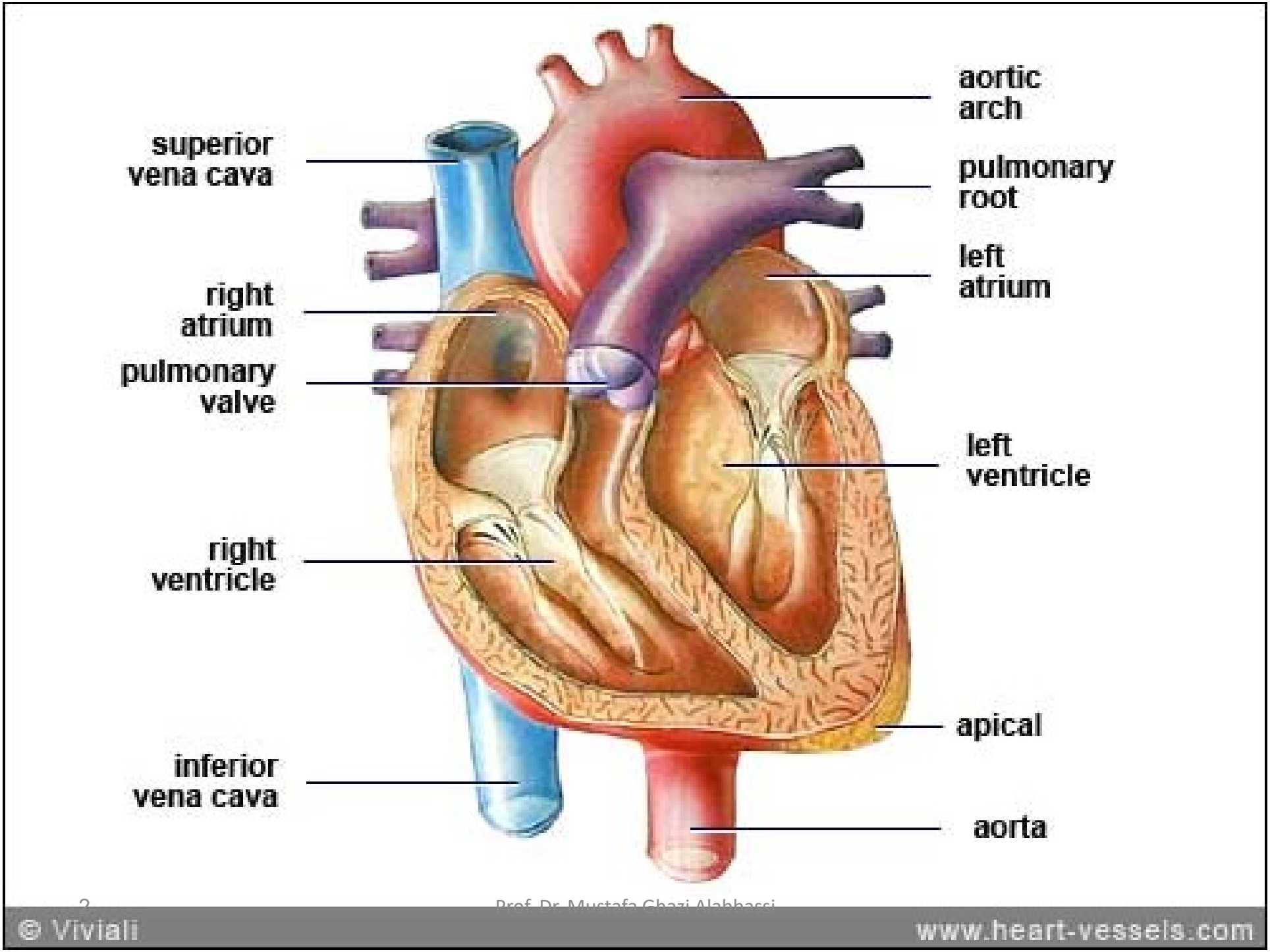
# Heart Failure

Chapter 19


aortic arch
superior vena cava
pulmonary root
left atrium
right atrium
pulmonary valve
left ventricle
right ventricle
apical
inferior vena cava
aorta
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Heart failure (HF) is a complex, progressive disorder in which the heart is unable to pump sufficient amount of blood to meet the needs of the body. The patients suffered from dyspnea, fatigue, & fluid retention.

HF is due to an impaired ability of the heart to be fill adequately &/or impaired ejection of blood.

It is often accompanied by abnormal increases in blood volume and interstitial fluid (hence the term “congestive” HF, because symptoms include dyspnea from pulmonary congestion in left HF and peripheral edema in right HF).

Underlying causes of HF include arteriosclerotic heart disease( change in the elasticity of the arteries, meanwhile atherosclerosis is accompanied by atheroma which a fatty degeneration plaques),

Myocardial infarction, hypertensive heart disease, valvular heart disease, dilated cardiomyopathy, and congenital heart disease.

**Pre-load**: ventricular tension at the end of the diastole.

**After load:** The load on the heart that is created from pumping of blood against vascular resistant.

## Goals of pharmacologic intervention in HF

Goals of treatment are to alleviate symptoms, slow disease progression, and improve survival. Accordingly, seven classes of drugs have been shown to be effective:

1) Angiotensin-converting enzyme inhibitors
2) Angiotensin-receptor blockers,
3) Aldosterone antagonists,
4) β-blockers,
5) Diuretics,
6) Direct vaso- and venodilators
7) Inotropic agents.

Depending on the severity of HF and individual patient factors, one or more of these classes of drugs are administered. Pharmacologic intervention provides the following benefits in HF:

reduced myocardial work load, decreased extracellular fluid volume, improved cardiac contractility, and a reduced rate of cardiac remodeling.

## Physiology of Muscle contraction

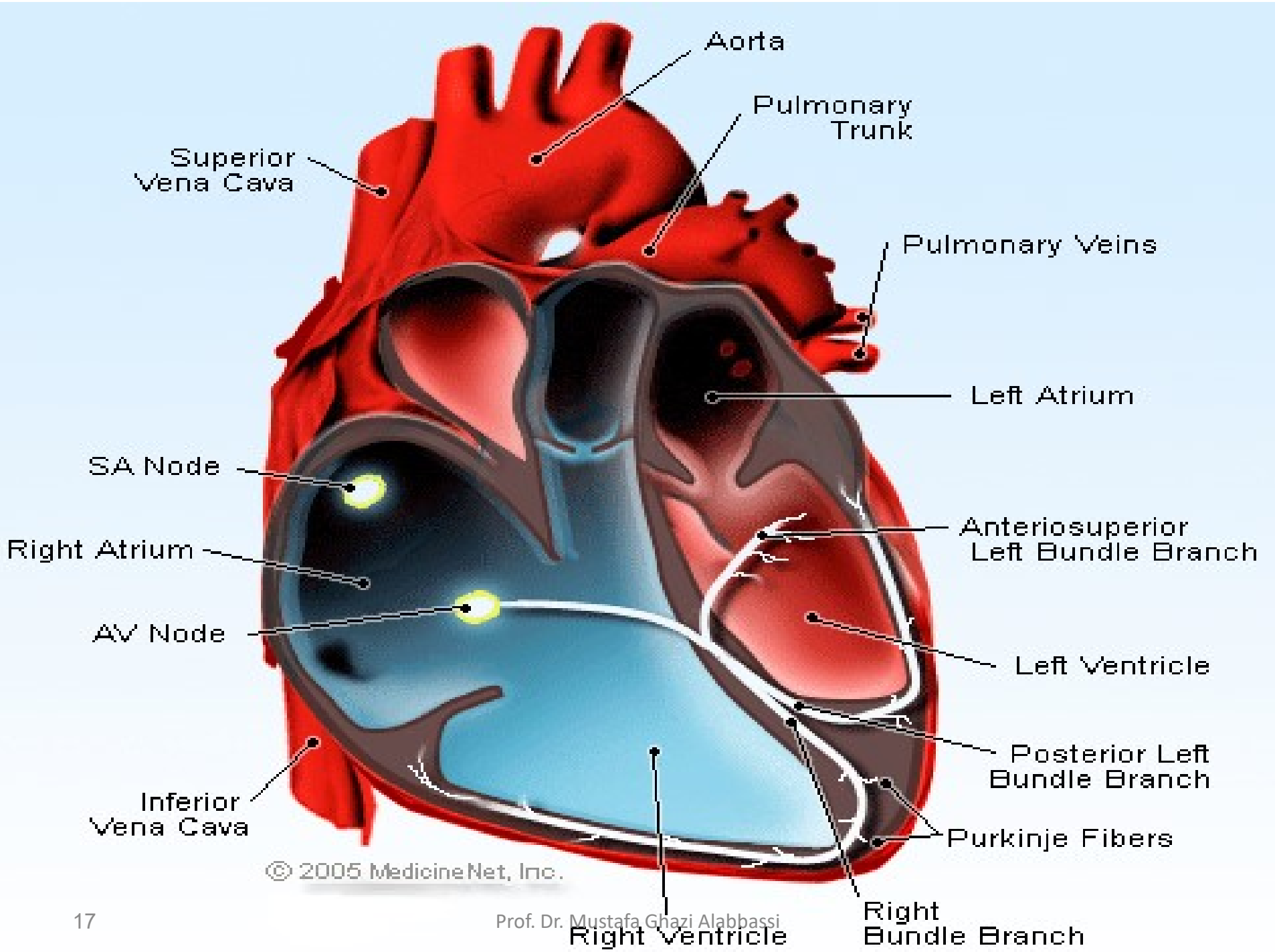
The myocardium, like smooth and skeletal muscle, responds to stimulation by depolarization of the membrane, which is followed by shortening of the contractile proteins and ends with relaxation and return to the resting state( repolarization).

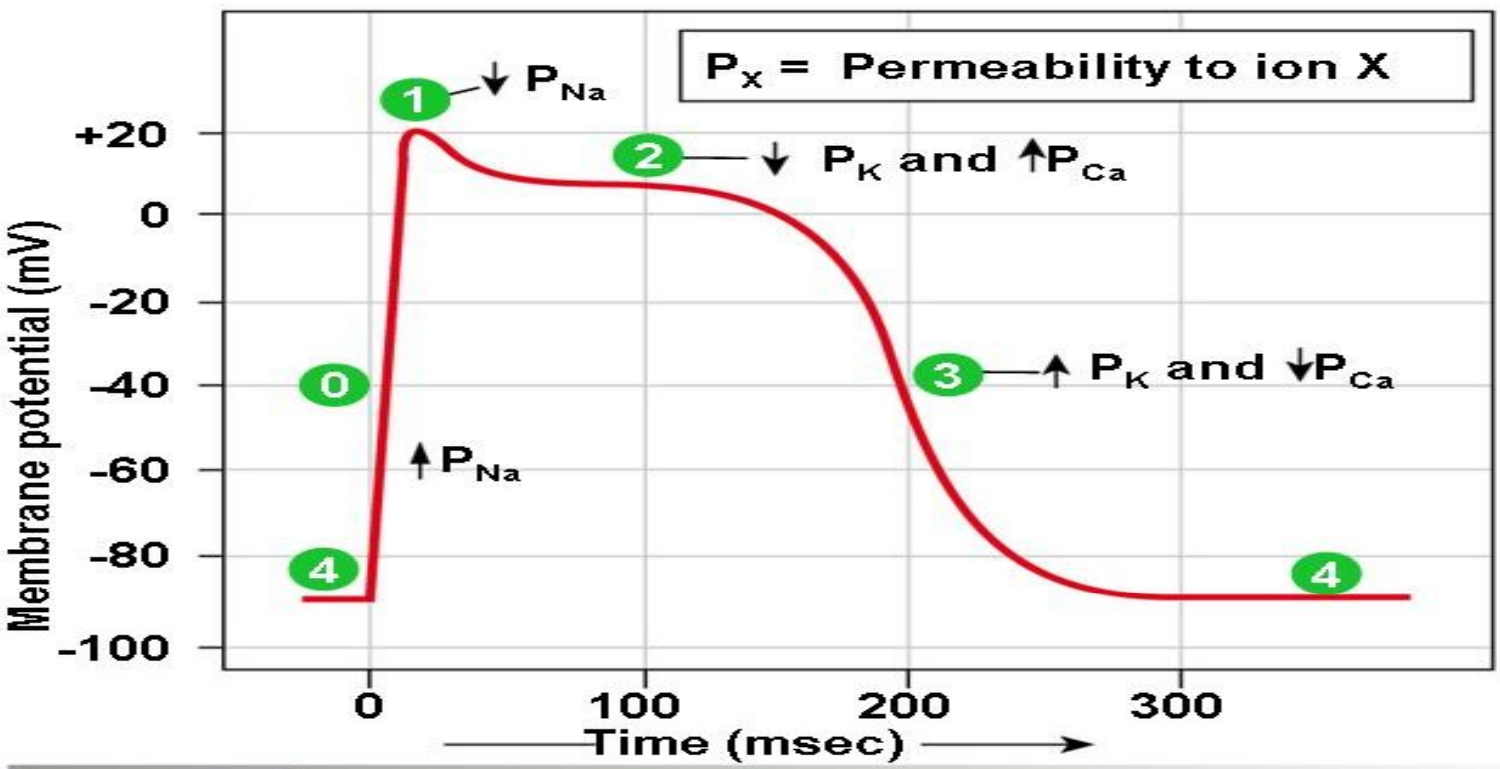
Cardiac myocytes are interconnected in groups that respond to stimuli as a unit, contracting together whenever a single cell is stimulated.

# A. Action potential

Cardiac myocytes are electrically excitable and have a spontaneous, intrinsic rhythm generated by specialized “pacemaker” cells located in the sinoatrial and atrioventricular (AV) nodes.

Cardiac myocytes also have an unusually long action potential, which can be divided into five phases (0 to 4).


Aorta
Pulmonary Trunk
Superior Vena Cava
Pulmonary Veins
Left Atrium
SA Node
Right Atrium
Anteriosuperior Left Bundle Branch
AV Node
Left Ventricle
Posterior Left Bundle Branch
Inferior Vena Cava
Purkinje Fibers
© 2005 MedicineNet, Inc.
Right Ventricle
Right Bundle Branch




| Phase | Membrane channels |
|---|---|
| 0 | $Na^+$ channels open |
| 1 | $Na^+$ channels close |
| 2 | $Ca^{2+}$ channels open; fast $K^+$ channels close |
| 3 | $Ca^{2+}$ channels close; slow $K^+$ channels open |
| 4 | Resting potential |

**The cardiac cells have action potential which can be divided into 5 phases:**

**Phase 0 (fast upstroke)** in which there will be opening of $Na^+$ channels resulting in fast inward current (it is blocked by Quinidine).

**Phase 1 (Partial repolarization)** in this phase there is inactivation of $Na^+$ channels. $K^+$ channels rapidly open & close causing a transient outward current.

**Phase 2 (Plateau)** in this phase there is opening of the voltage sensitive $Ca^{2+}$ resulting in slow inward (depolarizing) that balances the slow outward of $K^{+}$ (polarizing).

**Phase 3 (Repolarization)** $Ca^{2+}$ channel is close with opening of $K^+$ channels resulting in outward current that leads to the membrane repolarization. The net result of the action potential to this point is a net gain of $Na^+$ & loss of $K^+$ . This imbalance is corrected by $Na^+$ /$K^+$ -ATPase.

**Phase 4 (Forward current)** increasing depolarization result from gradual increase in permeability to $Na^+$ resulting in spontaneous depolarization automatically brings the cell to the threshold of 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. Therefore, agents that increase intracellular calcium levels (or that increase the sensitivity of the contractile machinery to calcium) increase the force of contraction (inotropic effect).

[Note: The inotropic agents increase the contractility of the heart by directly or indirectly altering the mechanisms that control the concentration of intracellular calcium.]

Calcium comes from several sources. The first is from outside the cell, where opening of voltage sensitive calcium channels causes an immediate rise in free cytosolic calcium. Calcium may also enter by exchange with sodium.

Calcium entry from outside the cell triggers the release of a much larger quantity of $Ca^{2+}$ is from the sarcoplasmic reticulum, which further increases the cytosolic level of calcium, which initiates the contractile process.

In order to control the normal physiology of the myocardium the calcium is removed by sodium/calcium exchange reaction that reversibly exchanges calcium ions for sodium ions across the cell membrane. Also $Ca^{2+}$ re-captured by sarcoplasmic reticulum.(Note: Sodium balance is restored by $Na^{+}/K^{+}$ ATPase).

## Compensatory Physiological Response in Heart Failure

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 (located in the wall carotid sinus, aorta & present in kidney) 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 (α1 mediated) enhances venous return and increases cardiac preload. These compensatory responses increase the work of the heart, which, in the long term, contribute to further decline in cardiac function.

## 2. Activation of 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 result in increase in peripheral resistant(afterload) & $Na^+$ water retention, thus increase in blood volume & venous pressure with developing of peripheral & pulmonary edema. Resulting; increase in the work of the heart & further decline in cardiac function.

## 3. Myocardial Hypertrophy:

The heart increases in size & the chambers dilate & 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 diminishes the ability to eject blood. This type of failure is termed “systolic failure” or HF with reduced ejection fraction (HFrEF) 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” or HF with preserved ejection fraction.

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.

# 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 Heart Failure

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);

use of diuretics, inhibitors of the renin–angiotensin–aldosterone system, and inhibitors of the sympathetic nervous system. Inotropic agents are reserved for acute HF signs and symptoms in mostly the inpatient setting.

Drugs that may precipitate or exacerbate HF, such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol, nondihydropyridine calcium channel blockers, and some antiarrhythmic drugs, should be avoided if possible.

# Drugs Use in Treatment of Heart Failure

## I. Inhibitors of the renin-angiotensin-aldosterone System

HF leads to activation of the renin–angiotensin–aldosterone system via two mechanisms:

1) increased renin release by juxtaglomerular cells in renal afferent arterioles due to diminished renal perfusion pressure produced by the failing heart.

2) renin release by juxtaglomerular cells promoted by sympathetic stimulation and activation of β receptors.

The production of AngII, a potent vasoconstrictor, & the subsequent stimulation of aldosterone release that causes salt and water retention lead to the increases in both preload and afterload that are characteristic of the failing heart.

In addition, high levels of angiotensin II and of aldosterone have direct detrimental effects on the cardiac muscle, favoring remodeling, fibrosis, and inflammatory changes.

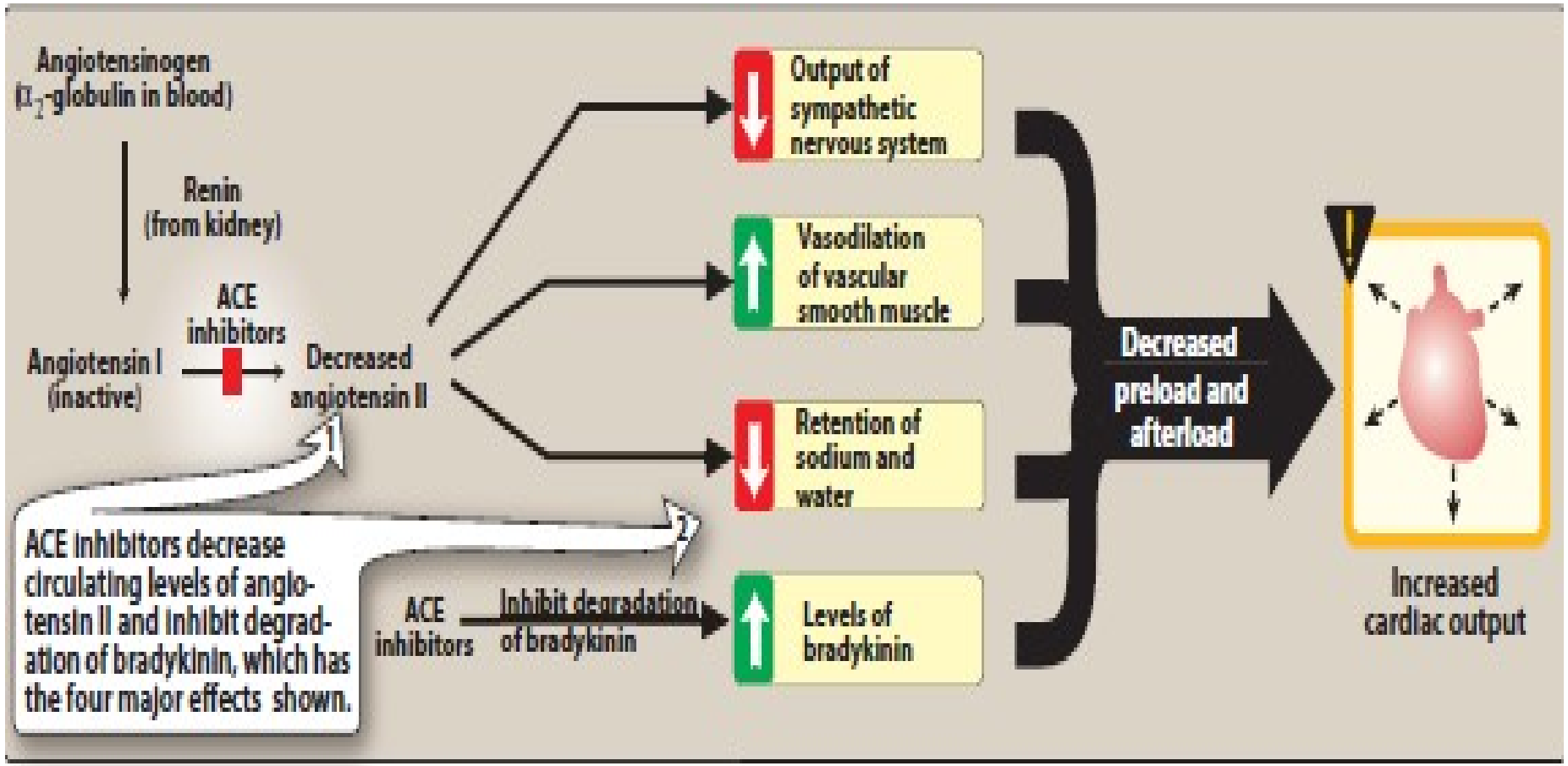



**Figure 19.5**

Effects of ACE inhibitors. [Note: The reduced retention of sodium and water results from two causes: decreased production of angiotensin II and aldosterone.]

## A. Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors are a part of standard pharmacotherapy in HFrEF. These drugs block the enzyme that cleaves angiotensin I to form the potent vasoconstrictor angiotensin II. These agents also diminish the rate of bradykinin inactivation.

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.

ACE inhibitors may be considered for patients with asymptomatic and symptomatic HFrEF. Importantly, ACE inhibitors are indicated for patients with all stages of left ventricular failure. Patients with the lowest ejection fraction show the greatest benefit from use of ACE inhibitors.

Depending on the severity of HF, ACE inhibitors may be used in combination with diuretics, β-blockers, digoxin, aldosterone antagonists, and hydralazine/isosorbide dinitrate fixed-dose combination.

**Pharmacokinetics:**

ACE inhibitors are adequately absorbed following oral administration. Food may decrease the absorption of captopril [CAP-toe-pril], so it should be taken on an empty stomach.

Except for captopril, ACE inhibitors are prodrugs that require activation by hydrolysis via hepatic enzymes. Plasma half-lives of active compounds vary from 2 to 12 hours, although the inhibition of ACE may be much longer.

## Adverse effects:

These include postural hypotension, renal insufficiency, hyperkalemia, a persistent dry cough, and angioedema (rare). Serum creatinine levels should also be monitored, particularly in patients with underlying renal disease. ACE inhibitors are teratogenic and should not be used in pregnant women.

- Captopril
- Enalapril
- Fosinopril*
- Lisinopril
- Quinapril
- Ramipril* =long acting

## B. Angiotensin-receptor blockers

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.

ARBs use in HF mainly as a substitute for ACE inhibitors in those patients with severe cough or angioedema, which are thought to be mediated by elevated bradykinin levels.

All the drugs are orally active and are dosed once-daily, with the exception of valsartan which is twice a day

- Candesartan
- Losartan
- Telmisartan
- Valsartan

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 & Eplerenone are direct antagonist of aldosterone, thereby preventing salt retention, myocardial hypertrophy, and hypokalemia.

# II. β-BLOCKERS

The benefit of β-blockers is attributed, in part, to their ability to:

1. prevent the changes that occur because of chronic activation of the sympathetic nervous system.
2. decrease heart rate and inhibit release of renin in the kidneys.
3. 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(β1-selective antagonists) , carvedilol(a nonselective β-adrenoreceptor antagonist that also blocks α-adrenoreceptors), and long-acting metoprolol succinate (β1-selective antagonists).

# III. 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 the cardiac workload and the 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.

# IV. VASO- AND VENODILATORS

Dilation of venous blood vessels leads to a decrease in cardiac preload by increasing the venous capacitance. Nitrates are commonly used venous dilators for patients with chronic HF.

Arterial dilators, such as hydralazine [hye-DRAL-a-zeen] 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 [hye DRAL a zeen] and isosorbide dinitrate [eye soe SOR bide dye NYE trate] may be used. A fixed-dose combination of these agents has been shown to improve symptoms and survival in black patients with HFrEF on standard HF treatment (β-blocker plus ACE inhibitor or ARB).

Headache, hypotension, and tachycardia are common adverse effects with this combination. Rarely, hydralazine has been associated with drug-induced lupus.

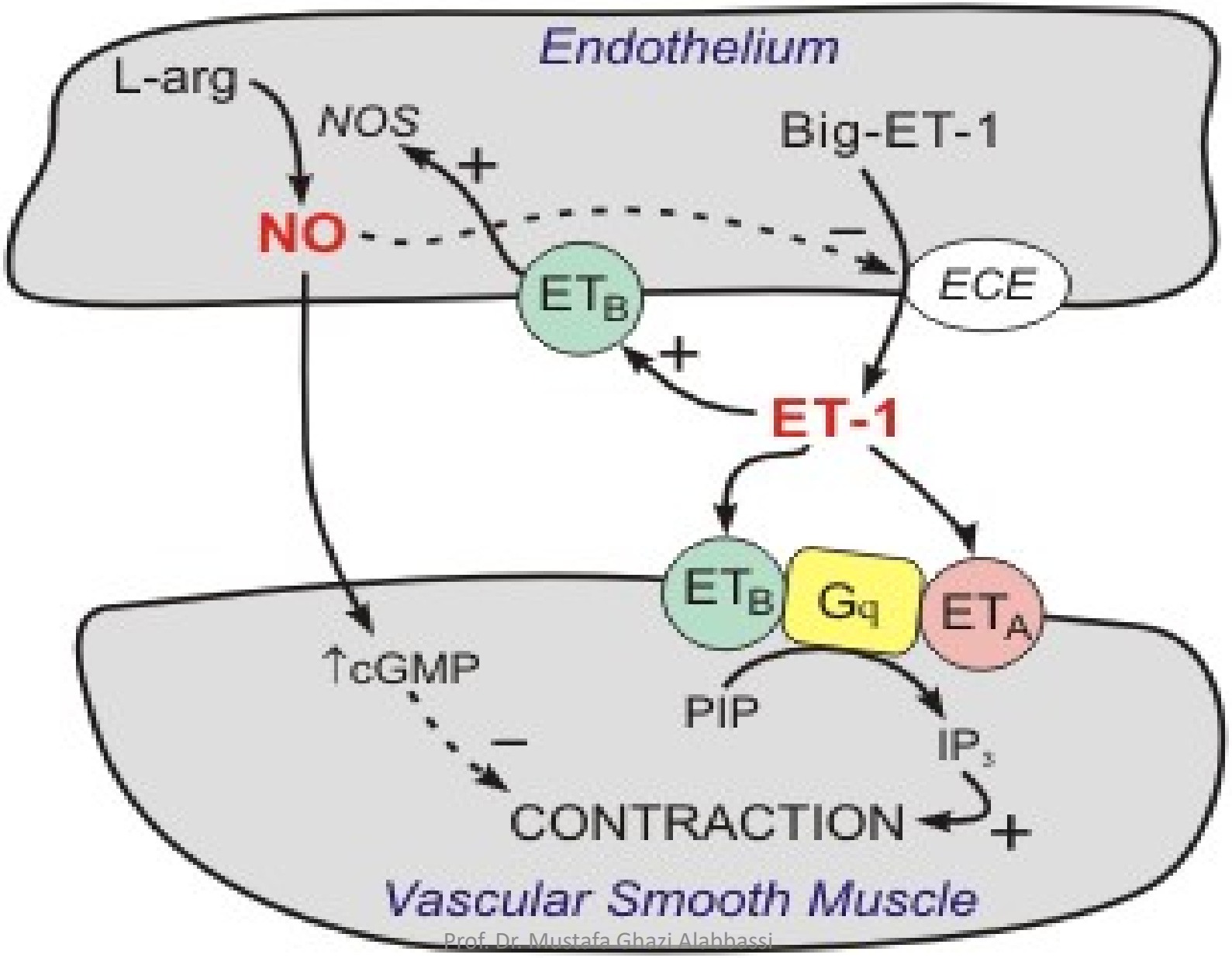
- **Mechanism of action**

Organic nitrates liberate nitric oxide which activates guanylate cyclase which increases cGMP result in de-phosphorylation of myosin light chain lead to vascular smooth relaxation.

Hydralazine promote vasodilation by:

1. Activating potassium channels→ increasing potassium efflux → inducing hyperpolarization of smooth muscle membrane→ calcium influx is inhibited → relaxation.

2. Hydralazine cause direct relaxation through interfering with a 2nd messenger of $IP_3$ result in limiting $Ca^{2+}$ release from sarcoplasmic reticulum in vascular smooth muscle. Also Hydralazine recently considered as nitric oxide donor.


Endothelium
L-arg
NOS
Big-ET-1
+
NO
–
ECE
ETB
+
ET-1
ETB
Gq
ETA
↑cGMP
PIP
IP3
–
CONTRACTION
+
Vascular Smooth Muscle

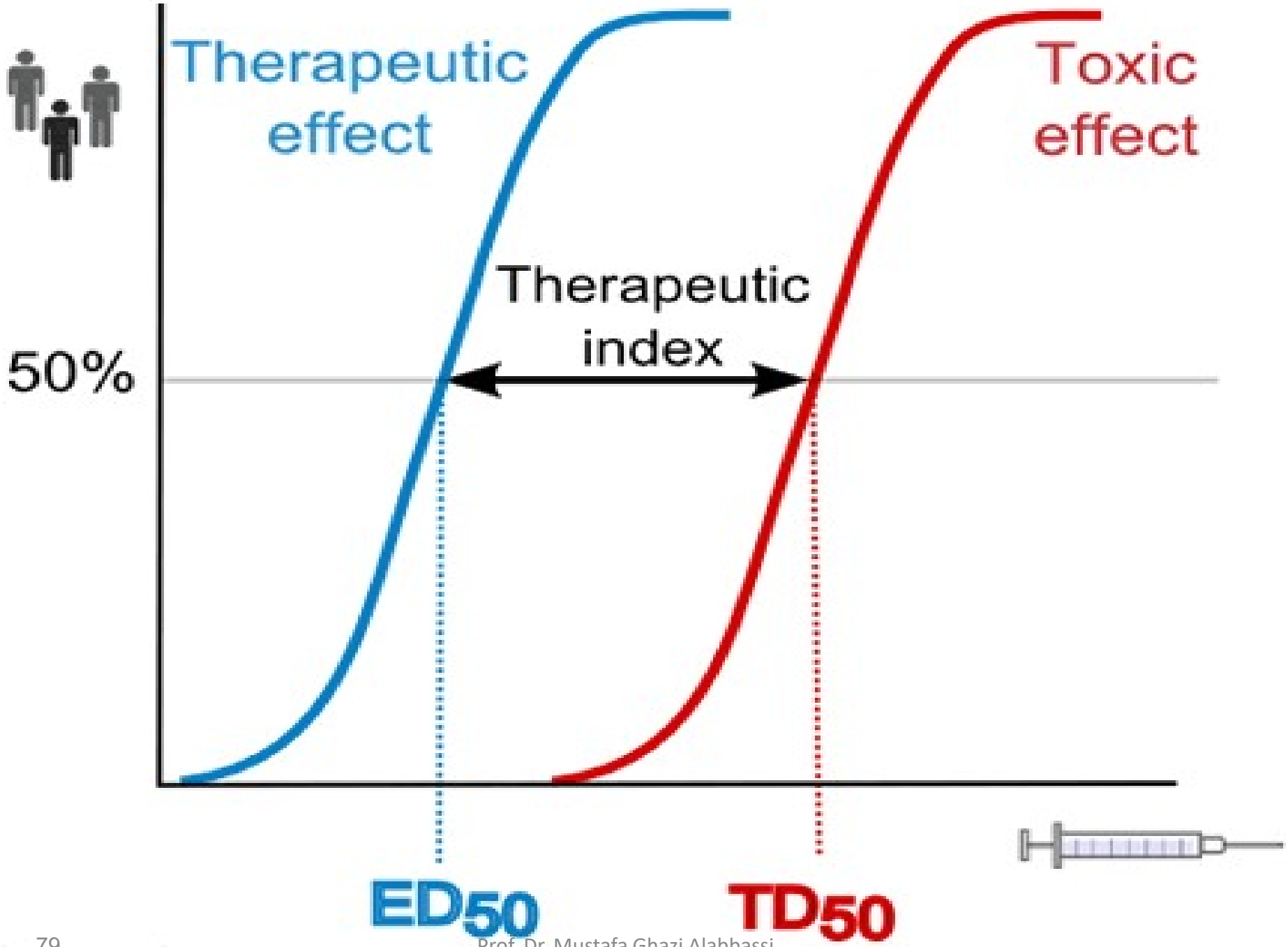
# V. INOTROPIC DRUGS

Positive inotropic agents enhance cardiac muscle contractility and, thus, increase cardiac output. Although these drugs act by different mechanisms, in each case the inotropic action is the result of an increased cytoplasmic calcium concentration that enhances the contractility of cardiac muscle.

## A. Digitalis glycosides

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 widely 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 [di-JOX-in]. Digitoxin [dij-i-TOK-sin] is seldom used due to its considerable duration of action.



## 1. Mechanism of action:

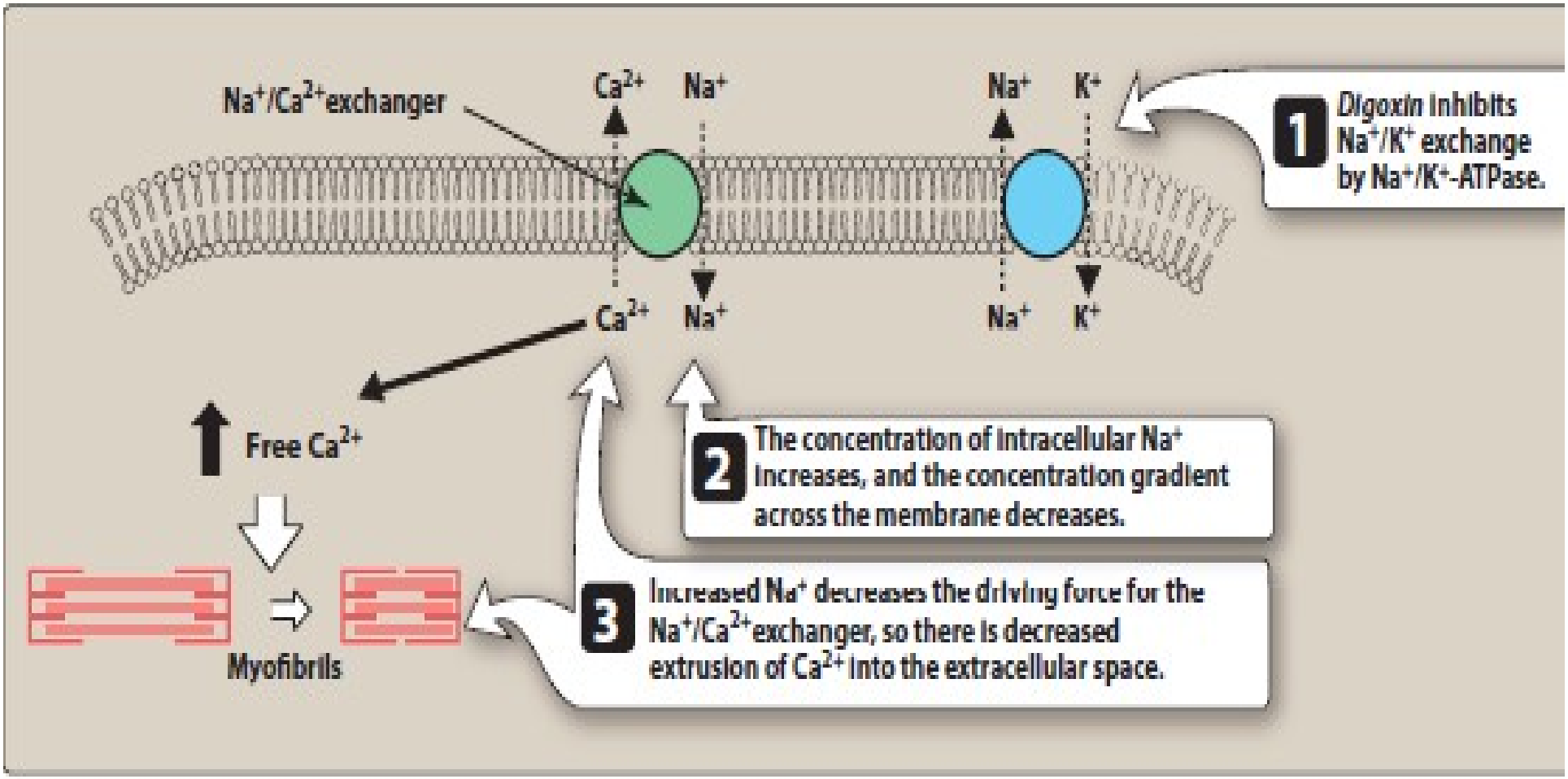



**Figure 19.8**
Mechanism of action of *digoxin*. ATPase = adenosine triphosphatase.

## 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 $Na^+$ / $Ca^{2+}$ -exchanger to move calcium out of the cell, resulting in increase of intracellular $Ca^{2+}$.

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 (toxicity).

**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.

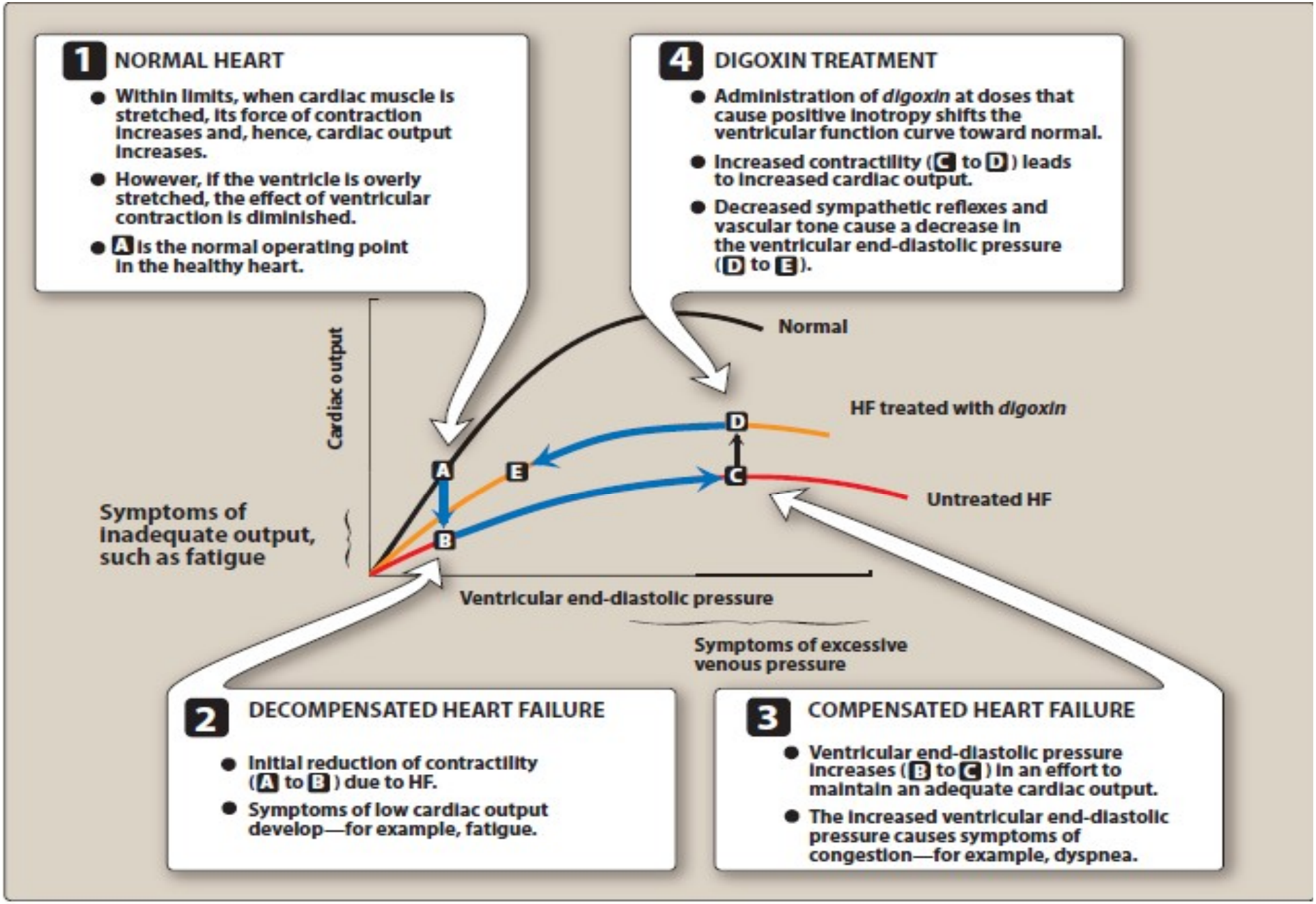



**Figure 19.9**



Ventricular function curves in the normal heart, in heart failure (HF), and in HF treated with *digoxin*.

**c. Neurohormonal inhibition:**

Low-dose digoxin inhibits sympathetic activation with minimal effects on contractility. This effect is the reason a lower serum drug concentration is targeted in HFrEF.

# Therapeutic Uses

Digoxin therapy is indicated in patients with severe HFrEF after initiation of ACE inhibitor, β-blocker, and diuretic therapy. A low serum drug concentration of digoxin (0.5 to 0.8 ng/ mL) is beneficial in HFrEF. At this level, patients may see a reduction in HF admissions, along with improved survival.

At higher serum drug concentrations, admissions are prevented, but mortality likely increases. Digoxin is not indicated in patients with diastolic or rightsided 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.

## Pharmacokinetics

Digoxin is available in oral and injectable formulations. It has a large volume of distribution, because it accumulates in muscle. Digoxin has a long half-life of 30 to 40 hours. It is mainly eliminated intact by the kidney, requiring dose adjustment in renal dysfunction.

## Adverse effects

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**:

1. Discontinuing digoxin.
2. 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.

3. Administration of antiarrhythmic drugs in ventricular tachycardia due to severe toxicity

4. The use of antibodies to digoxin (digoxin immune Fab), which bind and inactivate the drug.

## Factors predisposing to digoxin toxicity:

**a. Electrolytic disturbances:** Hypokalemia can precipitate serious arrhythmia. Reduction of serum potassium levels is most frequently observed in patients receiving thiazide or loop diuretics, which can usually be prevented by use of a potassium- sparing diuretic or supplementation with potassium chloride.

**b. Drugs:** Digoxin is a substrate of P-gp, and inhibitors of P-gp, such as clarithromycin, verapamil, and amiodarone, can significantly increase digoxin levels, necessitating a reduced dose of digoxin. Digoxin should also be used with caution with other drugs that slow AV conduction, such as β-blockers, verapamil, and diltiazem.

# B. β-Adrenergic agonists

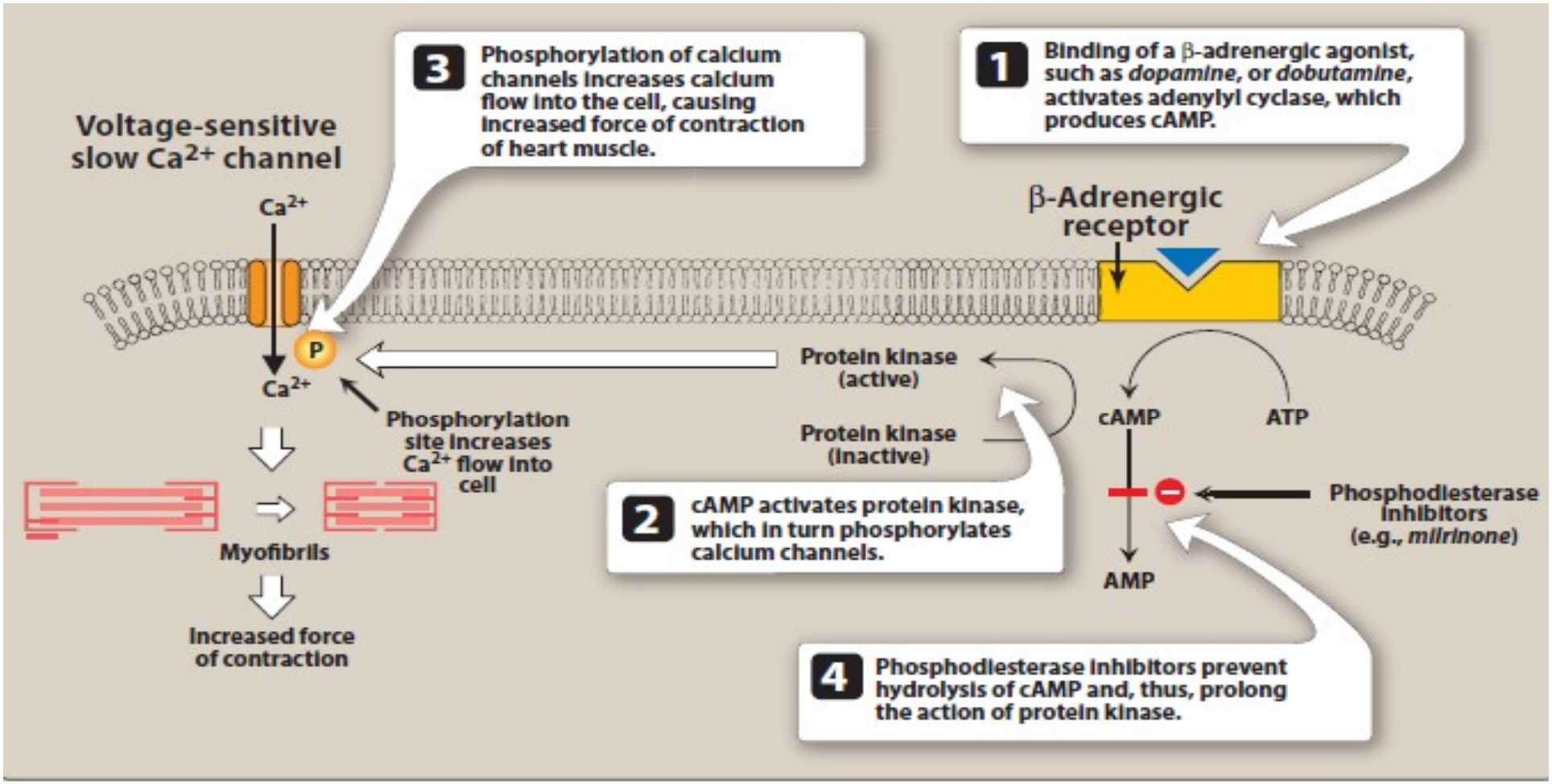



**Figure 19.10**
Sites of action by β-adrenergic agonists on heart muscle. AMP = adenosine monophosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; P = phosphate.

β-Adrenergic agonists, such as dobutamine [doe-BYOO-ta-meen] and dopamine [DOH-puh-meen], 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 cyclic adenosine monophosphate (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 [MIL-rih-nohn] 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.

## ORDER OF THERAPY

Experts(The American College of Cardiology (ACC) and the American Heart Association (AHA) have identified the stages of heart failure into four stages, from least severe to most severe(A,B,C & D).

In the last stage Digoxin, aldosterone antagonists, and fixed-dose hydralazine and isosorbide dinitrate are initiated in patients who continue to have HF symptoms despite optimal doses of an ACE inhibitor and β-blocker.

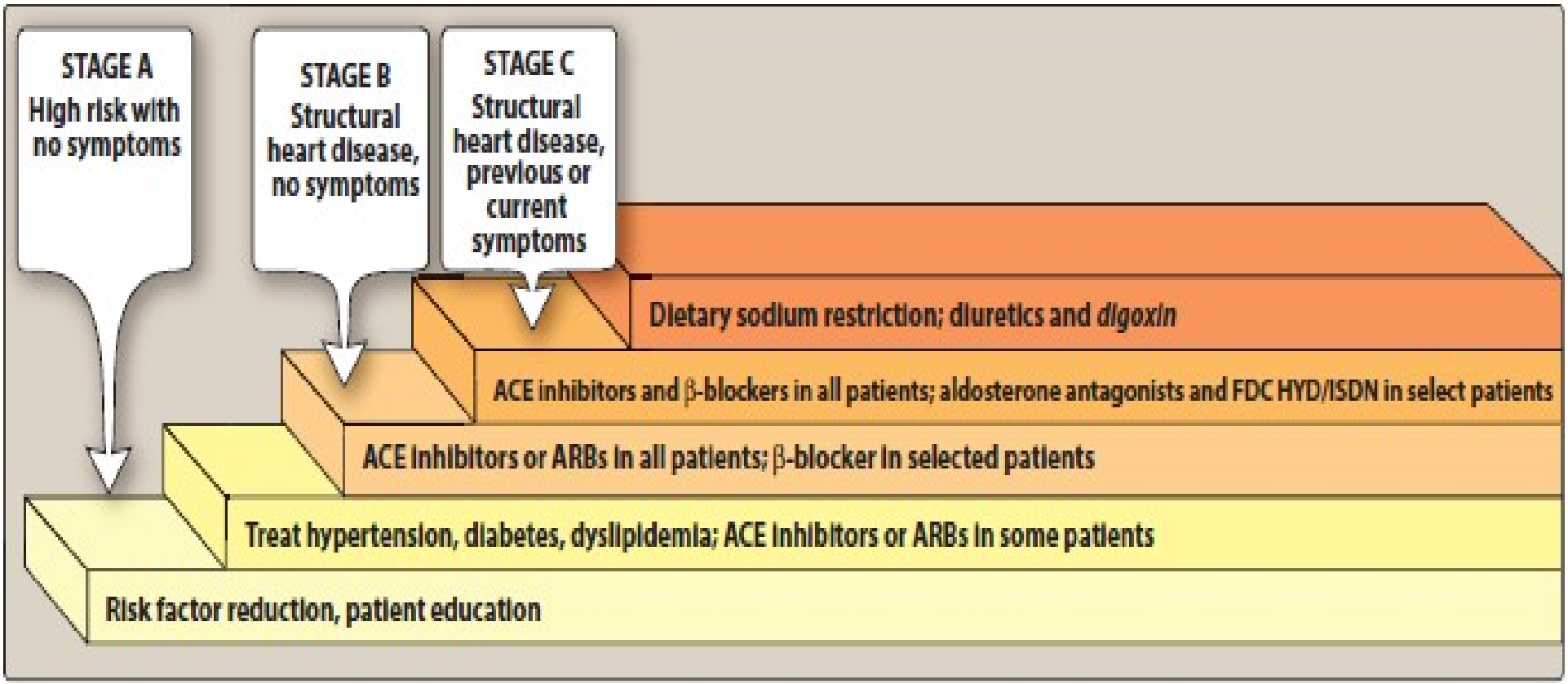



**Figure 19.11**

Treatment options for various stages of HF. ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; FDC = fixed dose combination; HYD = hydralazine; ISDN = isosorbide dinitrate. Stage D (refractory symptoms requiring special interventions) is not shown.

# Thank You for Listening