



Heart Failure

- Heart is unable to pump sufficient blood to meet the needs of the body. Its 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.

Physiological responses in HF

- Failure of the heart activate three major compensatory mechanism in order to enhance the heart out put:
- Increase sympathetic activity, Baroreflex activate the sympathetic activity (β , alpha 1 receptors) resulting in an increase the work on the heart, and so further declining in cardiac function.
- Activate the renin-angiotensin system, will also increase the work on the heart by increasing the peripheral resistance and blood volume.

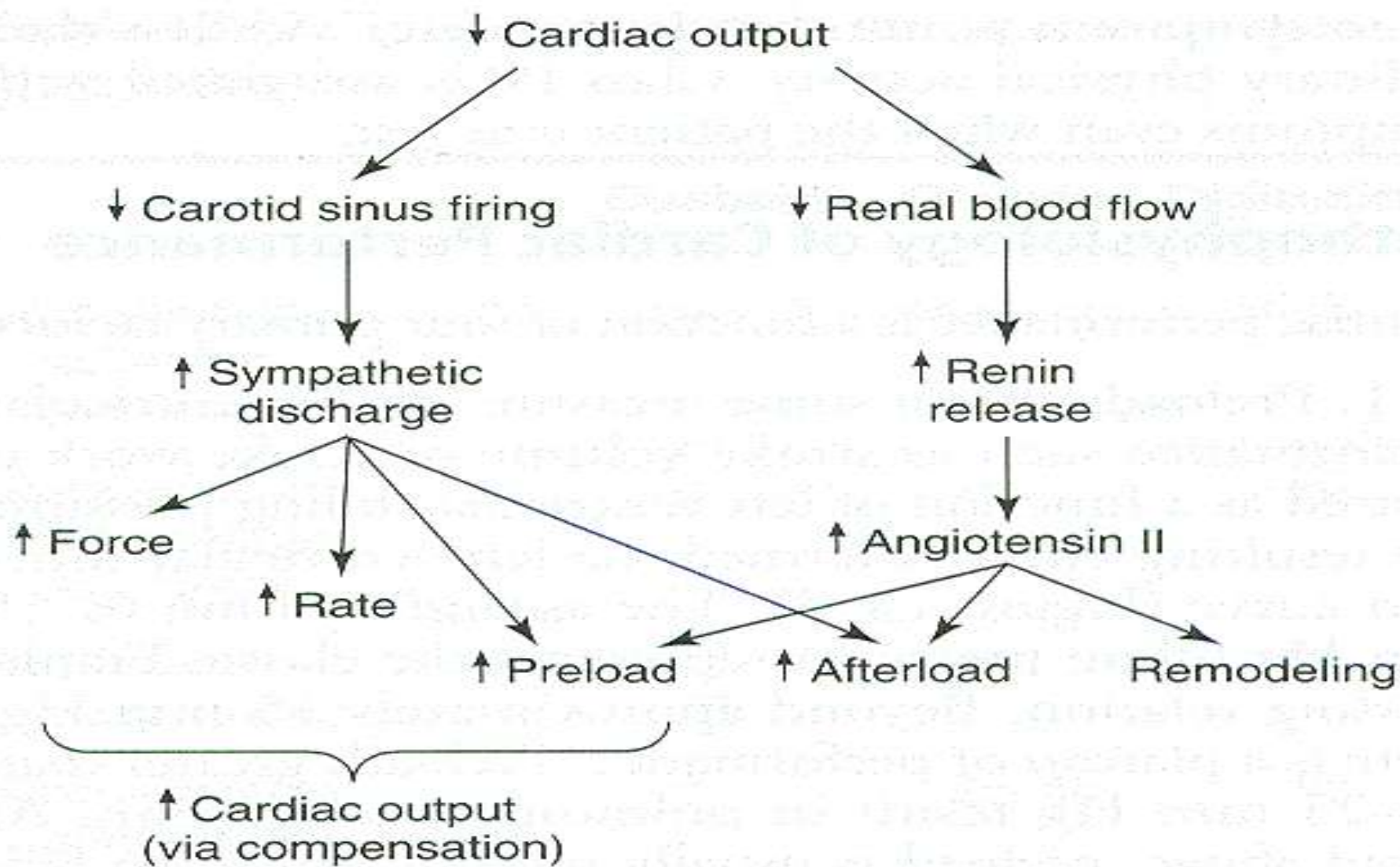


Figure 13–2. Some compensatory responses that occur during congestive heart failure. In addition to the effects shown, angiotensin II increases sympathetic effects by facilitating norepinephrine release.

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) decrease the symptoms.
- (2) slow disease progression,
- (3) improve survival.

Six Classes of drugs have been shown to be effective

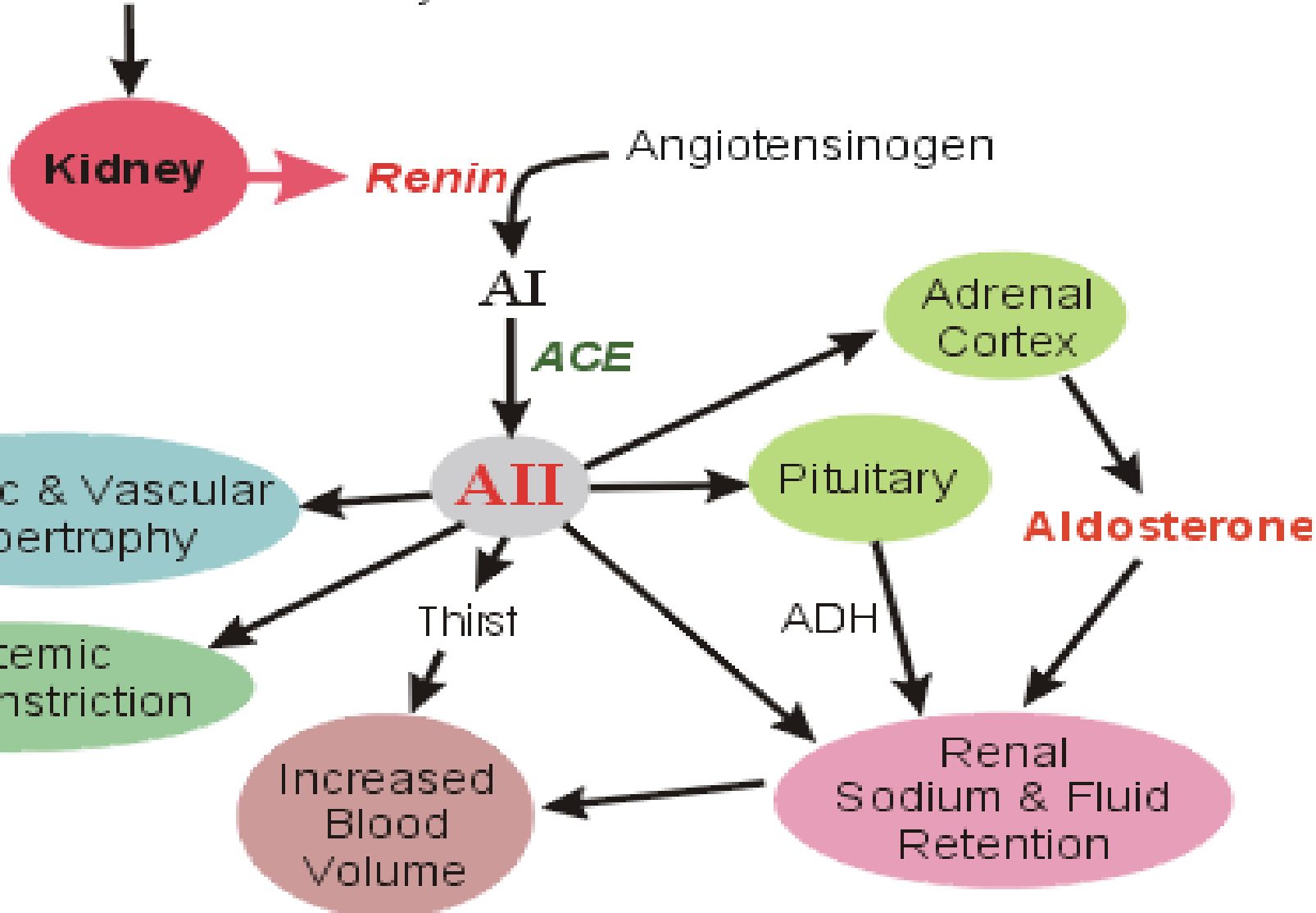
- (1) ACE inhibitors,
 - (2) β -adrenergic blocking agents,
 - (3) diuretics,
 - (4) **inotropic agents**,
 - (5) direct vasodilators, and
 - (6) aldosterone antagonist.
- Depending on the severity of HF and individual patient factors, one or more of these classes of drugs are administered.

ACE Inhibitors

- **Decreases vascular resistance and so blood pressure, resulting in an increase in the cardiac output.**
- **They also blunt the usual angiotensin II-mediated increase in adrenaline and aldosterone 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

Sympathetic Stimulation
Hypotension
Decreased Sodium Delivery



ACE Inhibitors

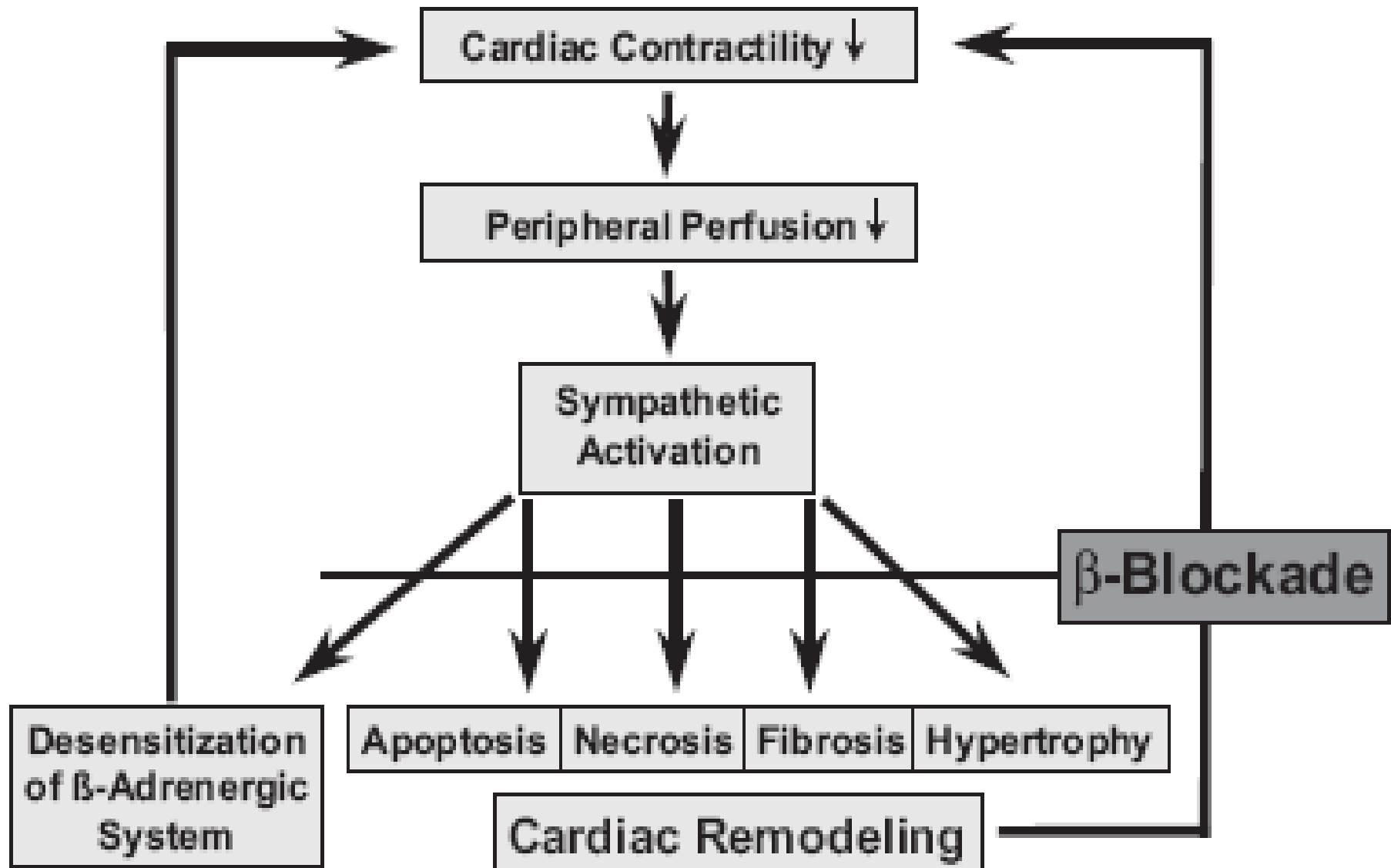
Adverse effects :

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



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.

Spirolactone

- Generally Patient with advanced heart disease have elevated levels of aldosterone due to angiotension II stimulation and decrease hepatic clearance of this hormone.
- Spirolactone is a direct antagonist of aldesterone, and so prevent sodium retention, myocardial hypertrophy, and hypokalemia.
- Spirolactone 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

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.

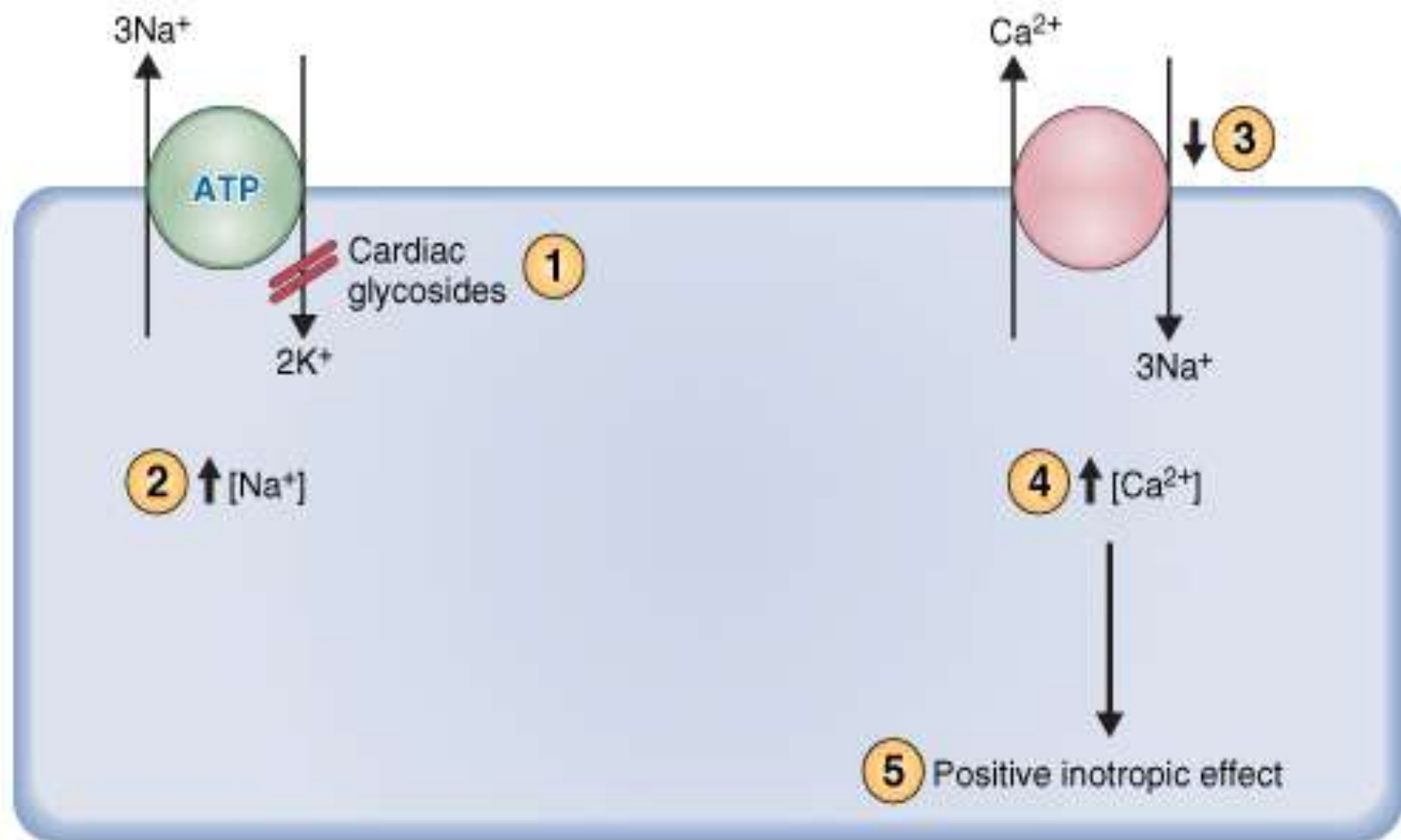


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Inotropic drugs (Digitalis)

- 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 fatal. So these agents have a low therapeutic index or window.

POSITIVE INOTROPIC EFFECT OF CARDIAC GLYCOSIDES



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 is 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.

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

these signs includes:

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

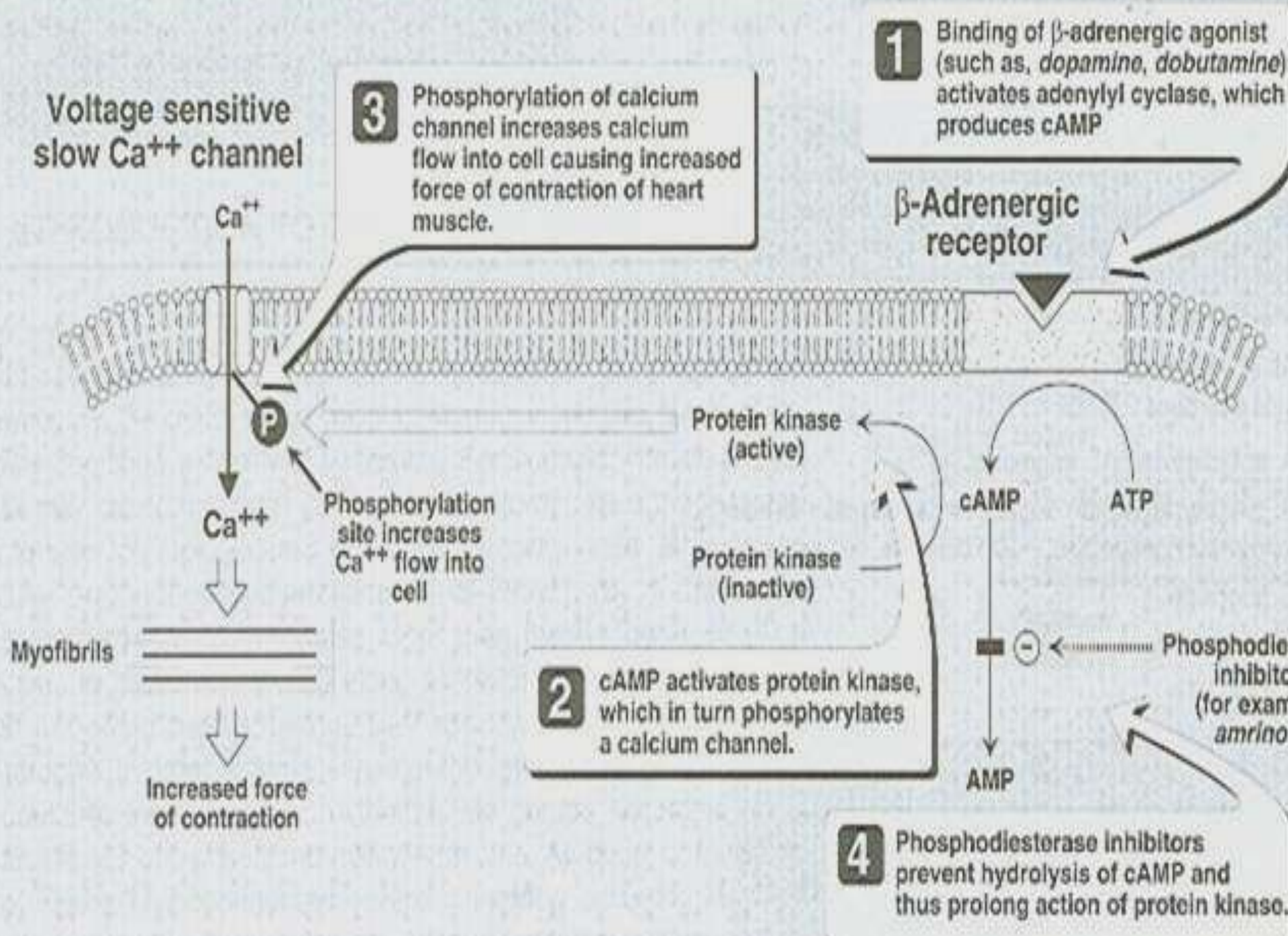
Digoxin interaction:

Quinidine, verapamil, 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

β -adrenergic agonist and Amrinone

- Dobutamine is a B1 adrenergic agonist that has positive inotropic effect and is the most used inotropic agent after digoxin.
- 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.
- Amrinone used in short term therapy of HF that is refractory to other agents.



Voltage sensitive slow Ca^{++} channel

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

2 cAMP activates protein kinase, which in turn phosphorylates a calcium channel.

4 Phosphodiesterase inhibitors prevent hydrolysis of cAMP and thus prolong action of protein kinase.

Myofibrils

Increased force of contraction

Phosphorylation site increases Ca^{++} flow into cell

Protein kinase (active)

Protein kinase (inactive)

Phosphodiesterase inhibitor (for example *amrinon*)

Ca^{++}

Ca^{++}

cAMP

ATP

AMP

Increased force of contraction

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.

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.



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- **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.