Pharmacology

Dentistry Department

3rd Grade

Drugs for Heart Failure

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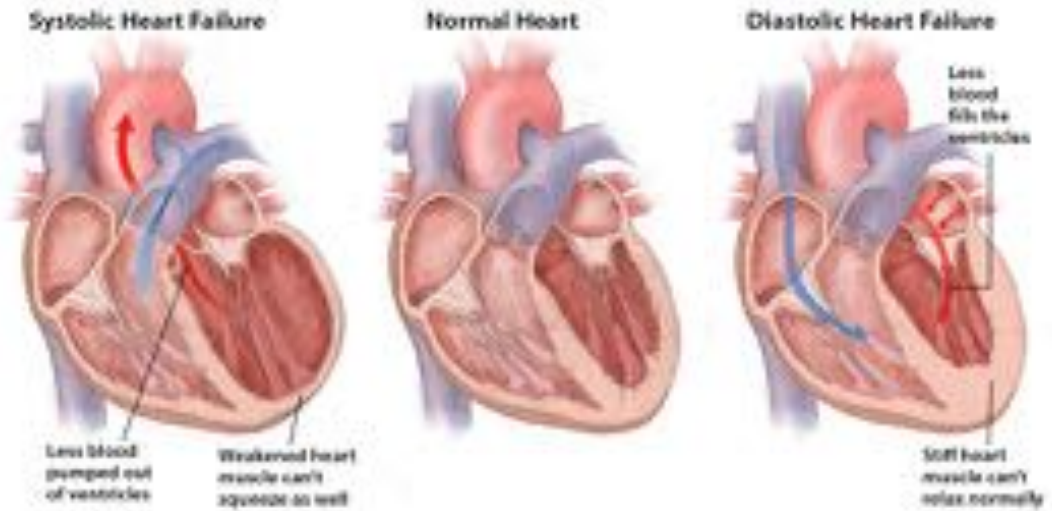
Heart Failure:

- **Heart failure (HF)** is a complex, progressive disorder in which **the heart is unable to pump sufficient blood to meet the needs of the body.**
- **Its cardinal symptoms are dyspnea, fatigue, and fluid retention**.
- HF is due to an **impaired ability of the heart to adequately fill with and/or eject blood.** It is often accompanied by **abnormal increases in blood volume and interstitial fluid.**
- Underlying causes of HF include **arteriosclerotic heart disease, myocardial infarction, hypertensive heart disease, valvular heart disease, dilated cardiomyopathy, and congenital heart disease**.

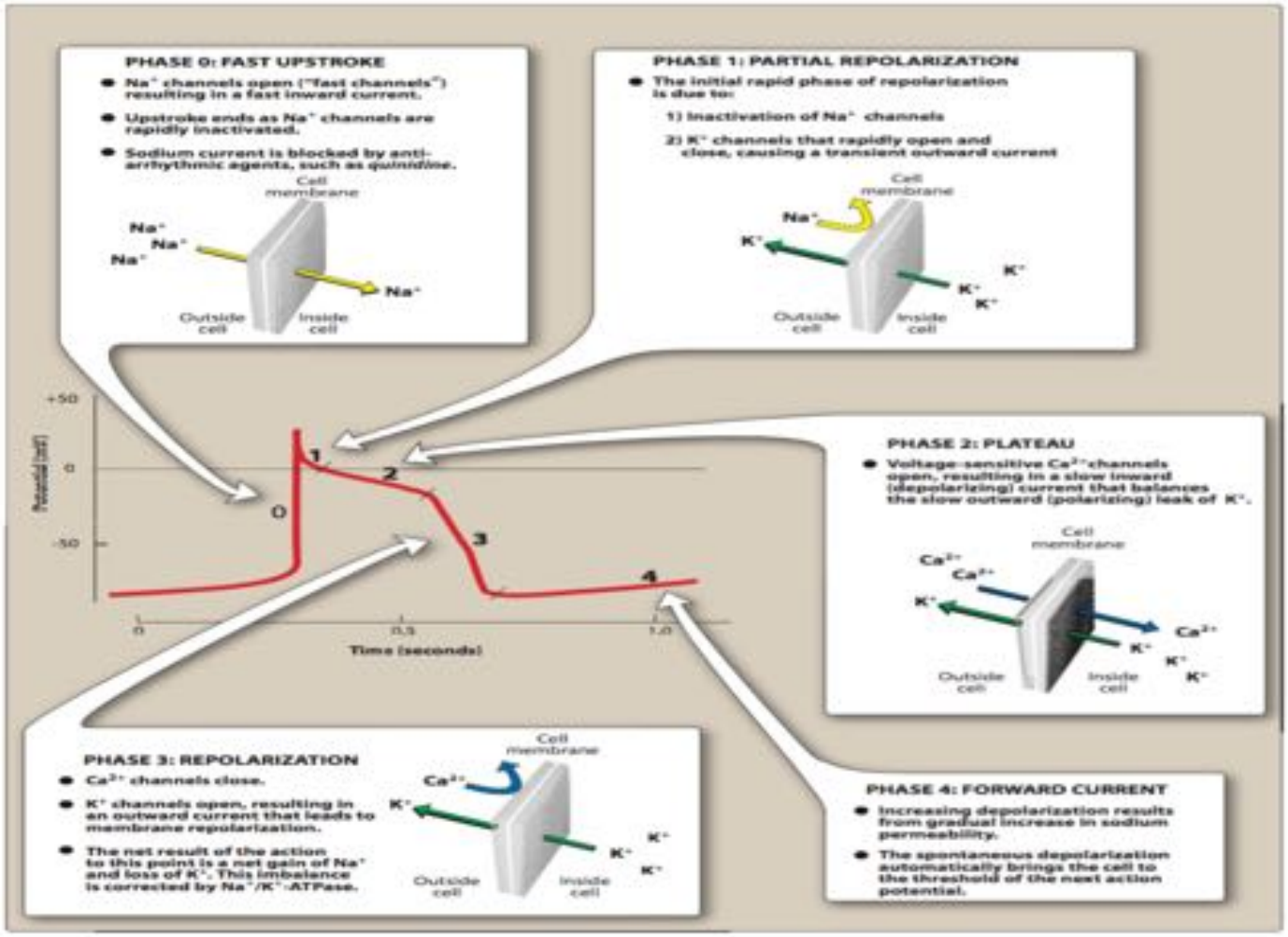


PHYSIOLOGY OF MUSCLE CONTRACTION

- **The myocardium**, like smooth and skeletal muscle, responds to stimulation by **depolarization of the membrane**, which is followed by **shortening of the contractile proteins (contraction)** and and return to the resting state (repolarization). Cardiac myocytes are interconnected in groups that respond to stimuli as a unit, contracting together whenever a single cell is stimulated.

A. Action potential:

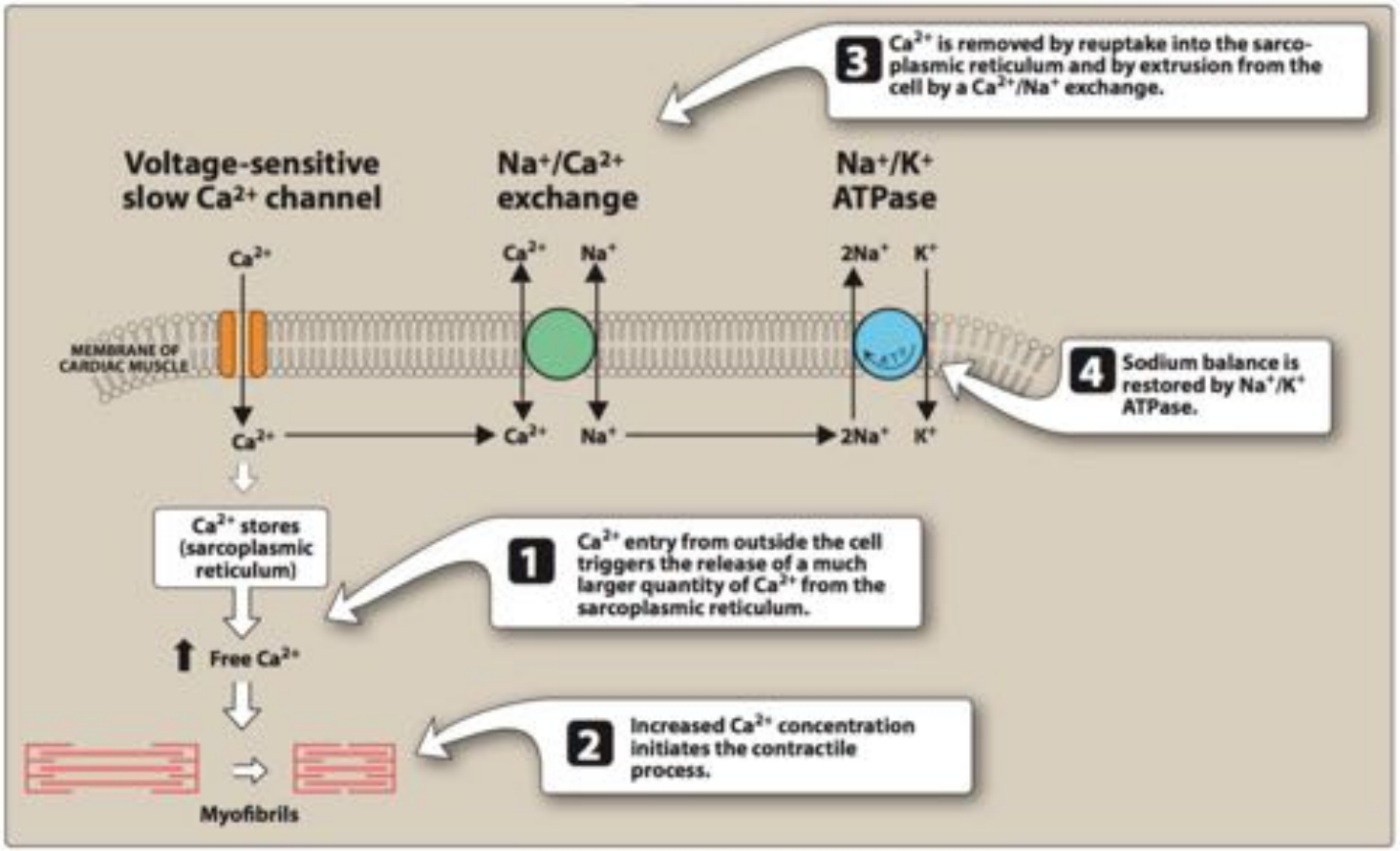
- Cardiac myocytes are **electrically excitable and have a spontaneous**, intrinsic rhythm generated by specialized **"pacemaker"** cells located in the **sinoatrial (SA)and atrioventricular (AV) nodes**. Cardiac myocytes also have an unusually long action potential, which can be divided **into five phases (0 to 4).**


PHASE 0: FAST UPSTROKE
Na+ channels open ("fast channels") resulting in a fast inward current.
Upstroke ends as Na+ channels are rapidly inactivated.
Sodium current is blocked by anti-arrhythmic agents, such as quinidine.
Cell membrane
Na+
Na+
Na+
Na+
Outside cell
Inside cell
PHASE 1: PARTIAL REPOLARIZATION
The initial rapid phase of repolarization is due to:
1) Inactivation of Na+ channels
2) K+ channels that rapidly open and close, causing a transient outward current
Cell membrane
Na+
K+
K+
K+
K+
Outside cell
Inside cell
+50
0
-50
Potential (mV)
0
1
2
3
4
0
0.5
1.0
Time (seconds)
PHASE 2: PLATEAU
Voltage-sensitive Ca2+ channels open, resulting in a slow inward (depolarizing) current that balances the slow outward (polarizing) leak of K+.
Cell membrane
Ca2+
Ca2+
K+
Ca2+
K+
K+
K+
Outside cell
Inside cell
PHASE 3: REPOLARIZATION
Ca2+ channels close.
K+ channels open, resulting in an outward current that leads to membrane repolarization.
The net result of the action to this point is a net gain of Na+ and loss of K+. This imbalance is corrected by Na+/K+-ATPase.
Cell membrane
Ca2+
K+
K+
K+
K+
Outside cell
Inside cell
PHASE 4: FORWARD CURRENT
Increasing depolarization results from gradual increase in sodium permeability.
The spontaneous depolarization automatically brings the cell to the threshold of the next action potential.

B. Cardiac contraction

- The **force of contraction of the cardiac muscle** is directly related to the **concentration of free (unbound) cytosolic calcium.**
- The agents **that increase intracellular calcium levels** (or that increase the sensitivity of the contractile machinery to calcium) **increase the force of contraction (inotropic effect).**

- The **inotropic agents** increase the contractility of the heart by directly or indirectly **altering the mechanisms that control the concentration of intracellular calcium.**


3 Ca2+ is removed by reuptake into the sarcoplasmic reticulum and by extrusion from the cell by a Ca2+/Na+ exchange.
Voltage-sensitive slow Ca2+ channel
Na+/Ca2+ exchange
Na+/K+ ATPase
Ca2+
Ca2+
Na+
2Na+
K+
MEMBRANE OF CARDIAC MUSCLE
4 Sodium balance is restored by Na+/K+ ATPase.
Ca2+
Ca2+
Na+
2Na+
K+
Ca2+ stores (sarcoplasmic reticulum)
1 Ca2+ entry from outside the cell triggers the release of a much larger quantity of Ca2+ from the sarcoplasmic reticulum.
Free Ca2+
2 Increased Ca2+ concentration initiates the contractile process.
Myofibrils

Compensatory physiological responses in HF:

- The **failing heart evokes three major compensatory mechanisms to enhance cardiac output.** Although initially beneficial, these alterations ultimately result in further deterioration of cardiac function.

1. Increased sympathetic activity:

- **Baroreceptors sense a decrease in blood pressure and activate the sympathetic nervous system.**
- In an attempt to sustain tissue perfusion, **this stimulation of β-adrenergic receptors results in an increased heart rate and a greater force of contraction of the heart muscle.**
- In addition, **vasoconstriction enhances venous return and increases cardiac pre- load.**
- **An increase in preload (stretch on the heart) increases stroke volume, which, in turn, increases cardiac output.** These compensatory responses **increase the work of the heart, which, in the long term, contributes to further decline in cardiac function.**

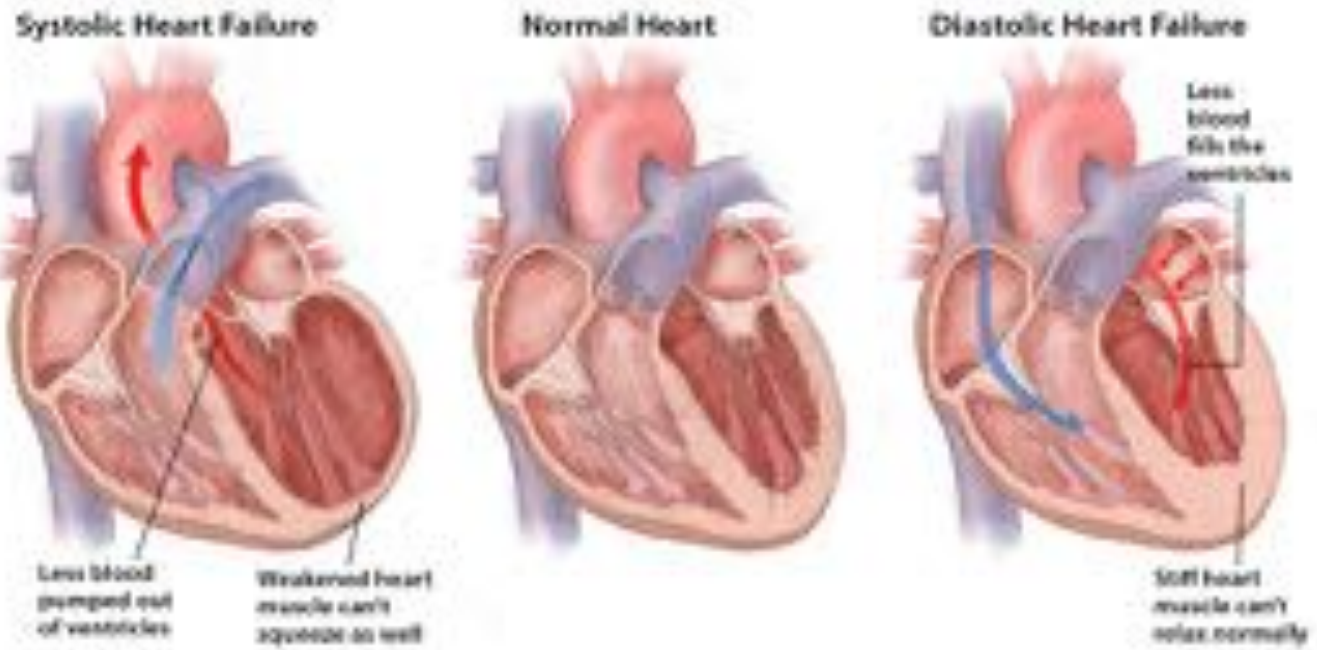
2. Activation of the renin–angiotensin–aldosterone system:

- A fall in cardiac output decreases blood flow to the kidney, prompting the **release of renin, and resulting in increased formation of angiotensin II and release of aldosterone.**
- This results **in increased peripheral resistance (afterload) and retention of sodium and water.**
- **Blood volume increases, and more blood is returned to the heart (increases the pre-load)**. If the heart is unable to pump this extra volume, venous pressure increases and peripheral and pulmonary edema occur.
- Again, these compensatory responses increase the work of the heart, contributing to further decline in cardiac function.

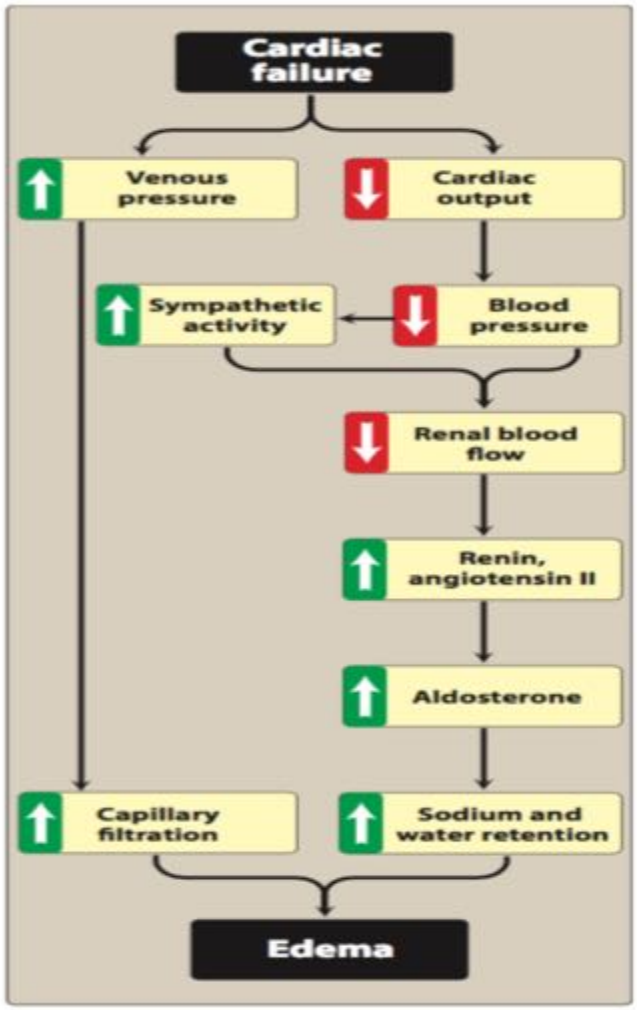
3. Myocardial hypertrophy:

- **The heart increases in size**, and the chambers dilate and become more globular. **Initially, stretching of the heart muscle leads to a stronger contraction of the heart**.
- However, **excessive elongation of the fibers results in weaker contractions**, and the geometry **diminishes the ability to eject blood**. This type of failure is **termed "systolic failure"** and is the result of the **ventricle being unable to pump effectively.**
- Less commonly, patients with HF may have **"diastolic dysfunction**," a term applied when the **ability of the ventricles to relax and accept blood is impaired by structural changes such as hypertrophy.**
- The **thickening of the ventricular wall and subsequent decrease in ventricular volume** decrease the ability of heart muscle to relax. In this case, the ventricle does not fill adequately, and the inadequacy of cardiac output is termed **"diastolic HF**".
- Diastolic dysfunction, in its pure form, is characterized by signs and symptoms of HF in the presence of a normal functioning left ventricle. **However, both systolic and diastolic dysfunction commonly coexist in HF.**

3. Myocardial hypertrophy:



- **Acute (decompensated) HF**
- If the adaptive mechanisms adequately restore cardiac output, **HF is said to be compensated.**
- If the adaptive mechanisms **fail to maintain cardiac output**, **HF is decompensated** and the patient develops worsening HF signs and symptoms.
- Typical HF signs and symptoms include **dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, fatigue, and peripheral edema.**



- **Therapeutic strategies in HF**
- Chronic HF is typically managed by **fluid limitations** (less than 1.5 to 2 L daily); **low dietary intake of sodium** (less than 2000 mg/d);
- Treatment of comorbid conditions; and judicious use of **diuretics**.
- **Inhibitors of the renin–angiotensin–aldosterone system**.
- **Inhibitors of the sympathetic nervous system**.
- **Inotropic agents** are reserved for acute HF signs and symptoms.
- Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, **some calcium channel blockers (verapamil and diltiazem),** and some antiarrhythmic drugs, should be avoided if possible.

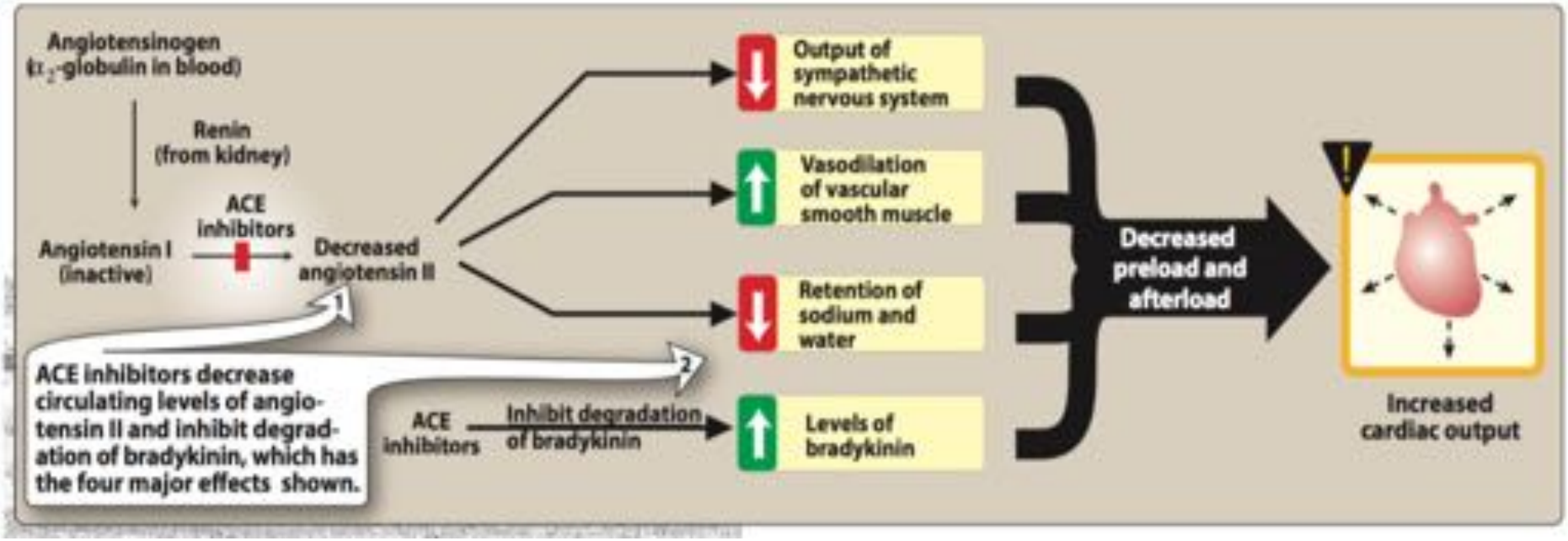
1-INHIBITORS OF THE RENIN–ANGIOTENSIN– ALDOSTERONE SYSTEM

A. Angiotensin-converting enzyme inhibitors

- Angiotensin-converting enzyme **(ACE) inhibitors** are a part of standard pharmacotherapy in HF.
- These **drugs block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II**.
- They also **diminish the inactivation of bradykinin** .
- **Vasodilation occurs as a result of decreased levels of the vasoconstrictor angiotensin II and increased levels of bradykinin (a potent vasodilator).**
- By reducing **angiotensin II levels, ACE inhibitors also decrease the secretion of aldosterone**.

Actions on the heart:

- ACE inhibitors **decrease vascular resistance (afterload) and venous tone (preload), resulting in increased cardiac output**.
- **ACE inhibitors also blunt the usual angiotensin II–mediated increase in epinephrine and aldosterone seen in HF**.
- ACE inhibitors improve clinical signs and symptoms of HF and have been shown to significantly improve patient survival in HF



Adverse effects:

- **Postural hypotension, renal insufficiency, hyperkalemia, a persistent dry cough, and angioedema (rare).**
- Potassium levels must be monitored, particularly with concurrent use of potassium supplements, potassium-sparing diuretics, or aldosterone antagonists due to risk of hyperkalemia.
- **ACE inhibitors are teratogenic and should not be used in pregnant women.**

B. Angiotensin receptor blockers (ARBs):

- Angiotensin receptor blockers **(ARBs)** are orally active compounds that **are competitive antagonists of the angiotensin II type 1 receptor.**
- **ARBs have the advantage of more complete blockade of angiotensin II action, because ACE inhibitors inhibit only one enzyme responsible for the production of angiotensin II. Further, ARBs do not affect bradykinin levels.**
- **Although ARBs have a different mechanism of action than ACE inhibitors, their actions on preload and afterload are similar.**
- **Their use in HF is mainly as a substitute for ACE inhibitors in those patients with severe cough or angioedema, which are thought to be mediated by elevated brady-kinin levels.**
- ARBs have an adverse effect profile similar to that of ACE inhibitors. **However, the ARBs have a lower incidence of cough and angioedema.**
- Like ACE inhibitors, **ARBs are contraindicated in pregnancy.**

C. Aldosterone antagonists:

- Patients with advanced heart disease have elevated levels **of aldosterone due to angiotensin II stimulation and reduced hepatic clearance of the hormone.**
- ***Spironolactone*** **is a direct antagonist of aldosterone, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia**.
- ***Eplerenone*** is a competitive antagonist of aldosterone **at mineralocorticoid receptors.** Although similar in action to *spironolactone* at the mineralocorticoid receptor, ***eplerenone*** **has a lower incidence of endocrine-related side effects due to its reduced affinity for glucocorticoid, androgen, and progesterone receptors.**
- Aldosterone antagonists are indicated in patients with **more severe stages of HF or HF and recent myocardial infarction.**

2-β-BLOCKERS

- β-blockers **prevent the changes that occur because of chronic activation of the sympathetic nervous system**.
- These agents **decrease heart rate and inhibit release of renin in the kidneys.**
- In addition, **β-blockers prevent the deleterious effects of norepinephrine on the cardiac muscle fibers, decreasing remodeling, hypertrophy, and cell death.**
- Three β-blockers have shown benefit in HF: ***bisoprolol*** **,*carvedilol*** **, and long-acting *metoprolol succinate***.
- ***Carvedilol*** **is a nonselective β-adrenoreceptor antagonist that also blocks α-adrenoreceptors**, whereas ***bisoprolol*** **and *metoprolol succinate* are β1-selective antagonists.**
- β-Blockade is recommended for all patients **with chronic, stable HF**.
- β-Blockers should also be used with caution with other drugs **that slow AV conduction, such as *amiodarone*, *verapamil*, and *diltiazem*.**

3-DIURETICS:

- Diuretics **relieve pulmonary congestion and peripheral edema**.
- These agents are also useful in **reducing the symptoms of volume overload, including orthopnea and paroxysmal nocturnal dyspnea.**
- **Diuretics decrease plasma volume and, subsequently, decrease venous return to the heart (preload). This decreases cardiac workload and oxygen demand.**
- Diuretics may also **decrease afterload by reducing plasma volume, thereby decreasing blood pressure.**
- **Loop diuretics are the most commonly used diuretics in HF**. These agents are used for patients who require extensive diuresis and those with renal insufficiency.
- As diuretics have **not been shown to improve survival in HF, they should only be used to treat signs and symptoms of volume excess.**

4-VASO- AND VENODILATORS:

- Dilation of **venous blood vessels leads to a decrease in cardiac preload by increasing venous capacitance**. **Nitrates** are commonly used venous dilators to reduce preload for patients with chronic HF.
- **Arterial dilators**, such as ***hydralazine*** **reduce systemic arteriolar resistance and decrease afterload.**
- If the patient is intolerant of ACE inhibitors or β-blockers, or if additional vasodilator response is required, a **combination of *hydralazine* and *isosorbide dinitrate* may be used**.
- Headache, hypotension, and tachycardia are common adverse effects with this combination. Rarely, ***hydralazine*** **has been associated with drug-induced lupus.**

5-INOTROPIC DRUGS:

- **Positive inotropic agents enhance cardiac contractility and, thus, increase cardiac output.**
- Although these drugs act by different mechanisms, the inotropic action is the result of **an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle**.
- All positive inotropes in HF that increase **intracellular calcium concentration have been associated with reduced survival, especially in patients with HF due to coronary artery disease.**
- For this reason, these agents, **with the exception of *digoxin*, are only used for a short period mainly in the inpatient setting.**

A. <u>Digitalis glycosides:</u>

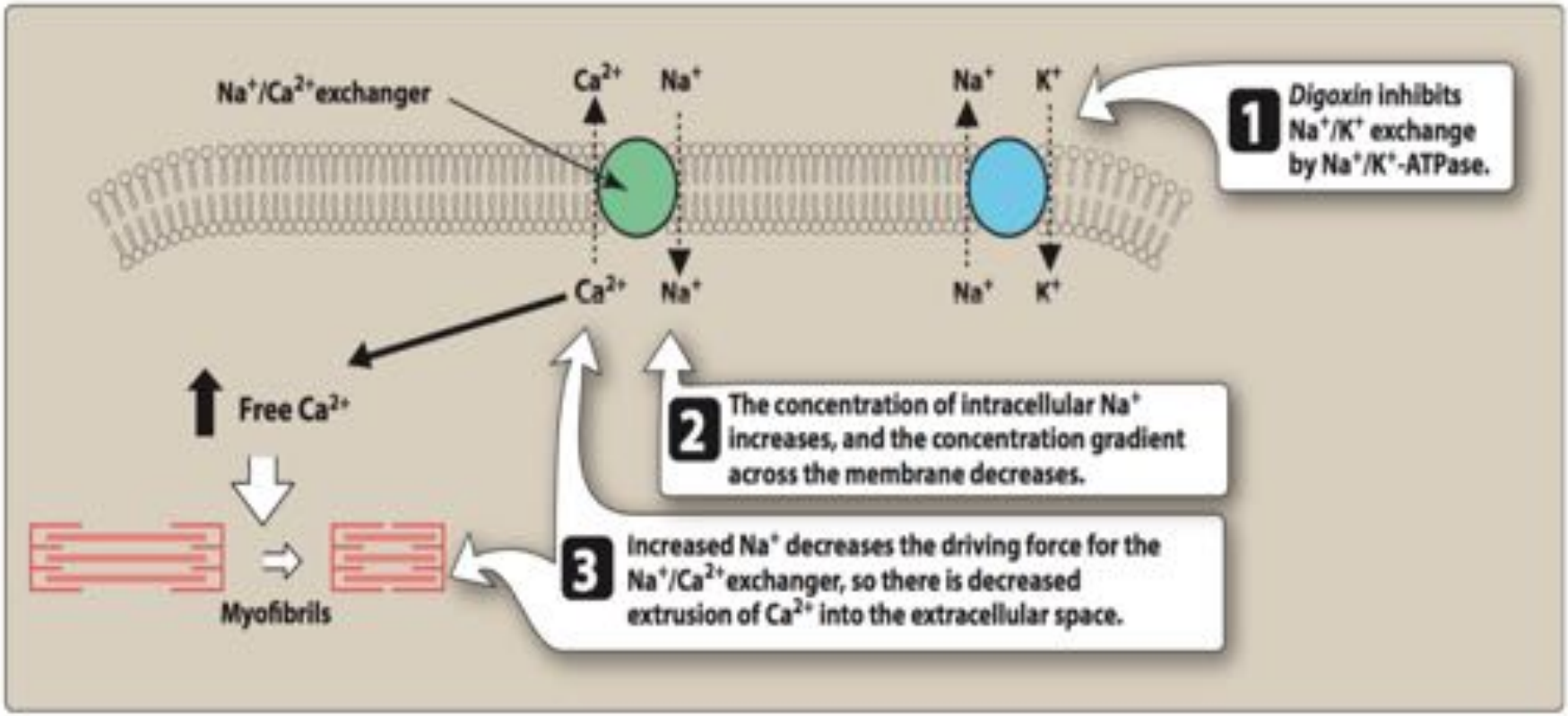
- The cardiac glycosides are often called **digitalis or digitalis glycosides,** because most of the drugs come from the **digitalis (foxglove) plant.**
- They are a group of chemically similar compounds that can **increase the contractility of the heart muscle and, therefore, are used in treating HF.**
- The digitalis glycosides have a **low therapeutic index, with only a small difference between a therapeutic dose and doses that are toxic or even fatal.**
- The most widely used agent is ***digoxin.***

Mechanism of action:

a. Regulation of cytosolic calcium concentration:

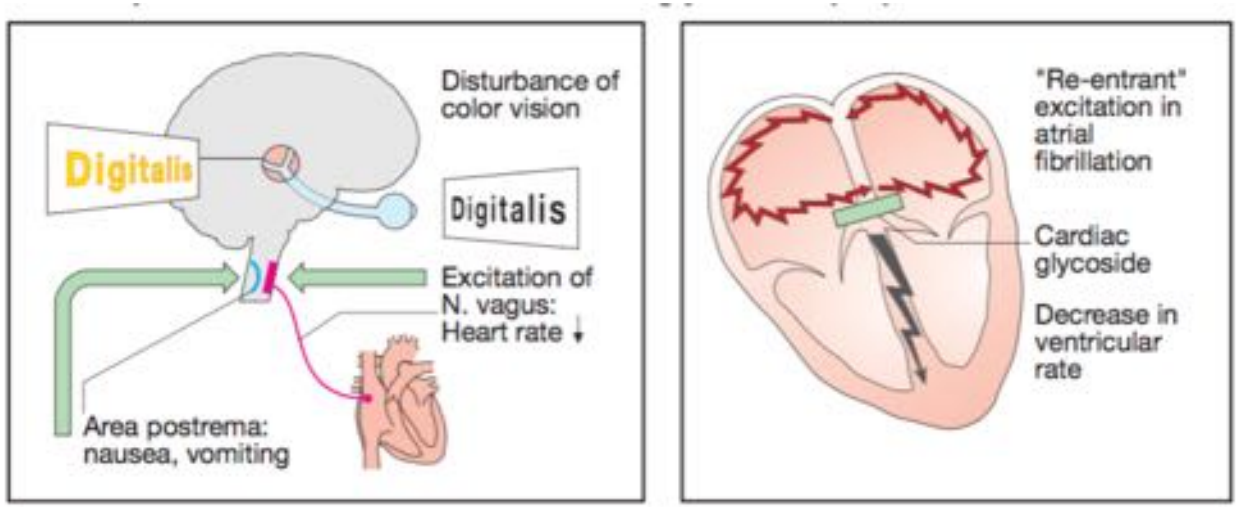
- By inhibiting the **Na+/K+ adenosine triphosphatase (ATPase) enzyme, *digoxin* reduces the ability of the myocyte to actively pump Na+ from the cell. This decreases the Na+ concentration gradient and, consequently, the ability of the Na+/ Ca2+ exchanger to move calcium out of the cell.**
- Further, the **higher cellular Na+ is exchanged for extracellular Ca2+ by the Na+/Ca2+ exchanger, increasing intracellular Ca2+.**
- A small but physiologically **important increase occurs in free Ca2+ that is available at the next contraction cycle of the cardiac muscle**, thereby **increasing cardiac contractility.**
- ***Toxicity:***
- When Na+/K+-ATPase is markedly inhibited by *digoxin*, the **resting membrane potential may increase (−70 mV instead of −90 mV), which makes the membrane more excitable, increasing the risk of arrhythmias**

Digoxin Mechanism of action:



b. Increased contractility of the cardiac muscle:

- *Digoxin* **increases the force of cardiac contraction, causing cardiac output to more closely resemble that of the normal heart .**
- **Vagal tone is also enhanced, so both heart rate and myocardial oxygen demand decrease.** *Digoxin* slows conduction velocity through the AV node, making it useful for atrial fibrillation.



c. Neurohormonal inhibition: Although the exact mechanism of this effect has not been elucidated, **low-dose *digoxin* inhibits sympathetic activation with minimal effects on contractility.**

<u>Therapeutic uses:</u>

- *Digoxin* therapy is indicated in patients with severe HF after initiation of ACE inhibitor, β-blocker, and diuretic therapy.
- *Digoxin* is not indicated in patients with diastolic or right- sided HF unless the patient has concomitant atrial fibrillation or flutter.
- Patients with mild to moderate HF often respond to treatment with ACE inhibitors, β-blockers, aldosterone antagonists, direct vaso- and venodilators, and diuretics and may not require *digoxin*.

- **4. Adverse effects:**
- **At low serum** drug concentrations(0.5 to 0.8 ng/ mL) , ***digoxin* is fairly well tolerated**.
- However, it has a **very narrow therapeutic index**, and *digoxin* toxicity is one of the most common adverse drug reactions leading to hospitalization. **Anorexia, nausea, and vomiting may be initial indicators of toxicity.** Patients may also experience **blurred vision, yellowish vision (xanthopsia), and various cardiac arrhythmias.**
- Toxicity can often be managed by **discontinuing *digoxin*, determining serum potassium levels, and, if indicated, replenishing potassium**. Decreased levels of serum potassium (hypokalemia) predispose a patient to *digoxin* toxicity, since *digoxin* normally competes with potassium for the same binding site on the Na+/K+-ATPase pump.
- **Severe toxicity resulting in ventricular tachycardia** may require administration of antiarrhythmic drugs and the use of **antibodies to *digoxin* (*digoxin immune Fab*), which bind and inactivate the drug.**

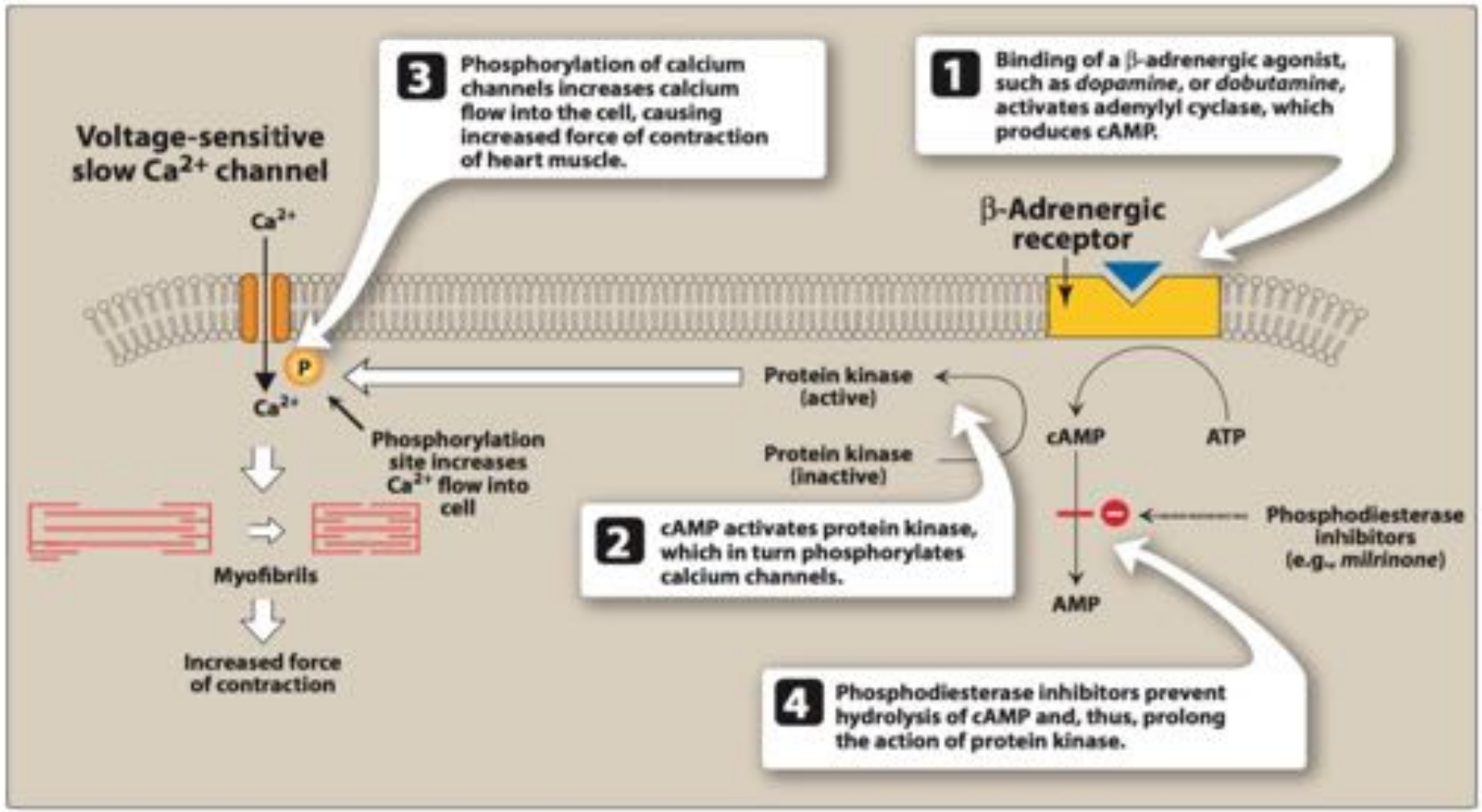
B. β-Adrenergic agonists:

- β-Adrenergic agonists, such as ***dobutamine*** and ***dopamine*** improve cardiac performance by causing **positive inotropic effects and vasodilation.**
- ***Dobutamine*** is the most commonly used inotropic agent other than *digoxin*. **β-Adrenergic agonists** lead to an **increase in intracellular cAMP**, which results in the **activation of protein kinase**. **Protein kinase then phosphorylates slow calcium channels, thereby increasing entry of calcium ions into the myocardial cells and enhancing contraction .**
- Both drugs must be given by intravenous infusion and are primarily used in the short-term treatment of acute HF in the hospital setting.

C. Phosphodiesterase inhibitors

- ***Milrinone* is a phosphodiesterase inhibitor that increases the intracellular concentration of cAMP** .
- Like β-adrenergic agonists, **this results in an increase of intracellular calcium and, therefore, cardiac contractility.**
- Long-term, *milrinone* therapy may be associated with a substantial increased risk of mortality.
- However, short-term use of intravenous *milrinone* is not associated with increased mortality in patients without a history of coronary artery disease, and some symptomatic benefit may be obtained in patients with **refractory HF**.

Sites of action by β-adrenergic agonists and phosphodiesterase inhibitors on heart muscle:




Thank
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