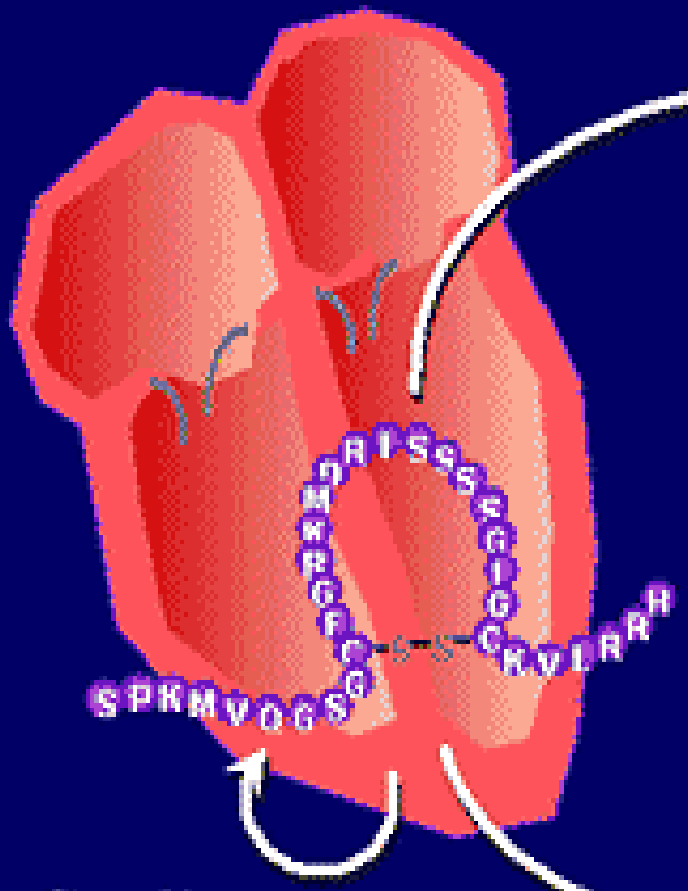
)BNP)-Niseritide

- Reduces systemic and pulmonary vascular resistances, causing an indirect increase in cardiac output and diuresis .

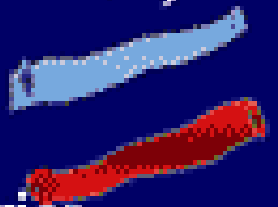
- Effective in HF because of reduction in preload and afterload.

- Hypotension is the main side effect.

Pharmacologic Actions of Human BNP



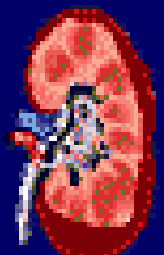
Hemodynamic
(balanced vasodilation)
- veins
- arteries
- coronary arteries



Neurohumoral
↓ aldosterone
↓ endothelin
↓ norepinephrine

Cardiac
lusiotropic
anti-fibrotic
anti-remodeling

Renal
↑ diuresis
↑ natriuresis



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.**