Drug Therapy of Heart Failure

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November, 2014

Drug Therapy of Heart Failure

Definition of Heart Failure

Causes

Classifications

Definition of Heart Failure

- Heart is unable to provide adequate perfusion of peripheral organs to meet their metabolic requirements
- Characterized by:

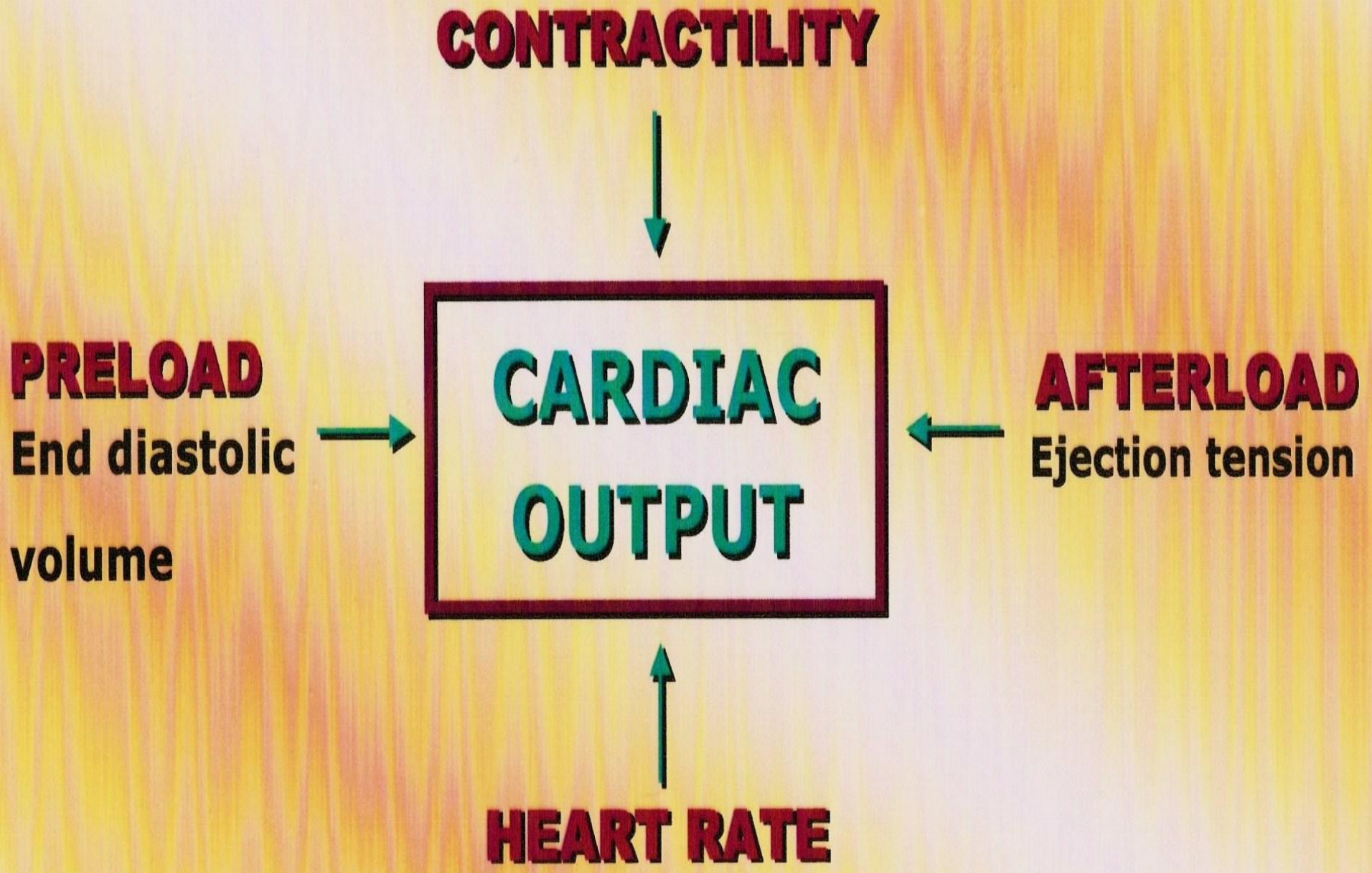
1. Decreased CO
2. Increased TPR
    - Progression to congestive heart failure (CHF) is accompanied by peripheral and pulmonary edema.

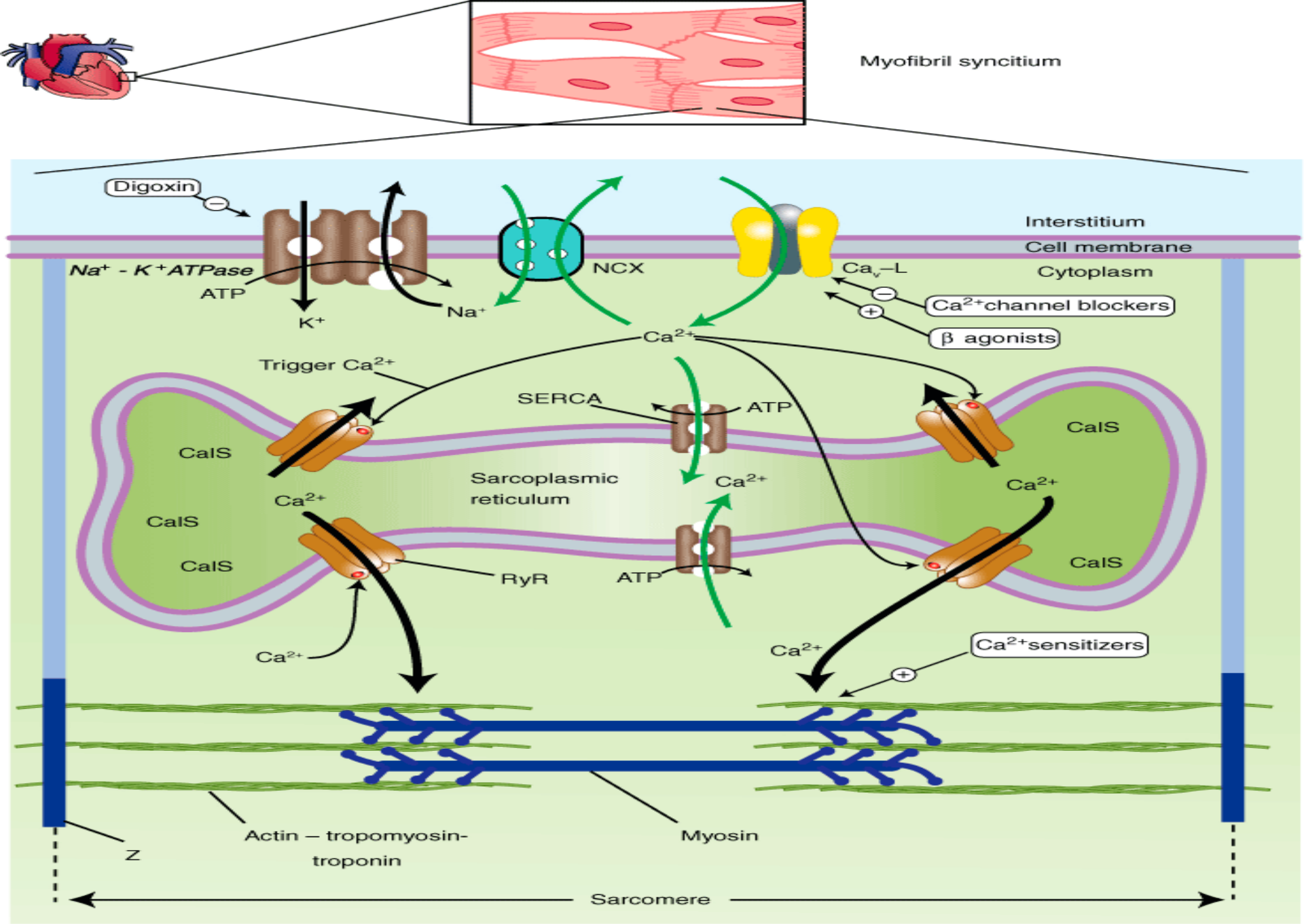
CAUSES OF CONGESTIVE HEART FAILURE

A. Mechanical Causes
   1. Pressure Overload
      a. Hypertension
      b. Aortic Valve Stenosis
      c. Pulmonary Hypertension
   2. Volume Overload
      a. Valvular Regurgitation
      b. Shunts
      c. Increased Blood Volume

B. Impaired Cardiac Filling
   1. Pericardial Disease (constriction or tamponade)
   2. Restrictive Heart Disease (endo- or myocardial)
   3. Ventricular Hypertrophy
   4. Ventricular Aneurysm

C. Myocardial Failure
   1. Primary
      a. Loss of functioning muscle (myocardial infarction)
      b. Cardiomyopathy
      c. Myocarditis
   2. Secondary
      a. Dysdynamic heart failure (response to chronic overload)
      b. Drug-induced
      c. Involvement in systemic disease (hypothyroidism)


CONTRACTILITY
PRELOAD
End diastolic
volume
CARDIAC
OUTPUT
AFTERLOAD
Ejection tension
HEART RATE



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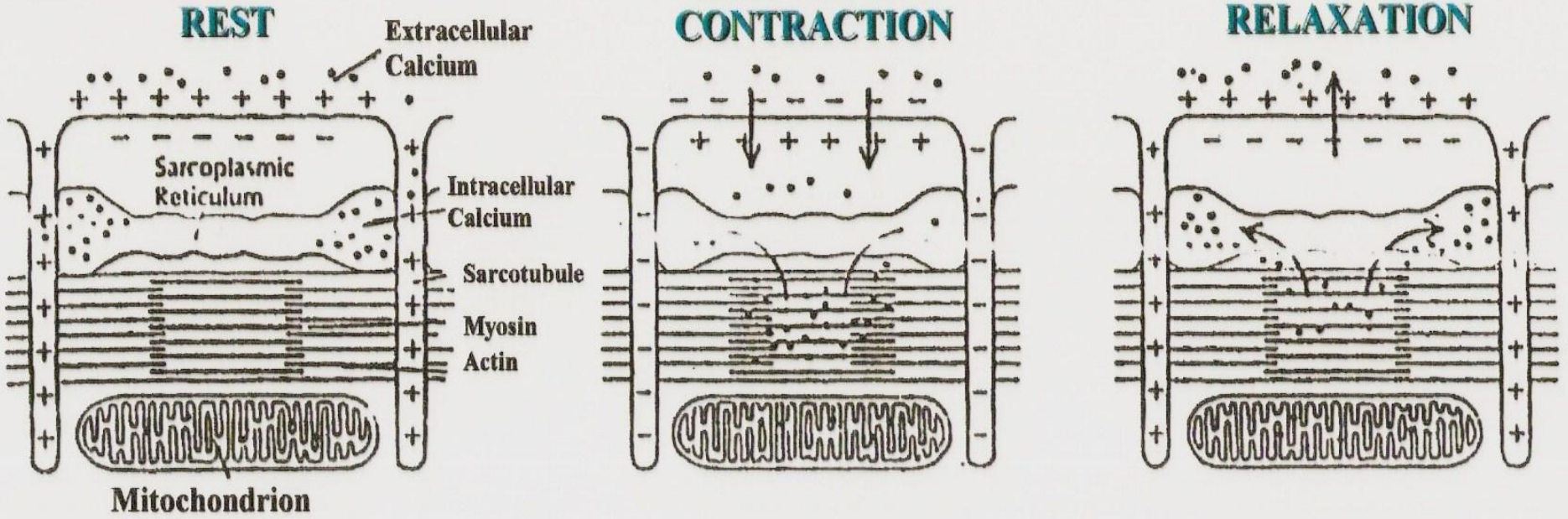
Mechanisms of H. F.

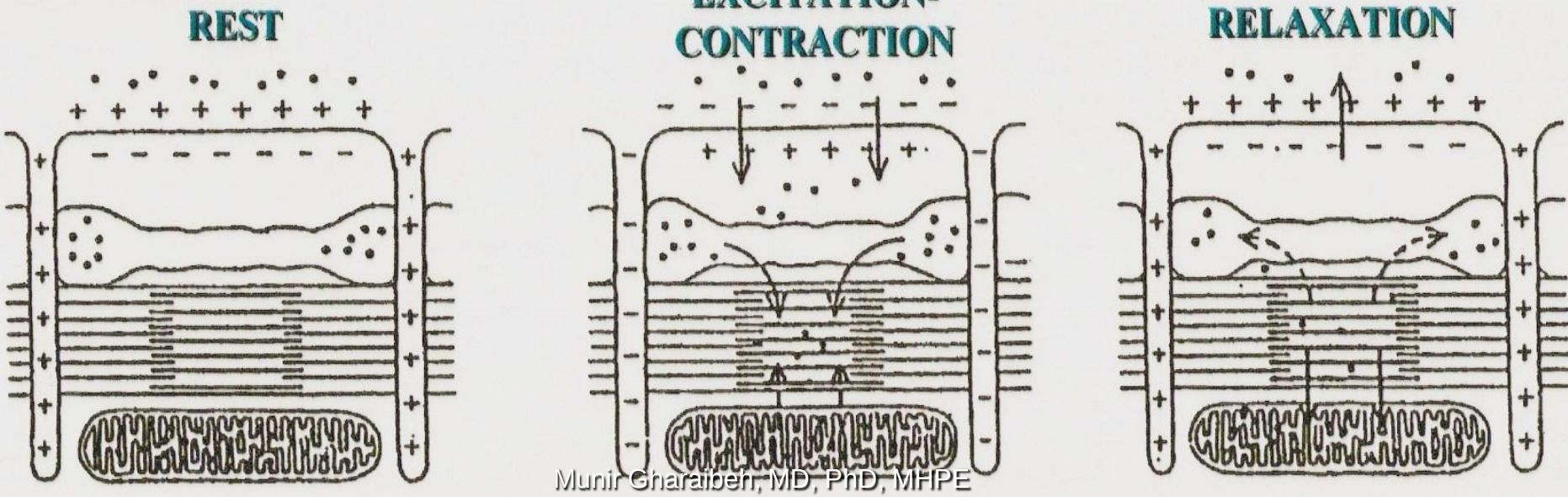
Reduction in the intrinsic myocardial contractility

1. Depletion of NE in heart muscle.
2. ↓ Myosine ATPase activity.
3. ↓ ATP and other high energy phosphate compounds.
4. ↓ β receptor density (due to down regulation after chronic exposure to high circulating catecholamines).
5. Abnormal Ca^{++} binding:
    1. Less stored in SR
    2. More stored in Mitochondria
    3. Less released
    4. Lesser reuptake into SR.
    5. Slow reuptake into mitochondria leading to slow relaxation.

NORMAL HEART:



HEART FAILURE:

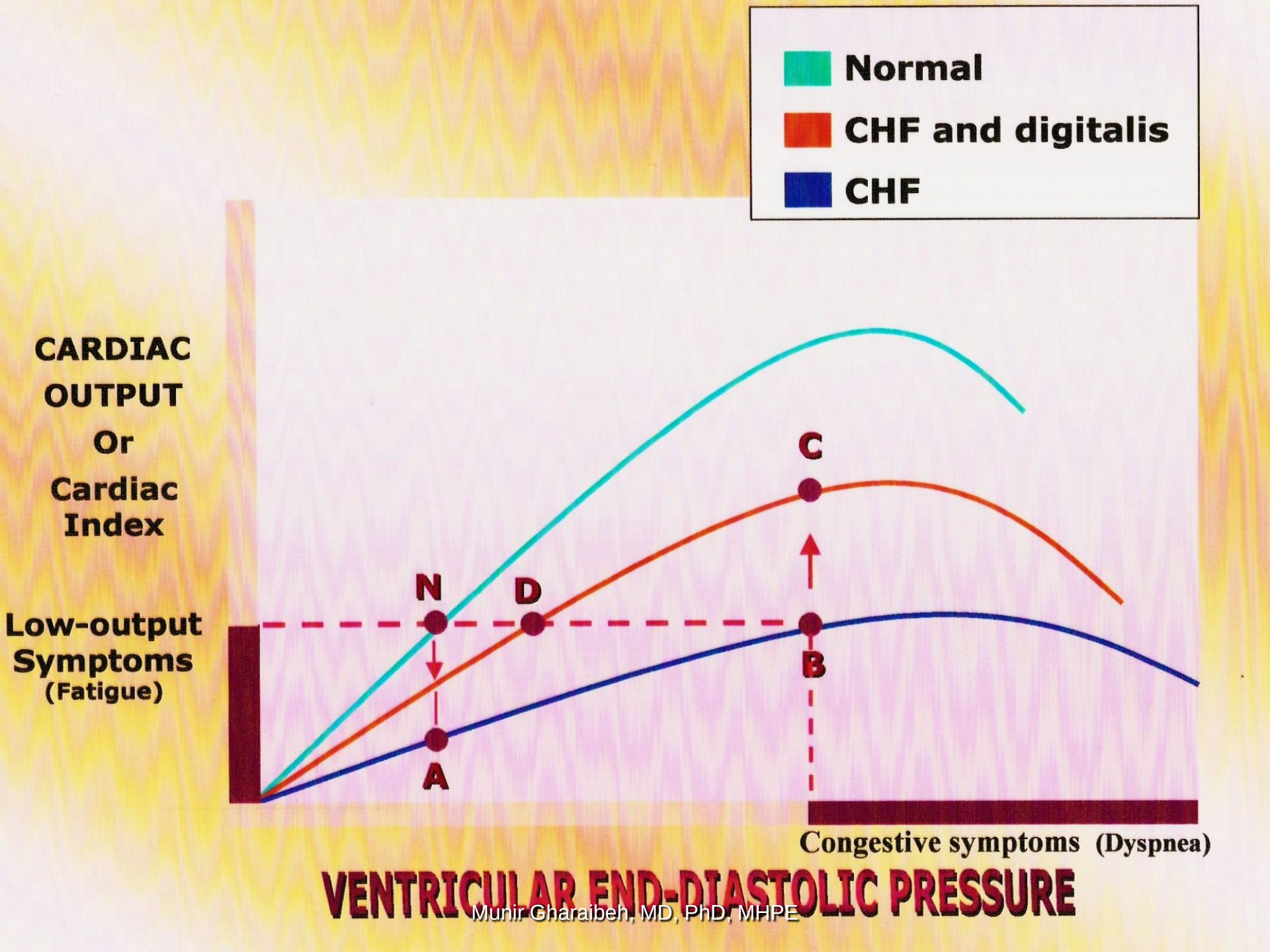


Compensatory Mechanisms in Heart Failure

- **Frank Starling Mechanism**

- **Increased Activity of SNS:**
- a- Tachycardia and increased CO.
- b- Increased myocardial contractility
- c- Vasoconstriction leading to redistribution of blood to important viscera
- d- Renin release leading to increased plasma volume

- **Myocardial Hypertrophy leading to increased wall tension.**



Compensatory SNS Mechanisms in HF

- In a failing heart, the loss of contractile function leads to a decline in CO and a decrease in arterial BP.

- Baroreceptors sense the hemodynamic changes and initiate countermeasures to maintain support of the circulatory system. This is achieved by activation of the SNS.

- This helps maintain adequate cardiac output by:

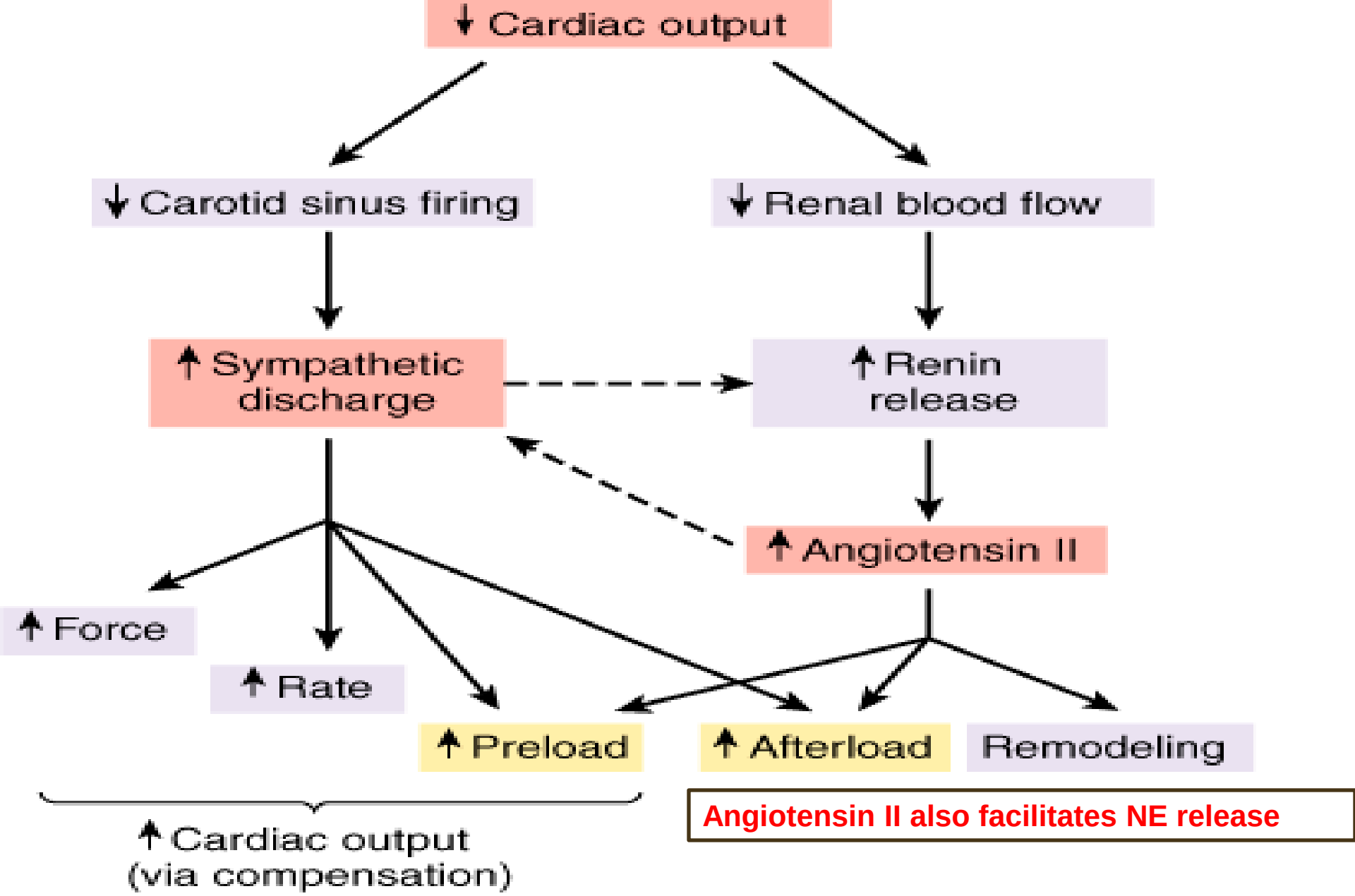
1. Increasing myocardial contractility and heart rate (β_1-adrenergic receptors)
2. Increasing vasomotor tone (α_1-adrenergic receptors) to maintain systemic blood pressure

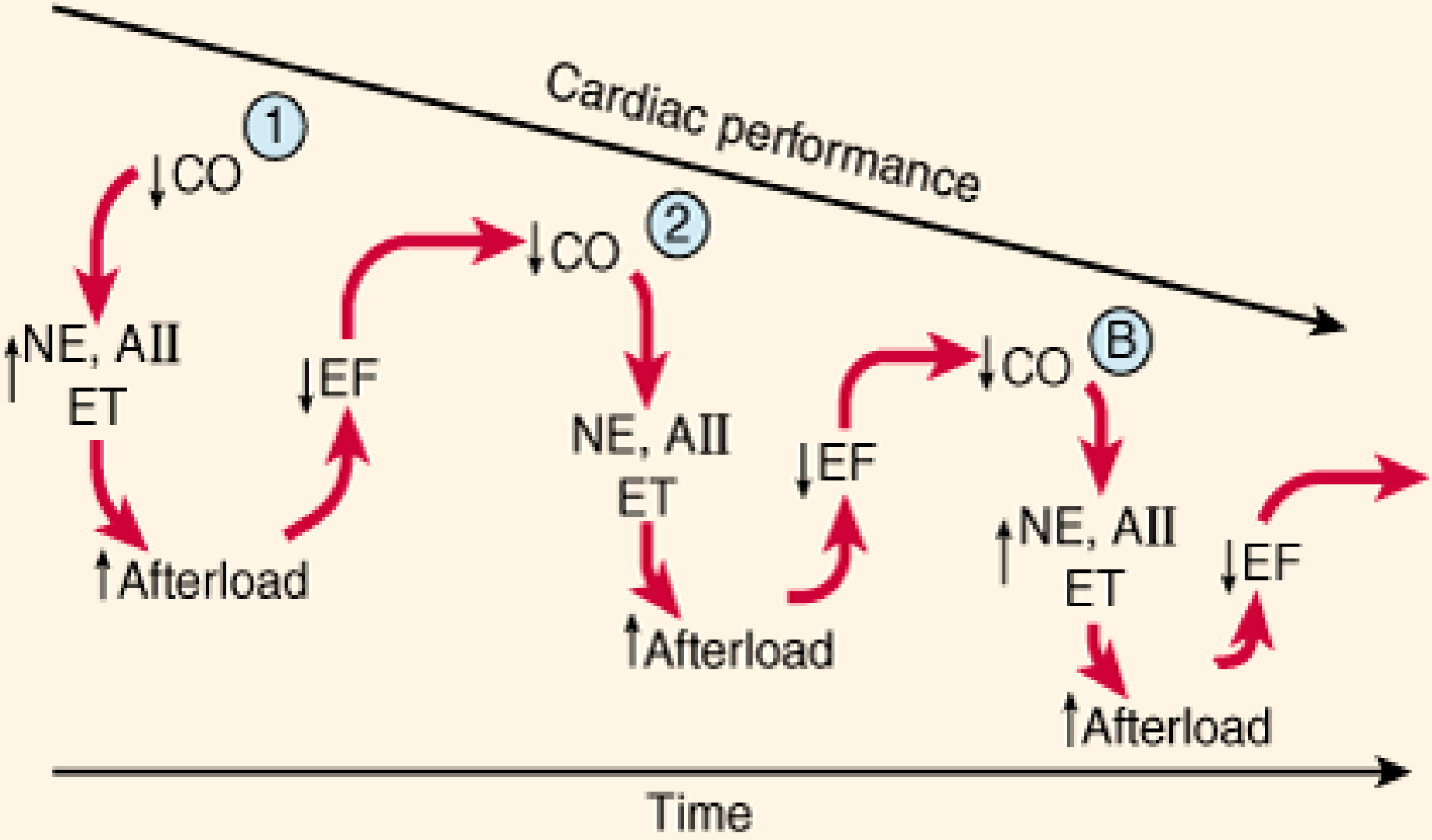
Consequences of hyperadrenergic state

- Enhancement of RAAS.

- Over the long term, hyperadrenergic state leads to irreversible myocyte damage, cell death, and fibrosis.
- In addition, the augmentation in peripheral vasomotor tone increases LV afterload.

- This places an added stress upon the left ventricle and an increase in myocardial O_2 demand (ventricular remodeling).
- The frequency and severity of cardiac arrhythmias are enhanced in the failing heart





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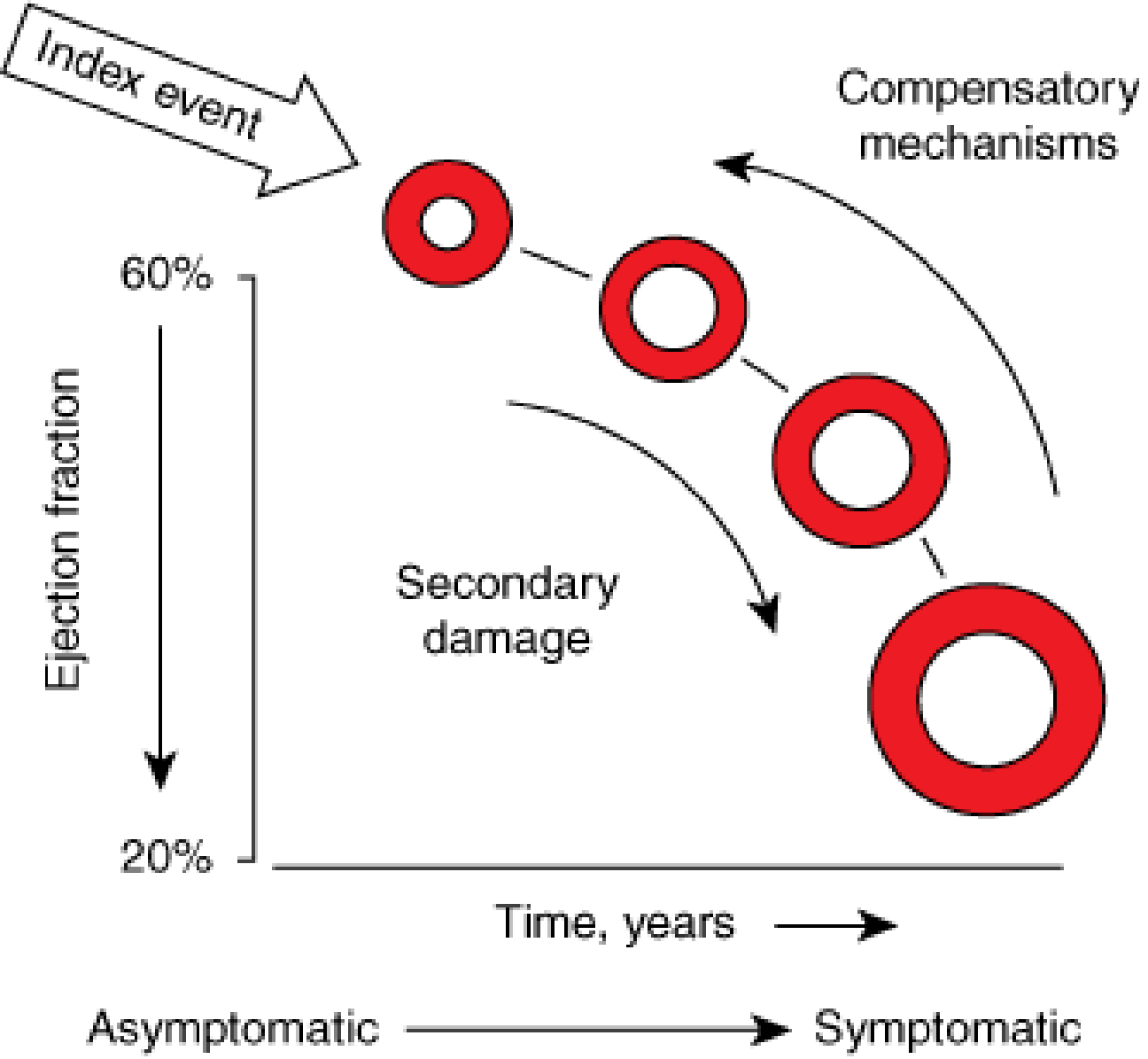
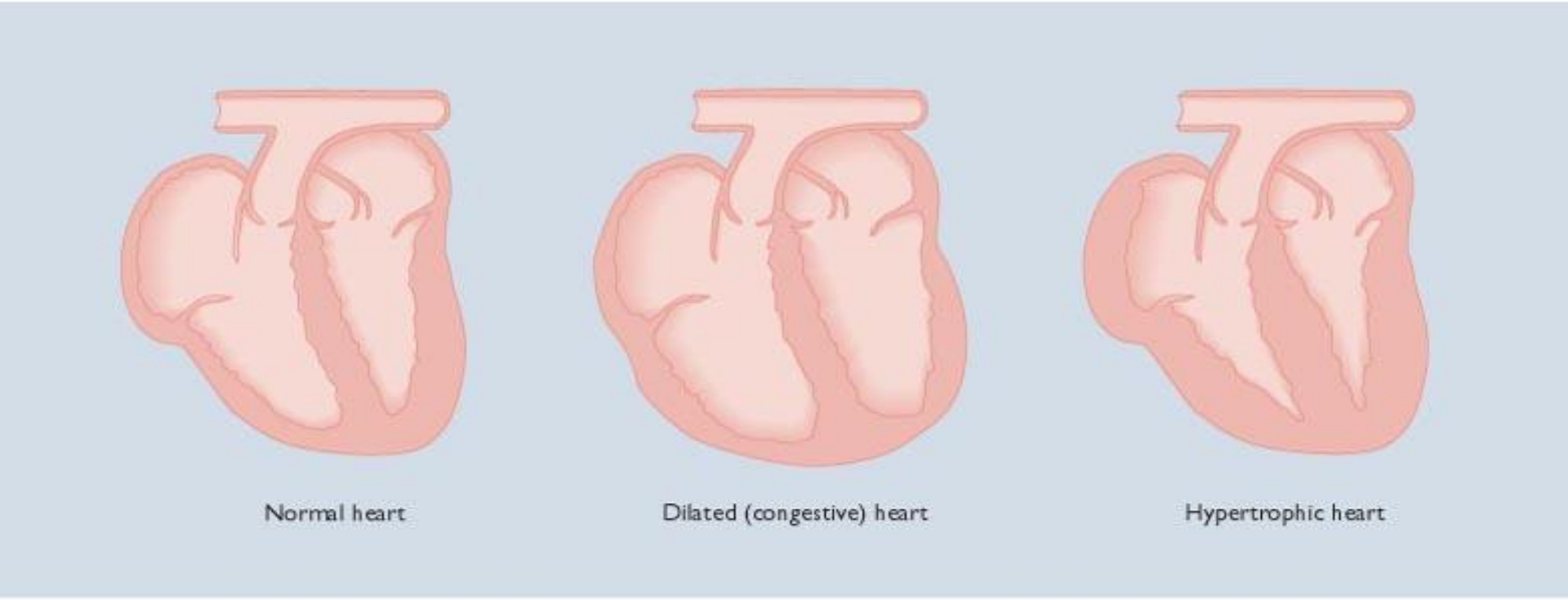


Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Signs and Symptoms of HF

- **Tachycardia, sweating**
- **Decreased exercise tolerance & SOB**
- **Peripheral and pulmonary edema**
- **Cardiomegaly**


Normal heart
Dilated (congestive) heart
Hypertrophic heart

Factors that May Precipitate Acute Decompensation in Patients with Chronic Heart Failure

- Dietary indiscretion
- Myocardial ischemia/infarction
- Arrhythmias (tachycardia or bradycardia)
- Discontinuation of HF therapy
- Infection
- Anemia
- Initiation of medications that worsen HF:
  - Calcium antagonists (verapamil, diltiazem)
  - Beta blockers
  - Nonsteroidal anti-inflammatory drugs
  - Antiarrhythmic agents [all class I agents, sotalol (class III)]
  - Anti-TNF antibodies
- Alcohol consumption
- Pregnancy
- Worsening hypertension
- Acute valvular insufficiency

Objectives of Long Term Management of Chronic Cardiac Failure

- Improve cardiac performance (hemodynamics) at rest and during exercise.
- Relieve symptoms.
- Improve myocardial efficiency.
- Improve quality of life(particularly symptom-free and effort tolerance).
- Improve patient survival.

Cardiac vs Noncardiac Therapeutic Targets

- Conventional belief that the primary defect in HF is in the heart.
- Reality is that HF involves many other processes and organs.
- Research has shown that therapy directed at noncardiac targets is more valuable than cardiac targets.
- CHF should be viewed as a complex, interrelated sequence of events involving hemodynamic, and neurohormonal events.

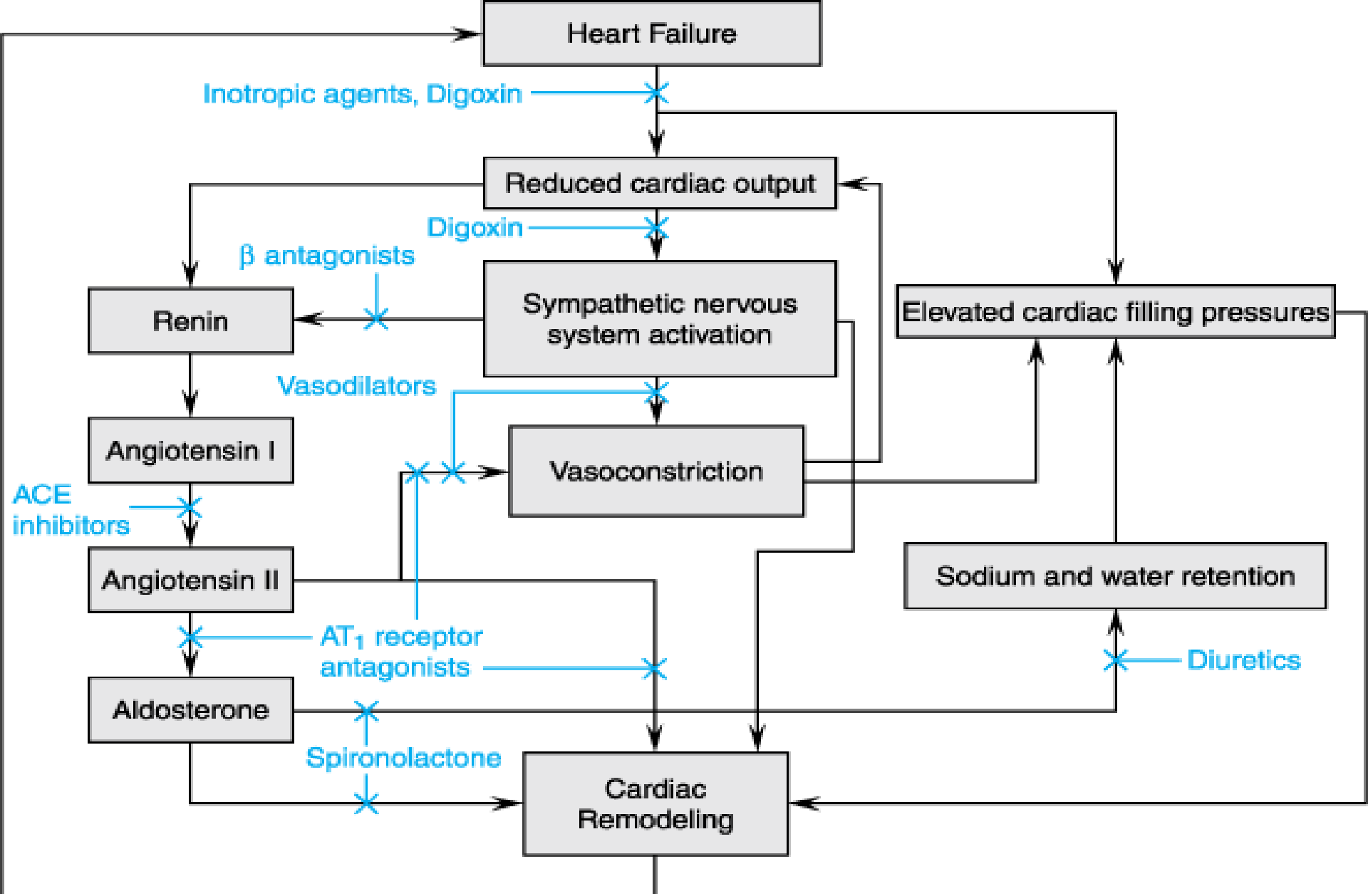
Therapeutic Overview

The Problems

- Reduced force of contraction
- Decreased cardiac output
- Increased total peripheral resistance
- Inadequate organ perfusion
- Edema
- Decreased exercise tolerance
- Ischemic heart disease
- Sudden death
- Ventricular remodeling and decreased function

Nonpharmacologic Treatment:

- Salt Restriction
- Treat the Cause
- Moderate Excercise
- Heart Transplantation



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Drug Groups Commonly Used in Heart Failure.

Diuretics

Aldosterone receptor antagonists

Angiotensin-converting enzyme inhibitors

Angiotensin receptor blockers

Beta blockers

Cardiac glycosides

Vasodilators

Beta agonists

Bipyridines

Natriuretic peptide

Diuretics

Only for congestive symptoms:

Do not ↑ C.O..... .....may ↓ Co

Can be used alone initially IV

May be used in combination with digitalis or others.

Cause K+ Loss, ↓ BP,.....etc.

Can be reduced or withdrawn

Causes of Diuretic Resistance in Heart Failure

*Noncompliance with medical regimen; excess dietary Na^+ intake

*Decreased renal perfusion and glomerular filtration rate

*Selective reduction in glomerular perfusion pressure following initiation (or dose increase) of ACE inhibitor therapy

*Nonsteroidal antiinflammatory drugs

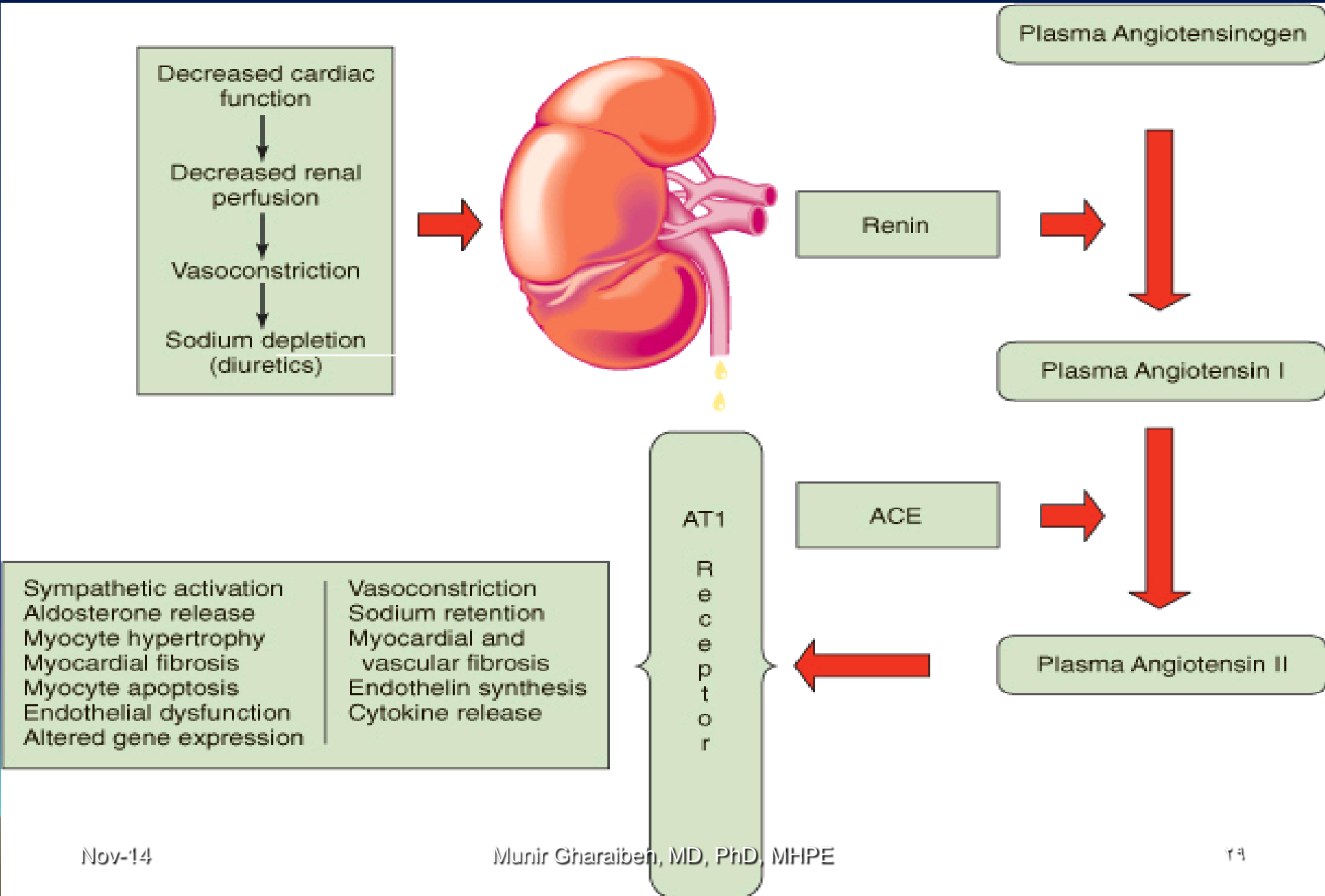
*Primary renal pathology

*Reduced or impaired diuretic absorption due to gut wall edema and reduced splanchnic blood flow

Angiotensin Converting Enzyme Inhibitors "ACEI"

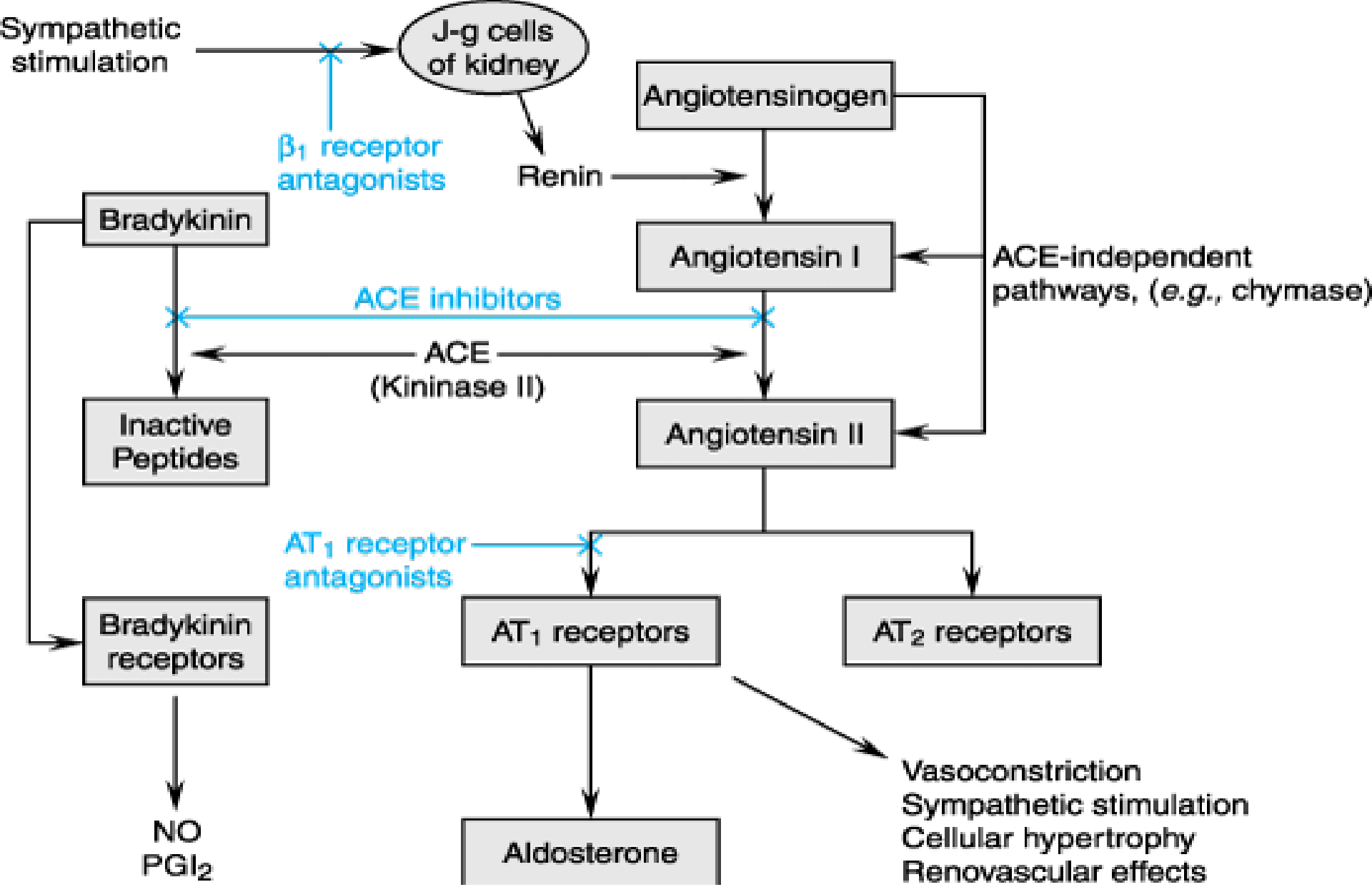
- **Pharmacological Actions:**
- Reduce angiotensin II levels.
- Increase bradykinin.
- Inhibit SNS, leading to decreased NE release and upregulation of β1 receptors.
- Balanced vasodilators.
- Reduce myocyte & fibroblast growth factors
- Reduce salt and water retention.
- Reduce K+ loss.
- Reduce ventricular arrhythmias.

Effects of AT-II



Potential Roles of Aldosterone in the Pathophysiology of Heart Failure

MECHANISM	PATHOPHYSIOLOGICAL EFFECT
Increased Na^+ and water retention	Edema, elevated cardiac filling pressures
K^+ and Mg^{2+} loss	Arrhythmogenesis and risk of sudden cardiac death
Reduced myocardial norepinephrine uptake	Potentiation of norepinephrine effects: myocardial remodeling and arrhythmogenesis
Reduced baroreceptor sensitivity	Reduced parasympathetic activity and risk of sudden cardiac death
Myocardial fibrosis, fibroblast proliferation	Remodeling and ventricular dysfunction
Alterations in Na^+ channel expression	Increased excitability and contractility of cardiac myocytes



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Therapeutic Actions of ACEI

- Blockade of ACE
- Decreased AT-II
- Decreased aldosterone
- Decreased fluid retention
- Vasodilation
- Reduced preload and afterload
- Slowing of cardiac remodeling
-

Therapeutic Values of ACEI

- Nowadays drugs of choice.
- No tolerance.
- Retard progression of HF.
- Decrease arrhythmias.
- The only drugs which decrease mortality, but only when the highest tolerated doses are used.

Preparations of ACEI

- **Captopril**
- **Enalapril**
- **Lisinopril**
- **Quinapril**
- **Fosinopril**

All are similarly effective

Might differ in toxicity

Toxicity of ACEI

- Hypotension …… First dose phenomenon
- Renal Impairment ..... Proteinurea
- K+ retention
- Cough

Angiotensin (AT1) Receptor Blockers ARBs

- **Losartan.**
- **Candesartan.**
- **Valsartan.**
- **Irbesartan(Approvel).**
- **Telmisartan(Micardis).**

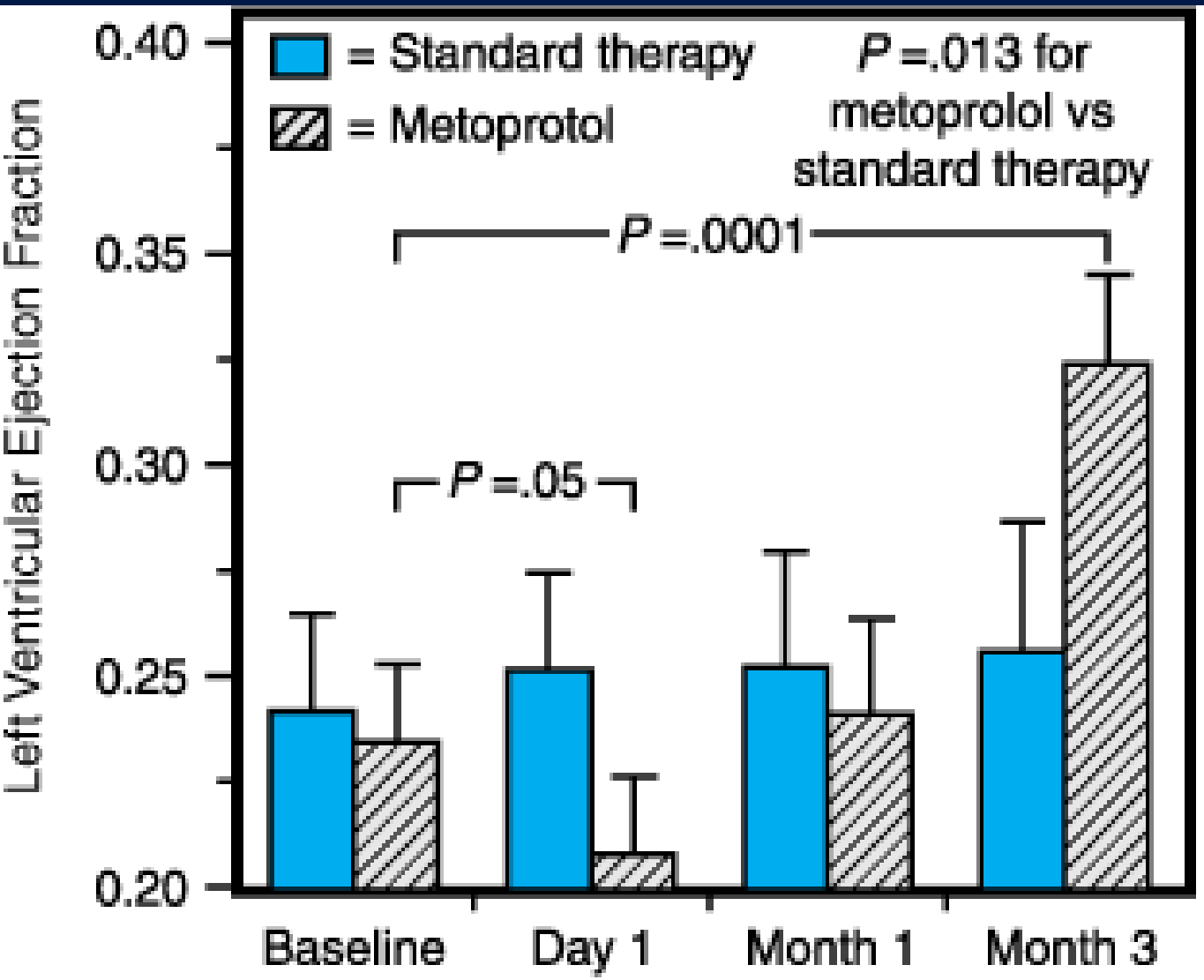
Not superior to ACEIs, but may be useful for patients who can not tolerate ACEIs because of cough.

Beta Blockers

- Traditionally, they have negative inotropic effects.
- However, nowadays there is overwhelming evidence to support the use of β-blockers in CHF.
- Not useful in refractory HF.
- Mechanism involved remains unclear.
- Part of their beneficial effects may derive from slowing of heart rate, decreased cardiac work and consequently decreased myocardial O_2 consumption and enhanced efficiency.
- This would lessen the frequency of ischemic events and arrhythmias.

Beta blockers

- Suggested mechanisms also include reduced remodeling of the heart muscle.
- β-Blockers may be beneficial through resensitization of the down-regulated receptor, thus improving myocardial contractility.
- Should be started with low doses and gradually increased.
- Recent studies with metoprolol, carvedilol, bicindolol, and bisiprolol showed a reduction in mortality in patients with these drugs.
- This does not mean that other older agents are not effective.
- Contraindicated in sever, refractory, unstable cases.



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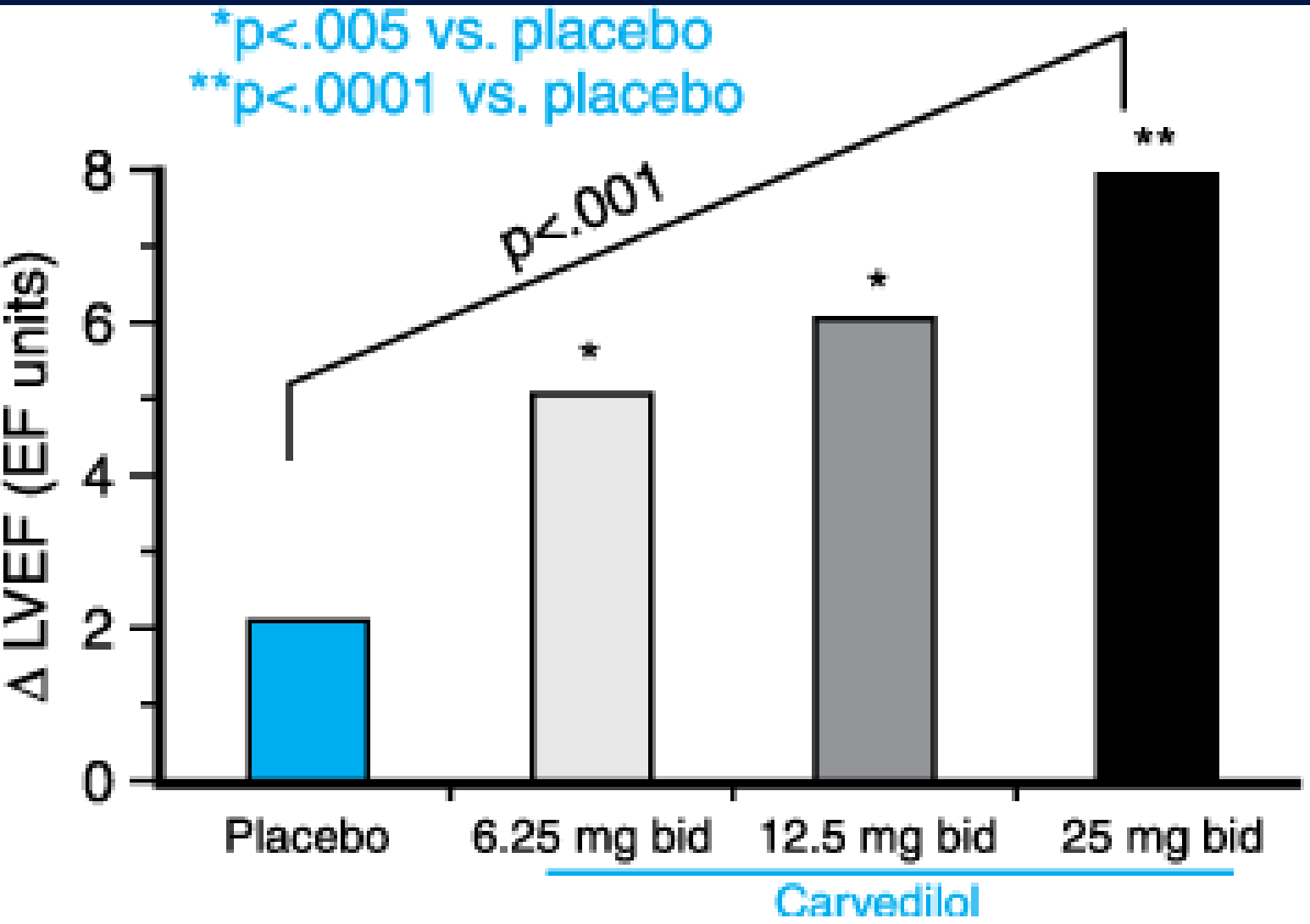

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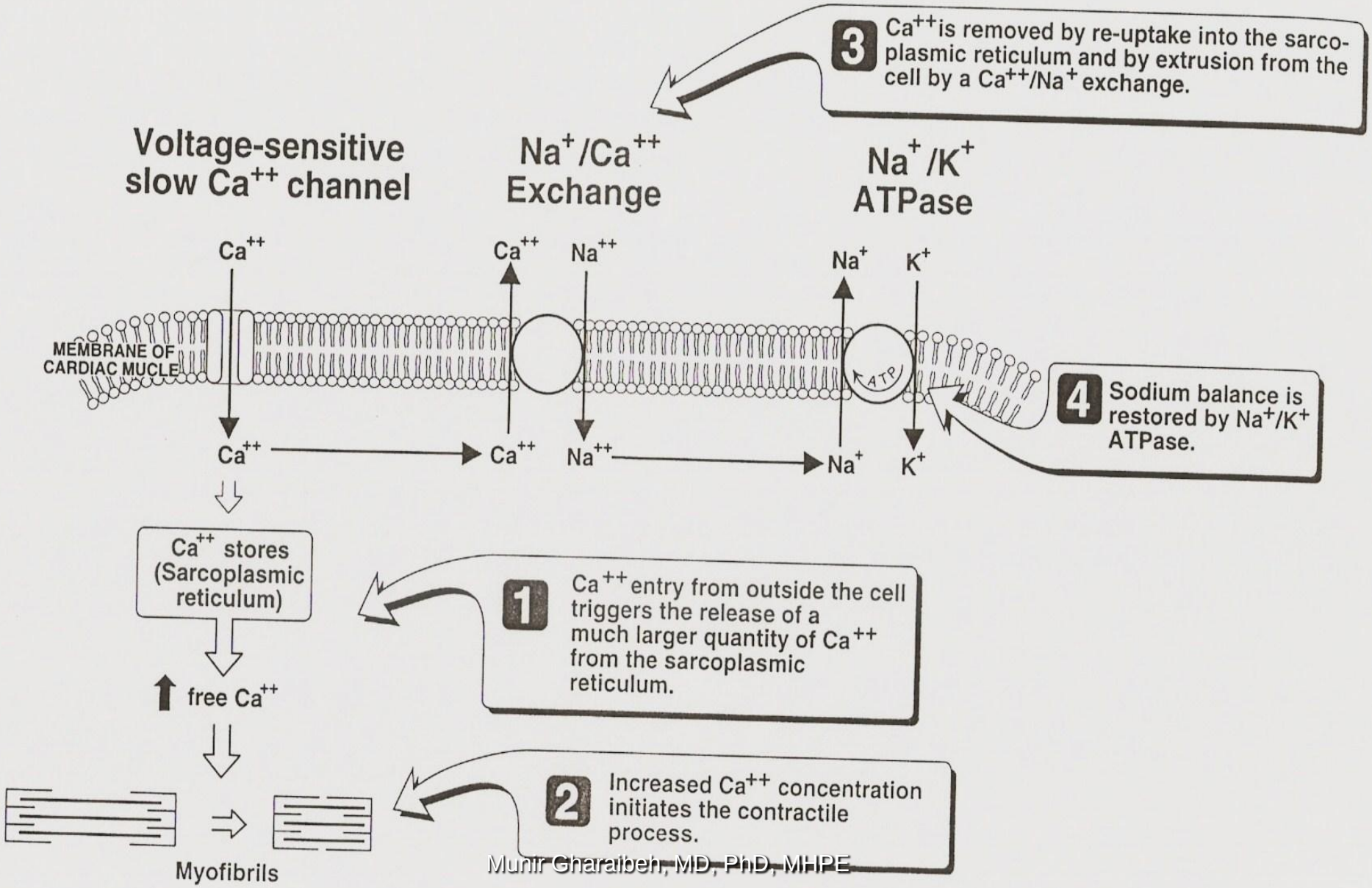
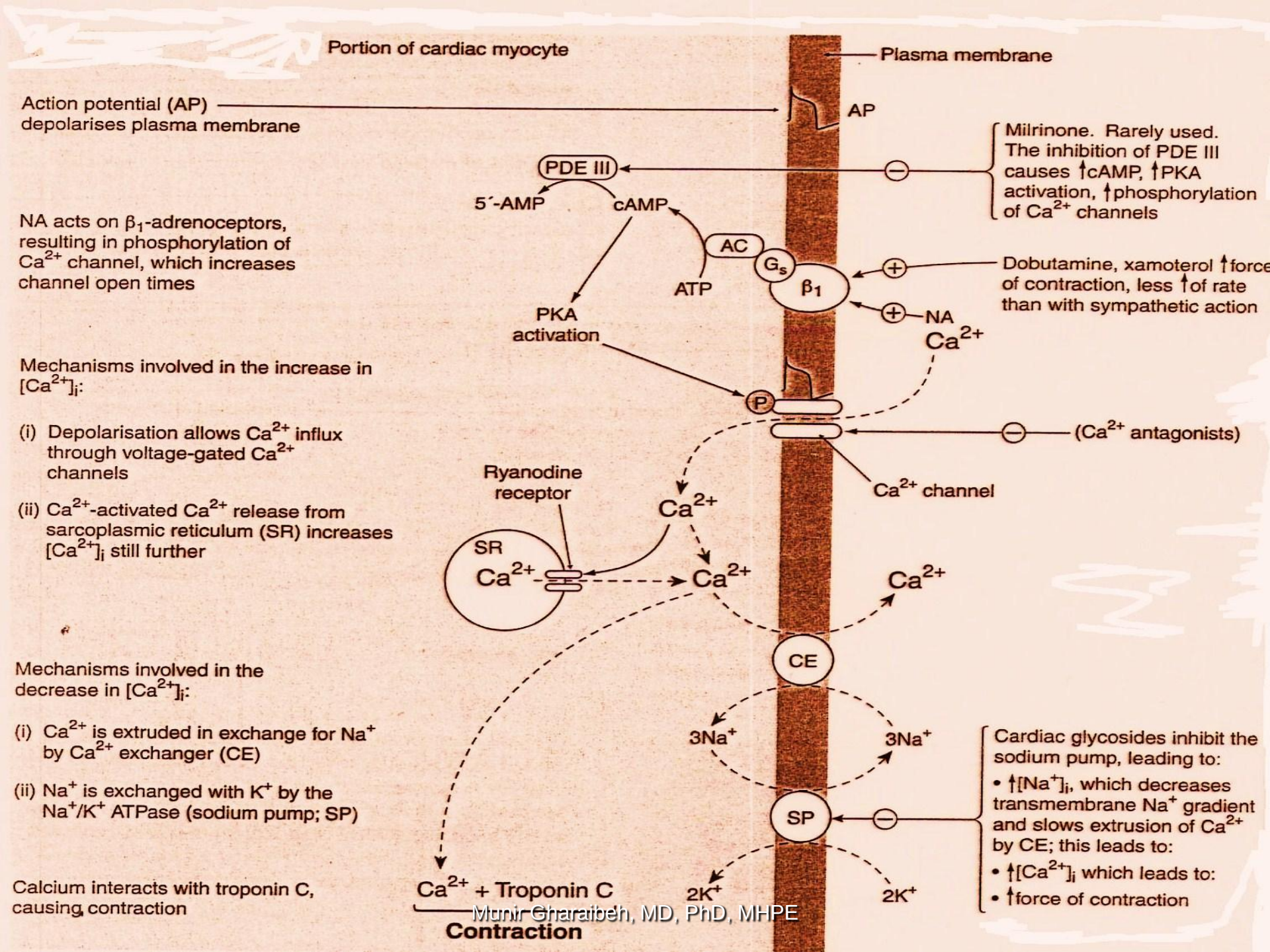
Positive Inotropic Agents

- Logically will improve cardiac function.
- These drugs increase force of contraction by increasing intracellular cardiac Ca^{++} concentration.
- **Cyclic AMP Independent Agents:**
  - **Digitalis**
  - **Pimobendan**
- **Cyclic AMP Dependant Agents:**
  - **β-adrenergic Agonists**
  - **Phosphodiesterase Inhibitors**

Role of Calcium and Sodium in Myocardial contraction





Positive Inotropic Agents

Cyclic AMP Independent Agents:

- **Digitalis**: inhibits Na/KATPase.
- **Pimobendan**: sensitizes myocytes to Ca^{++}, also inhibits PDE.

Digitalis Glycosides

History:

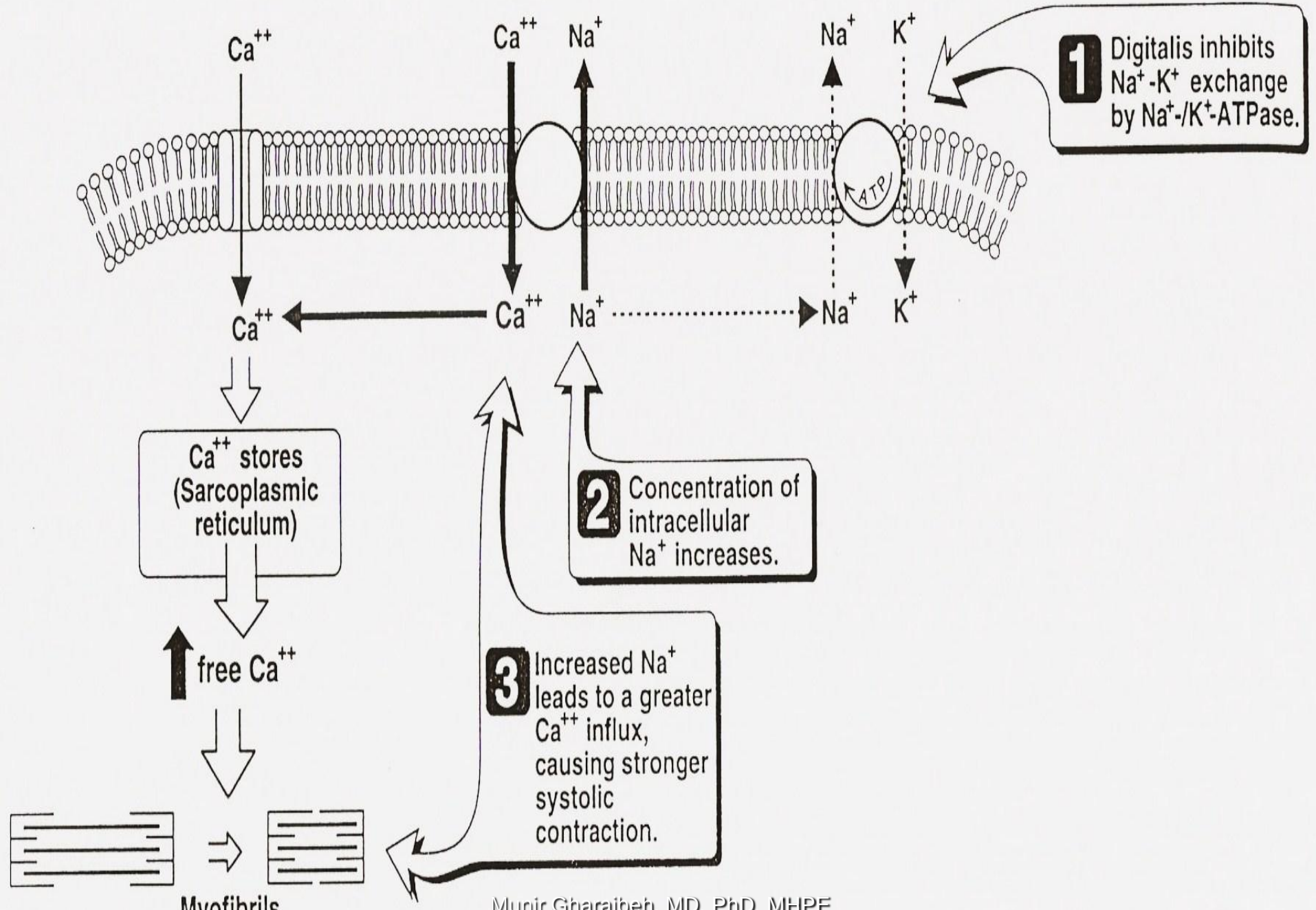
- Egyptians ------- Squill(العنصل)
- Chinese -------- Toad skin
- William Withering ----- Foxglove 1785

- *Digitalis purpura*
- *Digitalis lanata*
- *Strophanthus*

Digitalis Glycosides

Mechanism:

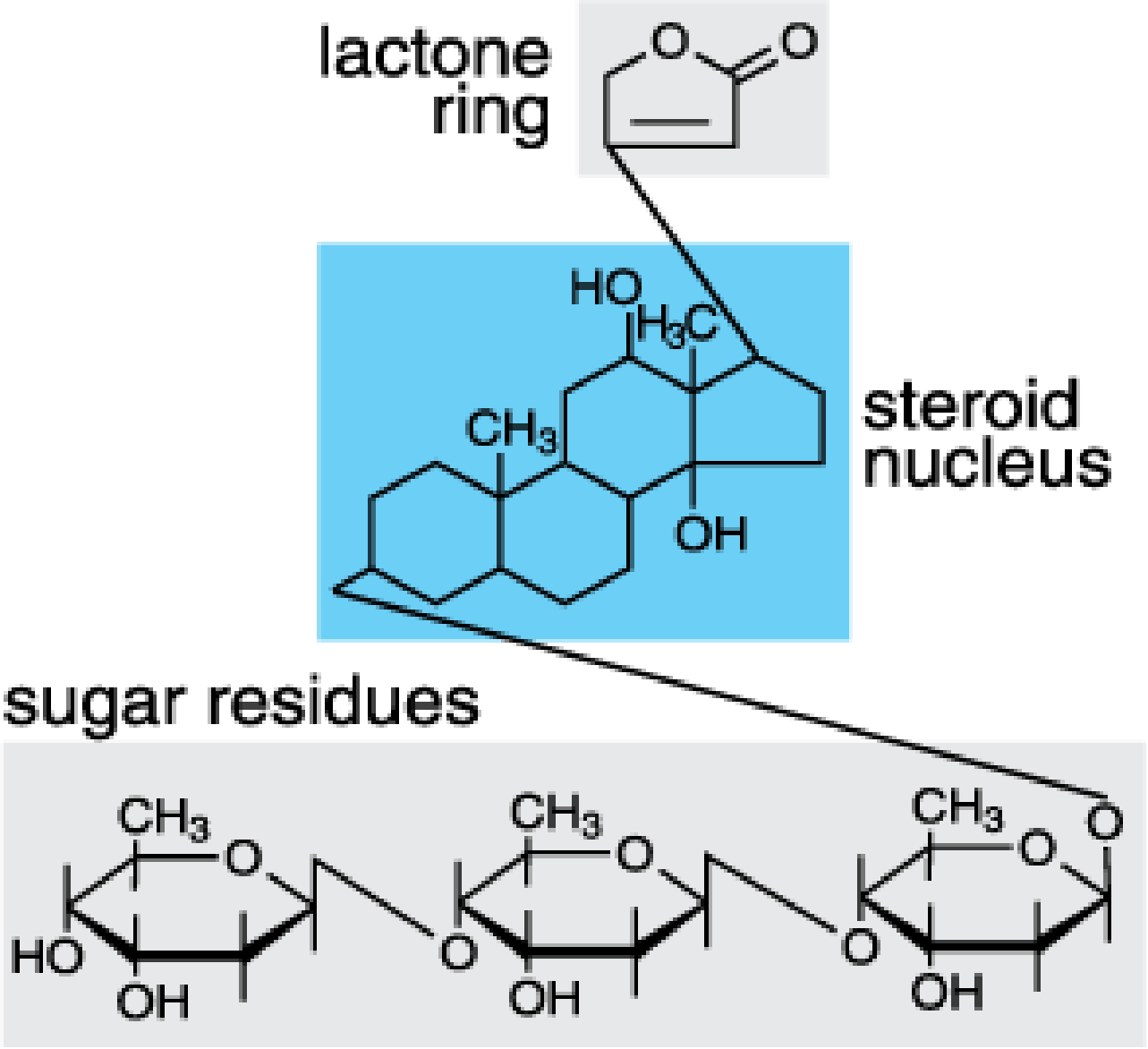
- Inhibition of Na+/K+ ATPase



Digitalis Glycosides

Actions:

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



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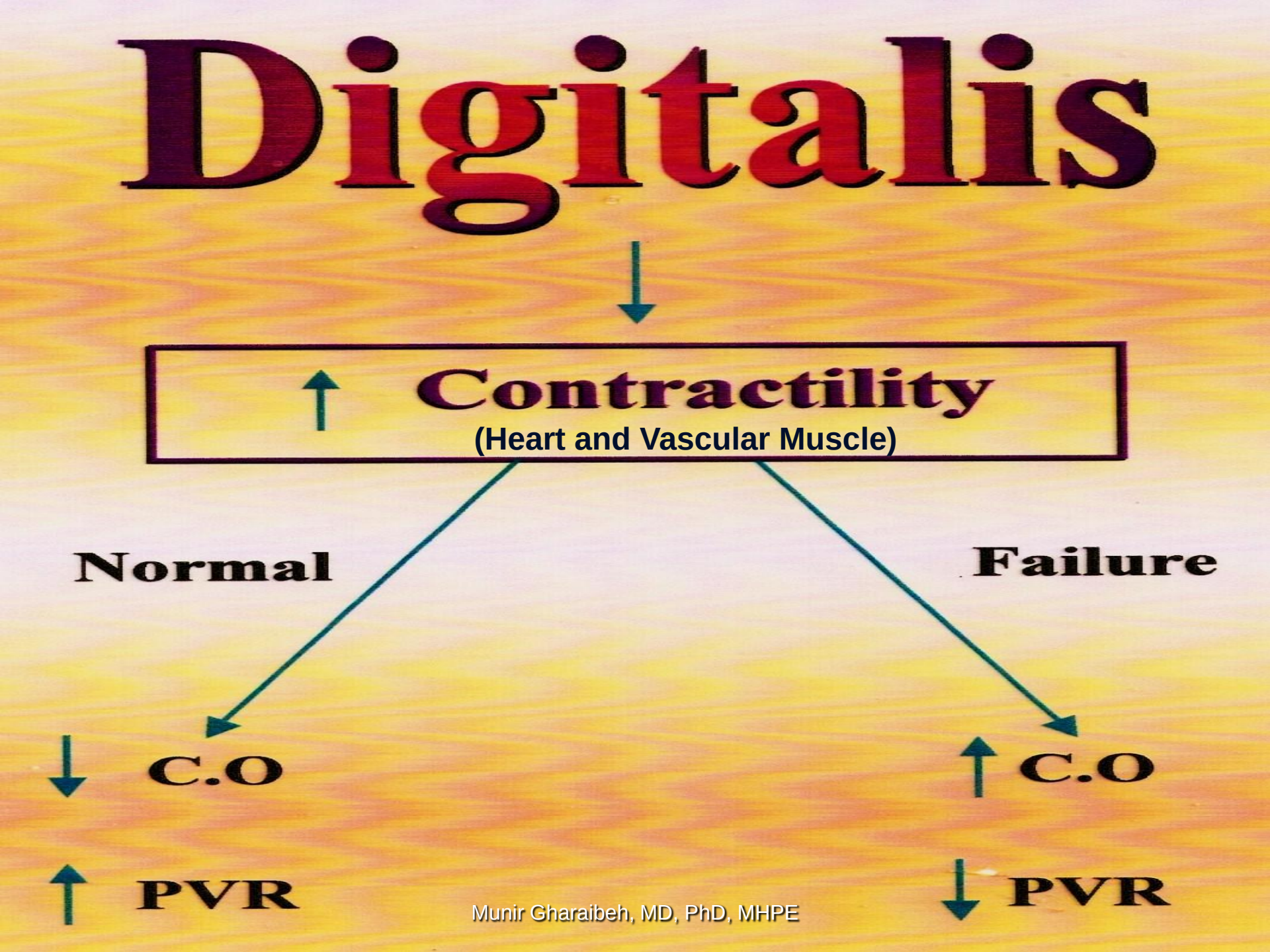
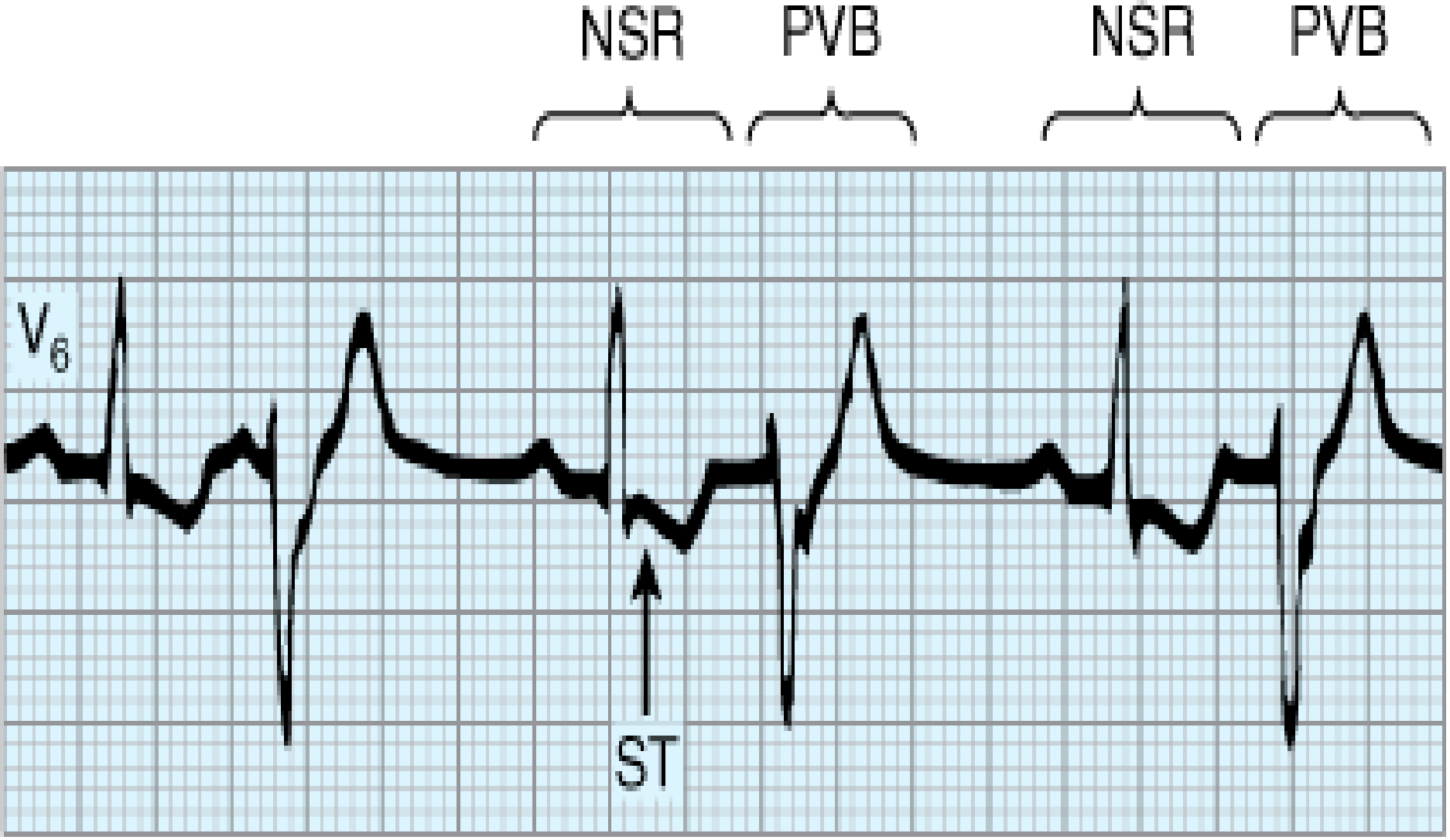

Digitalis
↑ Contractility
(Heart and Vascular Muscle)
Normal
Failure
↓ C.O
↑ PVR
↑ C.O
↓ PVR
Munir Gharaibeh, MD, PhD, MHPE

Effects of Digoxin on Electrical Properties of Cardiac Tissues.

Tissue or Variable	Effects at Therapeutic Dosage	Effects at Toxic Dosage
Sinus node	↓ Rate	↓ Rate
Atrial muscle	↓ Refractory period	↓ Refractory period, arrhythmias
Atrioventricular node	↓ Conduction velocity, ↑ refractory period	↓ Refractory period, arrhythmias
Purkinje system, ventricular muscle	Slight ↓ refractory period	Extrasystoles, tachycardia, fibrillation
Electrocardiogram	↑ PR interval, QT interval	Tachycardia, fibrillation, arrest at extremely high dosage

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).
- **Interactions.**
- *Pharmacological and toxic effects are greater in hypokalemic patients.*
- *K^+-depleting diuretics are a major contributing factor to digoxin toxicity.*



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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.

Digitalis Glycosides

Therapeutic Benefits:

- **Nowadays, o*nly useful in CCHF with supraventricular arrhythmia***
  - **Might decrease morbidity**
  - **? Withdrawal**
  - **? Mortality**

Basic Data of Three Cardiac Glycosides

	Digitoxin	Digoxin	Ouabain
GI absorption	100%	70 –85%	0
Polarity	Least	Somewhat	Highest
Protein binding	97%	< 30%	5 – 10%
Half-life	4 – 7 days	1.5-1.6 days	21 hr
Excretion route	Stool and kidneys; as hepatic metabolites*	Kidneys; largely unchanged	Kidneys; largely unchanged
Enterohepatic recycling	27%	6.8%	Unknown
Optimum serum levels	20-35 ng/ml	0.5-2.5 ng/ml	Unknown
V_d	0.6 L/kg	5-10 L/kg	Unknown

* About 8% of digitoxin is metabolized and excreted as digoxin in the urine. Digitoxin seems to be largely recycled to complete its metabolic degradation.

Positive Inotropic Agents

Cyclic AMP Dependent Agents:

β-adrenergic Agonists:

- NE
- Dopamine
- Dobutamine

Phosphodiesterase Inhibitors:

- 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 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.

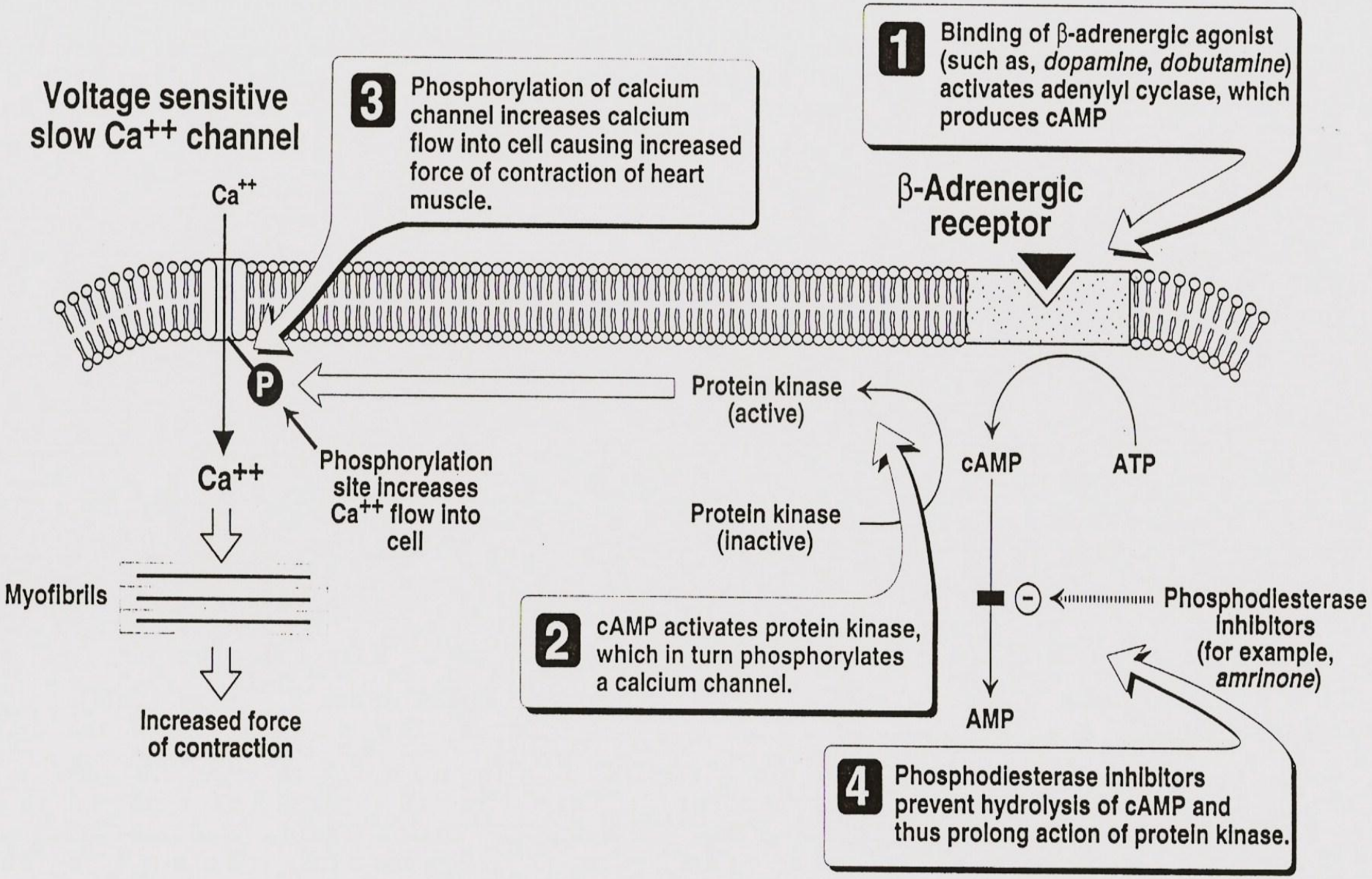


Figure 16.11
Sites of action of β-adrenergic agonists on heart muscle.

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

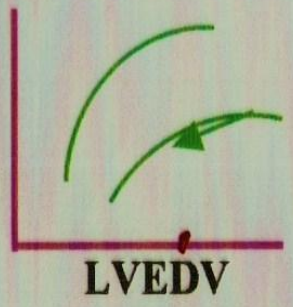
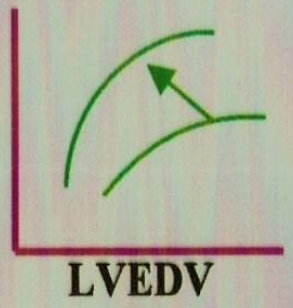
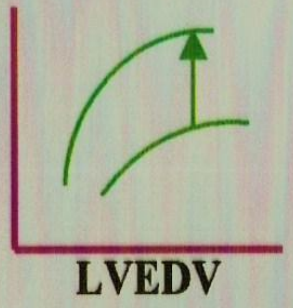
- Affect preload and/or afterload without directly affecting contractility.
- Consequently can decrease myocardial ischemia, enhance coronary blood flow and decrease MVO2.
- Can be used in acute heart failure and for short periods in CCHF.
- Hydralazine-Isosorbide dinitrate combination was found to decrease mortality, maybe by reducing remodeling of the heart.
- Can be combined with ACEI, Diuretics and digitalis.

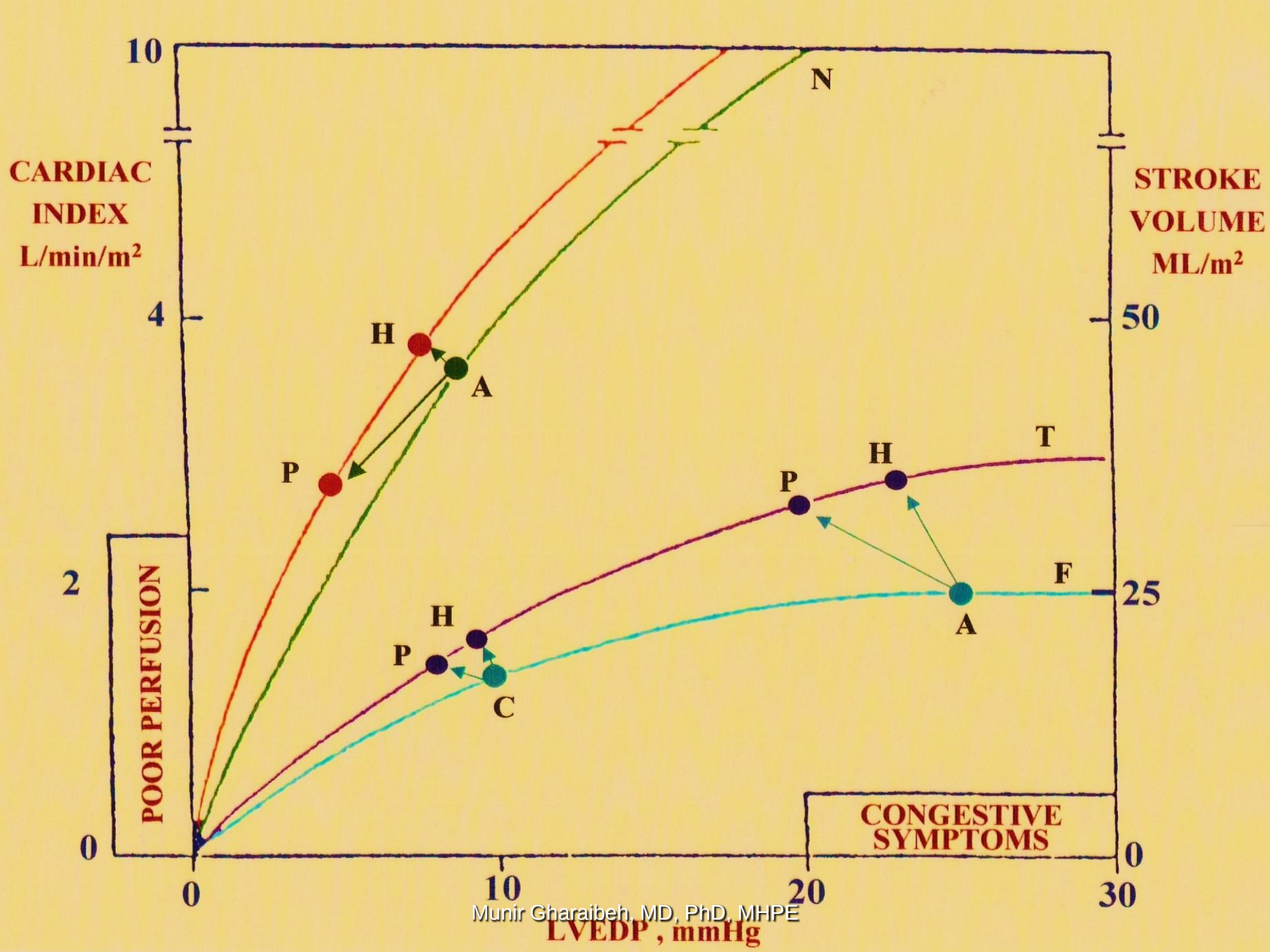
(BNP)-Niseritide

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

(BNP)-Niseritide

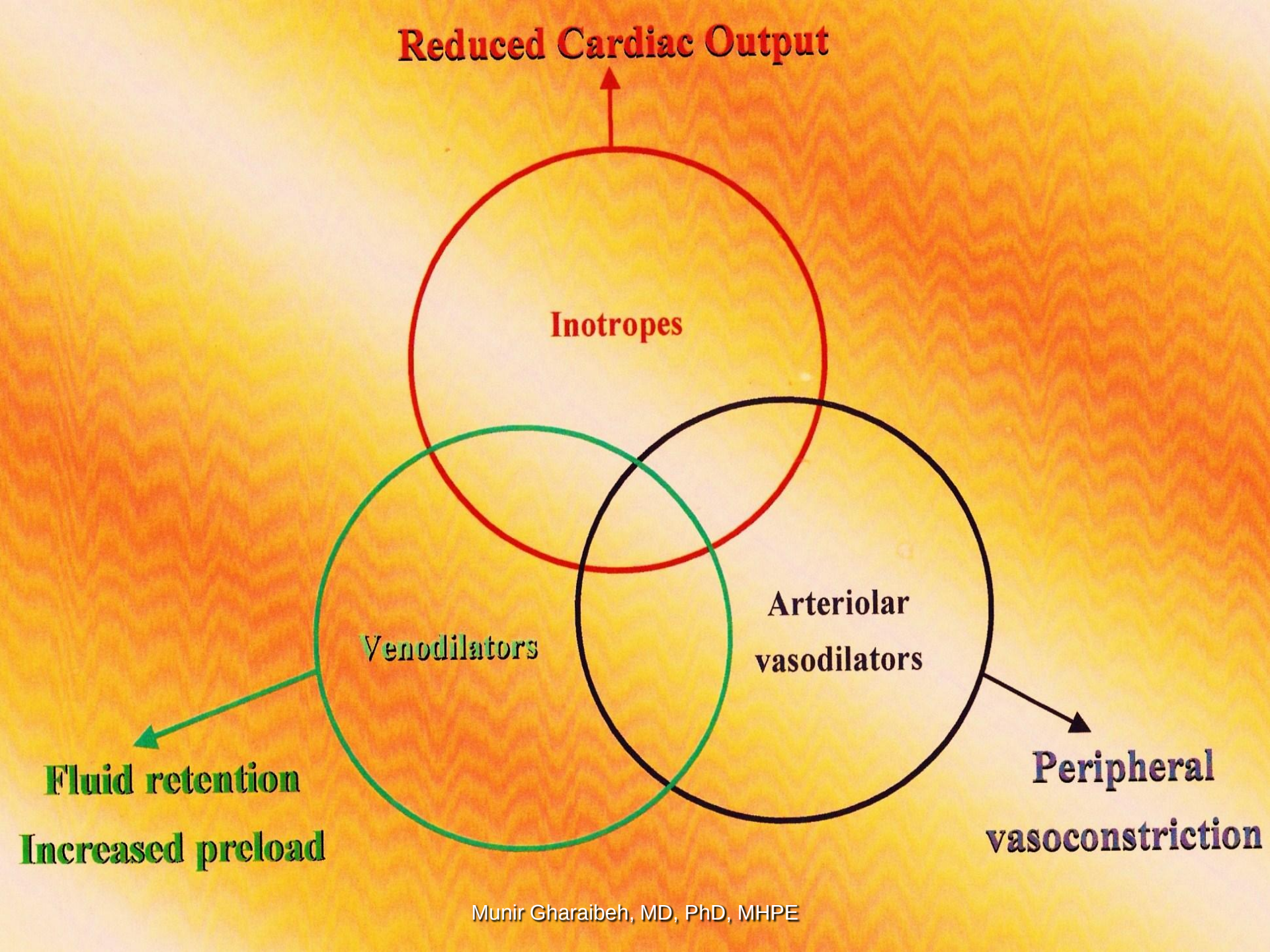
- Reduces systemic and pulmonary vascular resistances, causing an indirect increase in cardiac output and diuresis.
- Effective in HF because of reduction in preload and afterload.
- Hypotension is the main side effect.

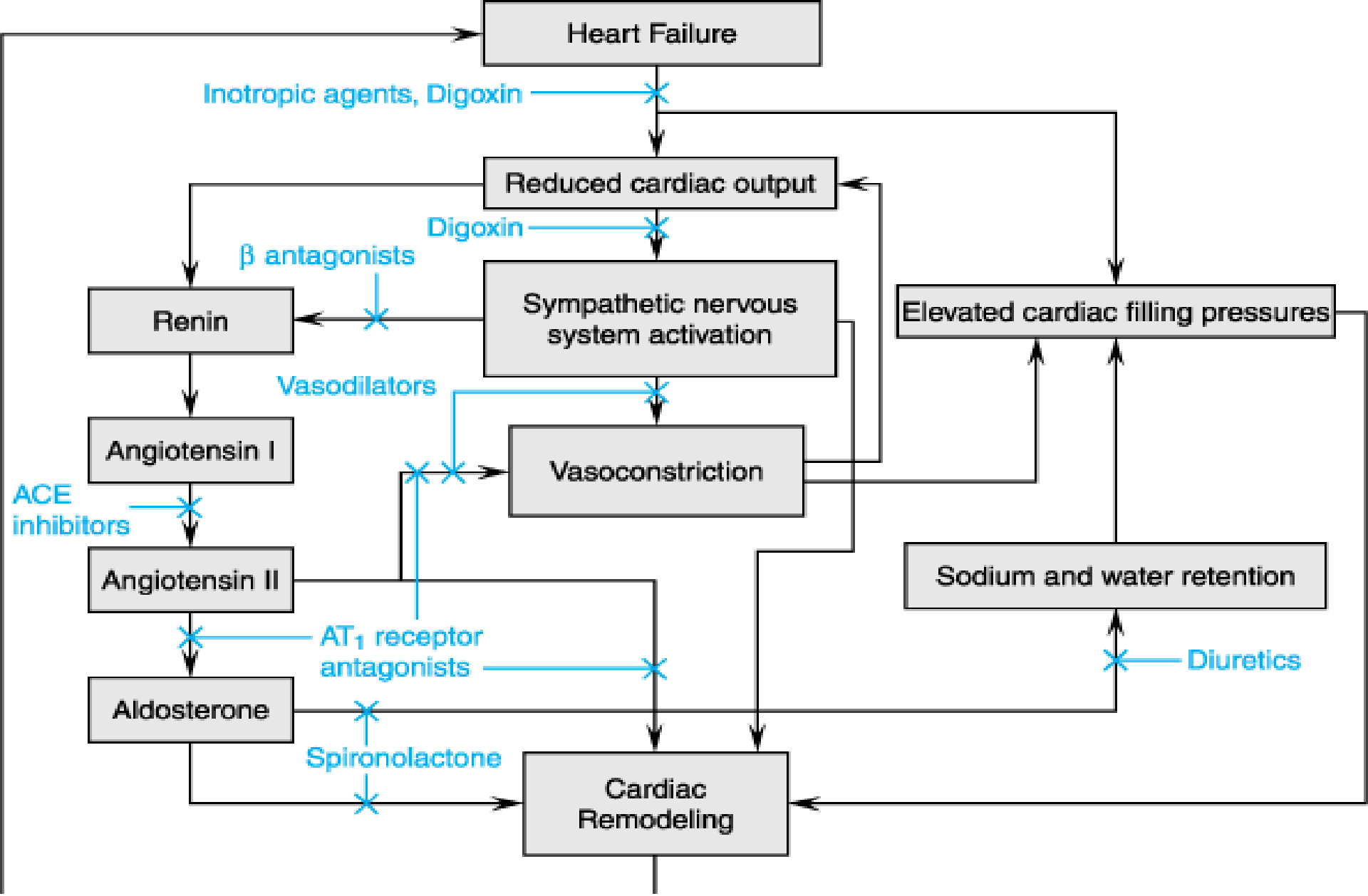
Venous Dilators	Mixed Action	Arterial Dilators
Nitroglycerin Isosorbide dinitrate	Nitroprusside Captopril Enalapril Hydralazine + Nitrate	Hydralazine Minoxidil
		
↓ LVEDV ↓ MVO2 — CO	↓ LVEDV ↓ MVO2 ↑ CO	— LVEDV ↓ MVO2 ↑ CO



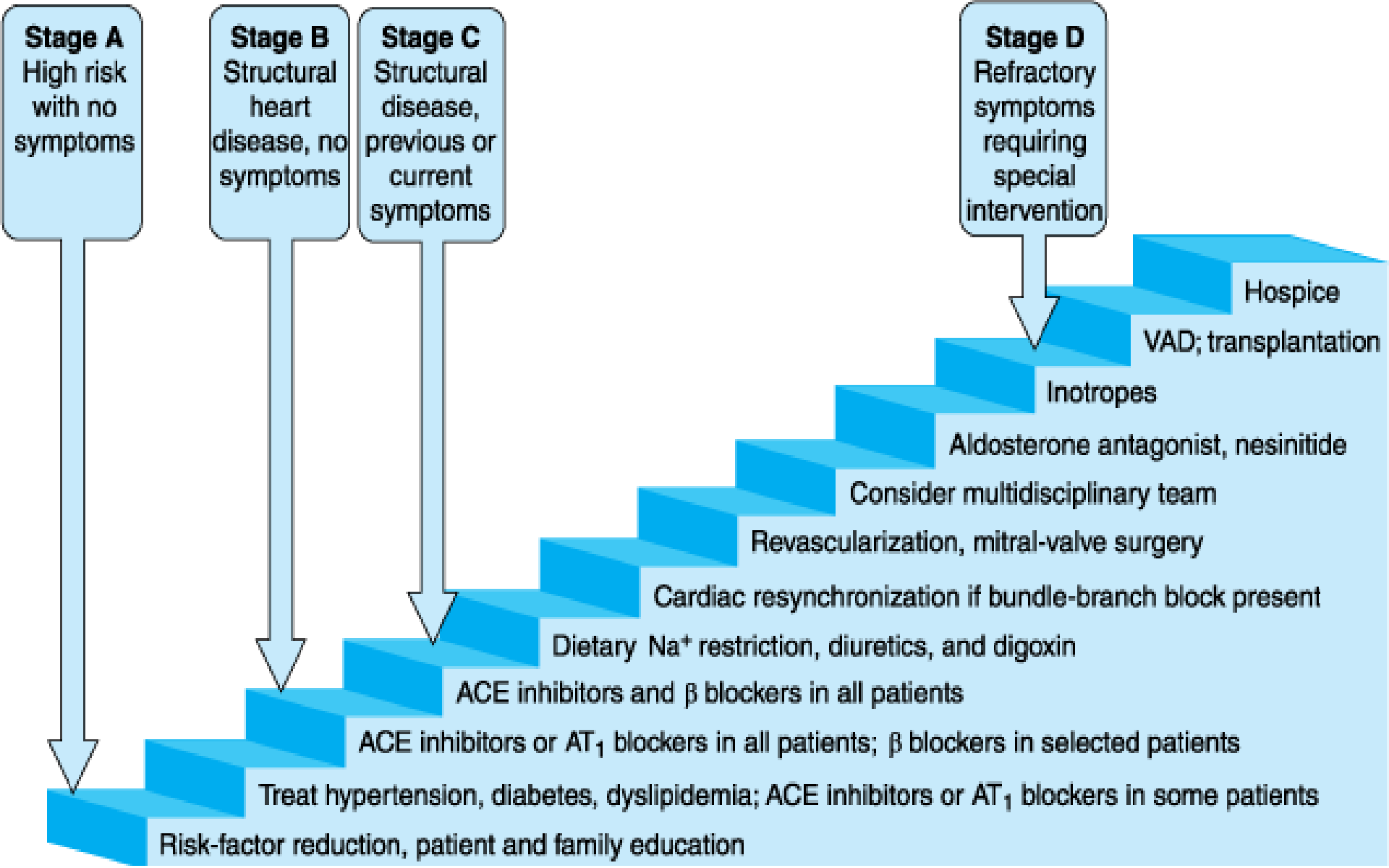
Vasodilator Drugs Used to Treat Heart Failure

DRUG CLASS	EXAMPLES	MECHANISM OF VASODILATING ACTION	PRELOAD REDUCTION	AFTERLOAD REDUCTION
Organic nitrates	Nitroglycerin, isosorbide dinitrate	NO-mediated vasodilation	+++	+
Nitric oxide donors	Nitroprusside	NO-mediated vasodilation	+++	+++
Angiotensin-converting enzyme inhibitors	Captopril, enalapril, lisinopril	Inhibition of Ang II generation, decreased bradykinin degradation	++	++
Angiotensin receptor blockers	Losartan, candesartan	Blockade of AT_1 receptors	++	++
Phosphodiesterase inhibitors	Milrinone, inamrinone	Inhibition of cyclic AMP degradation	++	++
Direct-acting K^+-channel agonist	Hydralazine	Unknown	+	+++
	Minoxidil	Hyperpolarization of vascular smooth muscle cells	+	+++
$_1$-Adrenergic antagonists	Doxazosin, prazosin	Selective $_1$ adrenergic receptor blockade	+++	++
Nonselective α adrenergic antagonists	Phentolamine	Nonselective adrenergic receptor blockade	+++	+++
Vasodilating β/ $_1$ adrenergic antagonists	Carvedilol, labetalol	Selective $_1$ adrenergic receptor blockade	++	++
Ca^{2+} channel blockers	Amlodipine, nifedipine, felodipine	Inhibition of L-type Ca^{2+} channels	+	+++
adrenergic	Isoproterenol	Stimulation of vascular $_2$	+	++


Reduced Cardiac Output
Inotropes
Venodilators
Arteriolar vasodilators
Fluid retention
Increased preload
Peripheral vasoconstriction



Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com



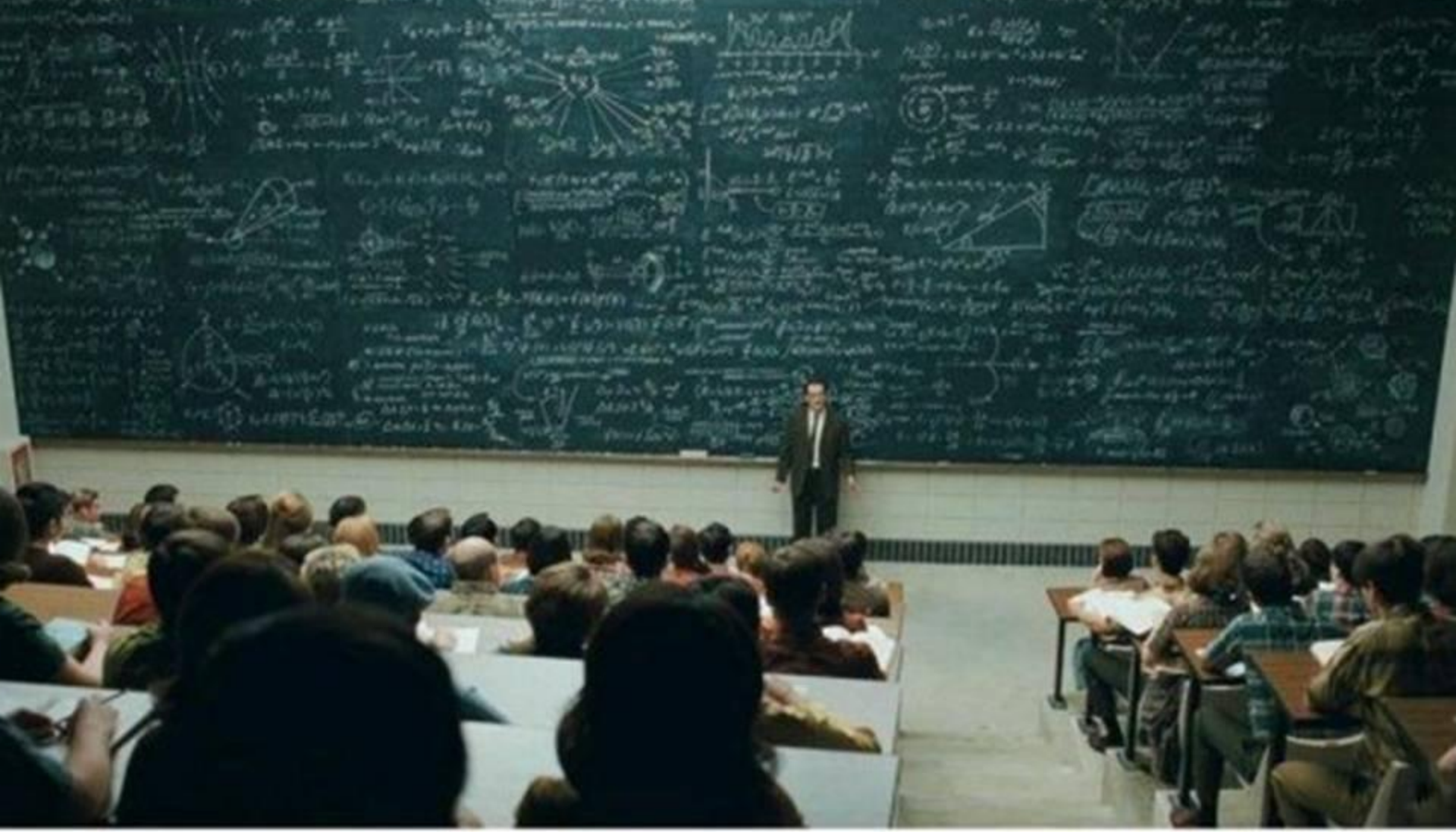
Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com

Steps in the Prevention and Treatment of Chronic Heart Failure.

ACC/AHA Stage	Step[1]	Intervention
A, B	1	Control hypertension, hyperlipidemia, glucose metabolism (diabetes), obesity
C	2	Reduce workload of the heart (limit activity, put on temporary bed rest)
	3	Restrict sodium intake, give diuretics
	4	Restrict water (rarely required)
C, D	5	Give angiotensin-converting enzyme inhibitor or angiotensin receptor blocker
	6	Give digitalis if systolic dysfunction with third heart sound or atrial fibrillation is present
	7	Give β blockers to patients with stable class II–IV heart failure
	8	Give aldosterone antagonist
	9	Give vasodilators
D	10	Cardiac resynchronization if wide QRS interval is present in normal sinus rhythm

Errors in Management of HF

- Missed diagnosis.
- Improper dosage of diuretics.
- Failure to assess quality of life.
- Failure to consider long term therapeutic goals.
- Underprescribing of ACEI.
- Use of potentially harmful drugs.
- Failure to use hydralazine-isosorbide combination which has proved evidence of benefit.



مفهوم لو اعيدلكم الدرس ....