Drug Therapy of Heart Failure

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Drug Therapy of Heart Failure

Definition of Heart Failure

Causes

Classifications



TABLE 13-1 Drug groups used in heart failure.

Chronic heart failure	Acute heart failure
Diuretics	Diuretics
Aldosterone receptor antagonists	Vasodilators
Angiotensin-converting enzyme inhibitors	Beta agonists
Angiotensin receptor blockers	Bipyridines
Beta blockers	Natriuretic peptide
Cardiac glycosides	
Vasodilators	

Definition of Heart Failure

- Heart is unable to provide adequate perfusion of peripheral organs to meet their metabolic requirements
- Characterized by:
- 1. Decreased CO 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
 - 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)
 - 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 systemis disease (hypothyroidism)

CONTRACTILITY



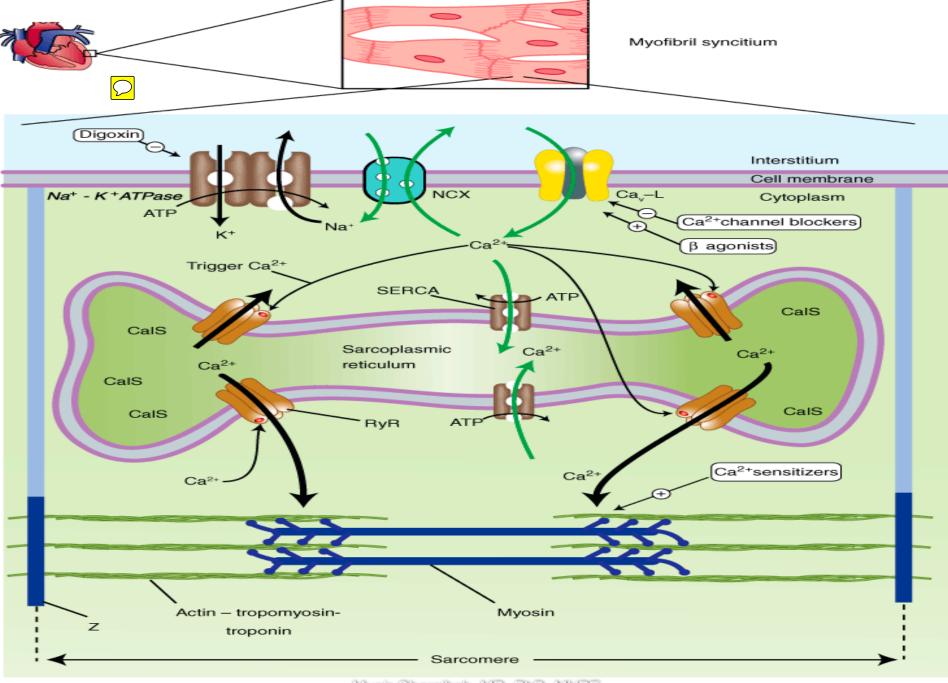
PRELOAD
End diastolic
volume



AFTERLOAD
Ejection tension

HEART RATE

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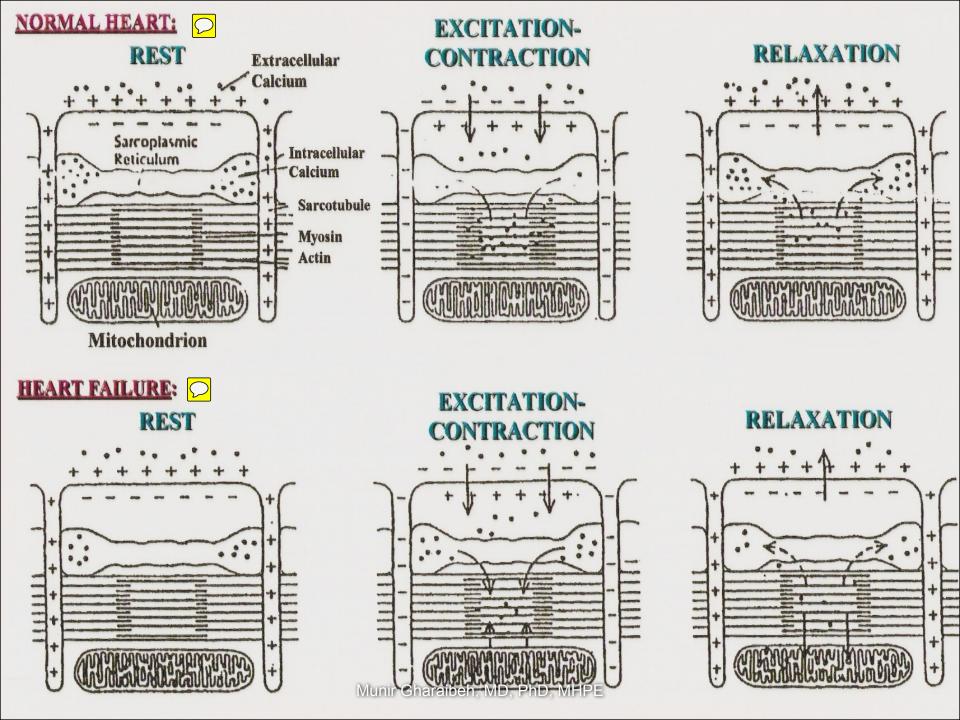
Mechanisms of H. F.

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.

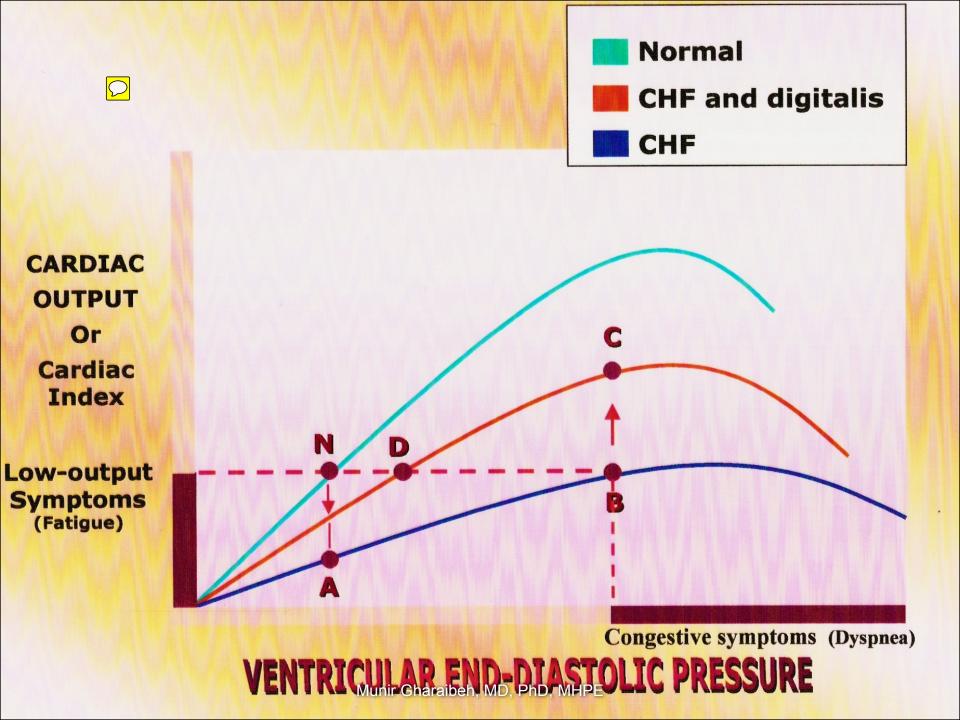
 β receptor density (due to down regulation after chronic exposure to high circulating catecholamines).

 □
- 5. Abnormal Ca++ binding: O
 - 1. Less stored in SR
 - 2. More stored in Mitochondria
 - 3. Less released
 - 4. Lesser reuptake into SR.
 - 5. Slow reupting a slow relaxation.



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.

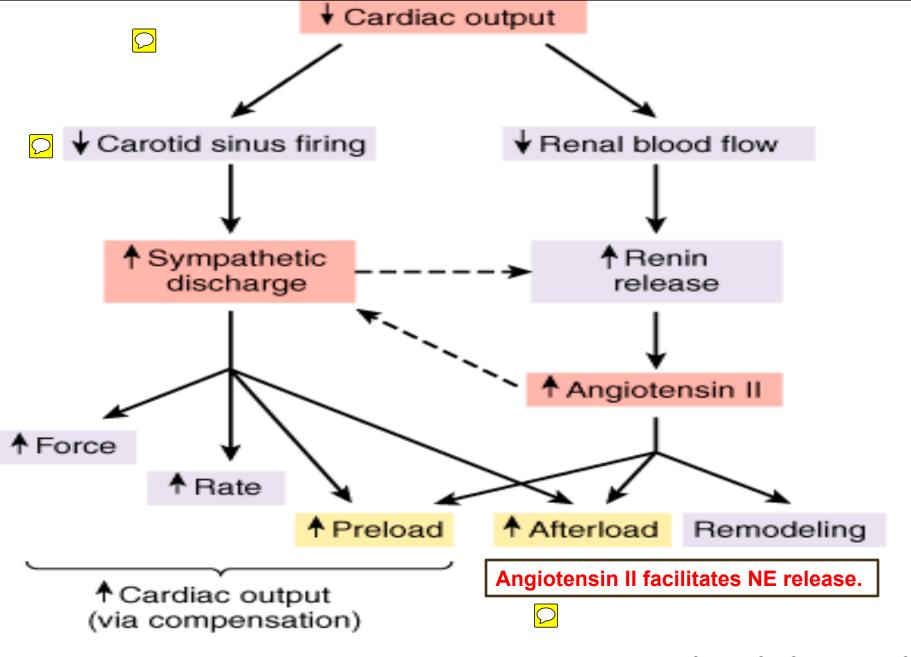


Compensatory SNS Mechanisms in HF

- In a failing heart, the loss of contractile function leads to a decline in CO and a decrease in 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:
- Increasing myocardial contractility and heart rate (β₁-adrenergic receptors)
- 2. Increasing vasomotor tone (α₁-adrenergic receptors) to maintain systemic blood pressure

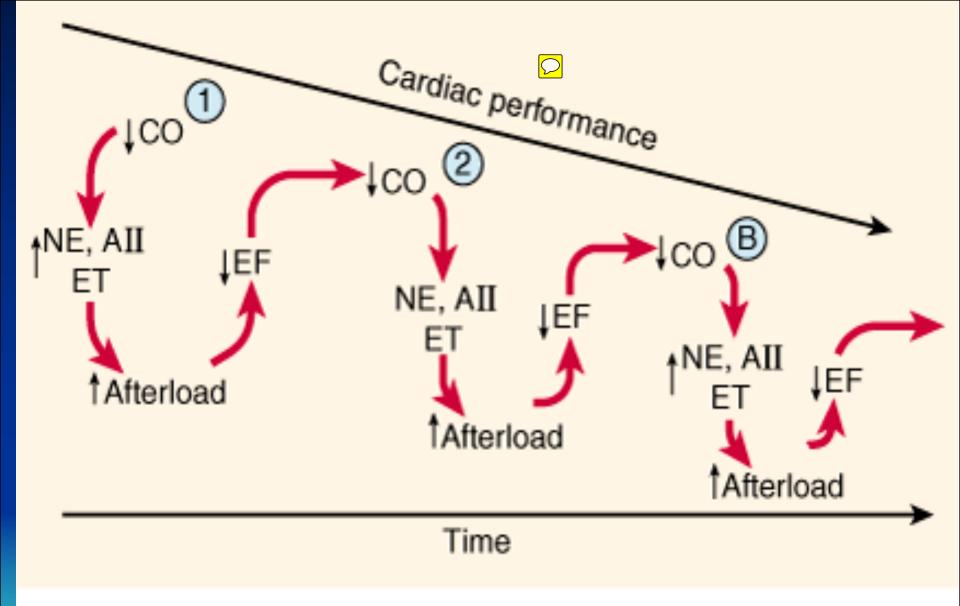
Consequences of hyperadrenergic state

- Enhancement of RAAS.
- Irreversible myocyte damage, cell death, and fibrosis.
- Increased peripheral vasomotor tone increases LV afterload.
- This places an added stress upon the left ventricle and an increase in myocardial O₂ demand (ventricular remodeling).
- The frequency and severity of cardiac arrhythmias are enhanced in the failing heart



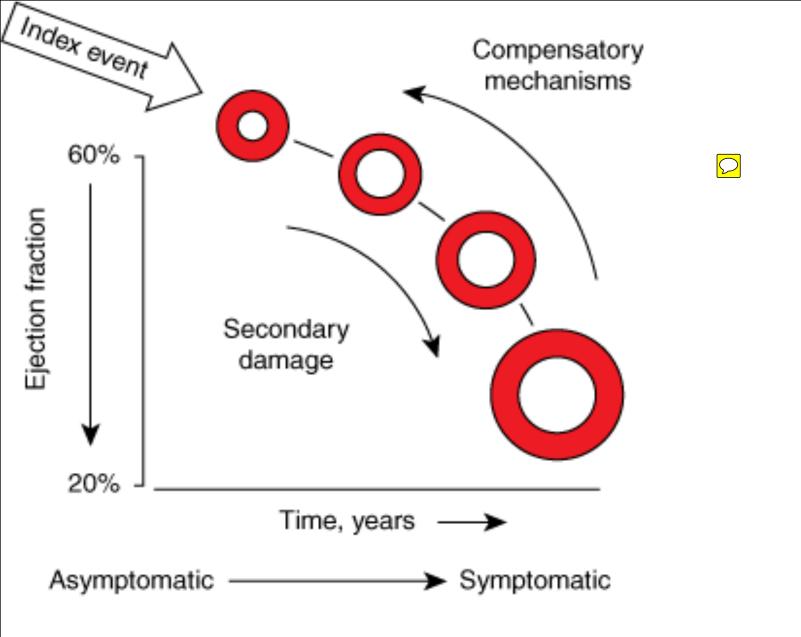
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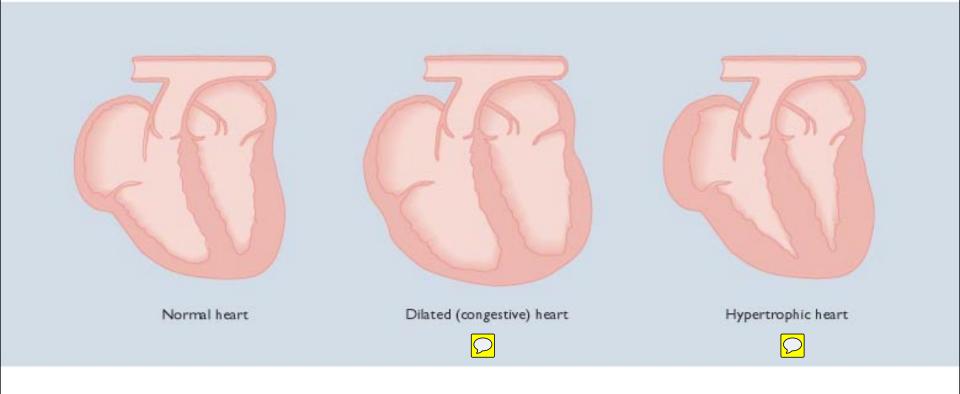
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Signs and Symptoms of HF

- Tachycardia, sweating
- Decreased exercise tolerance & SOB
- Peripheral and pulmonary edema
- Cardiomegaly (Cardiomegaly and Hypertrophy)



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

Dietary indiscretion \bigcirc

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

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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 symptomfree 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

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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

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TABLE 13-3 Classification and treatment of chronic heart failure.



ACC/AHA Stage ¹	NYHA Class ²	Description	Management
A	Prefailure	No symptoms but risk factors present ³	Treat obesity, hypertension, diabetes, hyperlipidemia, etc
В	1	Symptoms with severe exercise	ACEI/ARB, β blocker, diuretic 🔽
C	11/111	Symptoms with marked (class II) or mild (class III) exercise	Add aldosterone antagonist, digoxin; CRT, hydralazine/ nitrate ⁴
D	IV	Severe symptoms at rest	Transplant, LVAD 🔽

American College of Cardiology/American Heart Association classification.

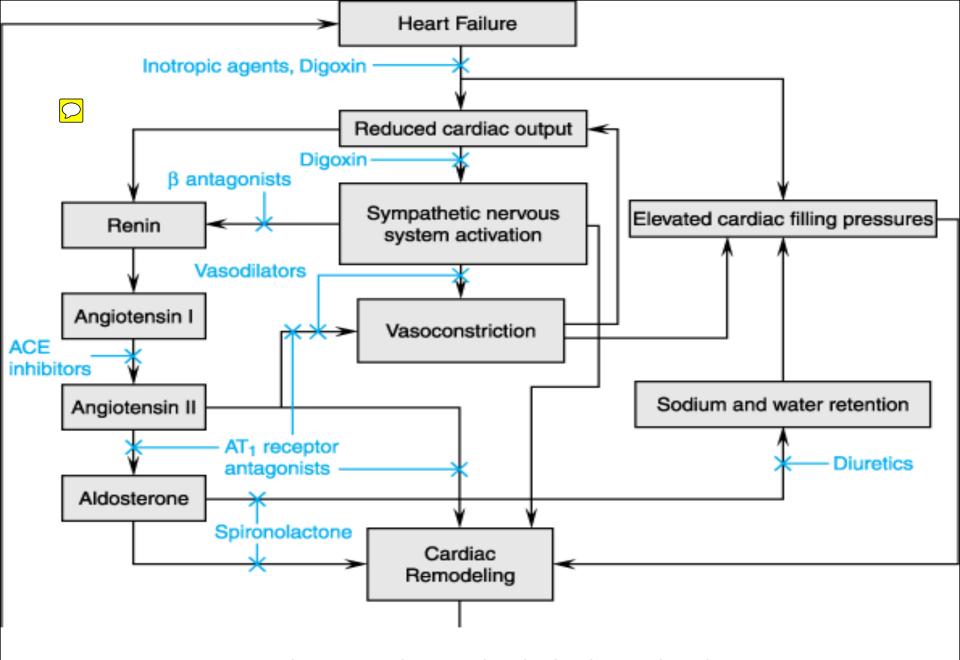
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CRT, cardiac resynchronization therapy; LVAD, left ventricular assist device. Nov-17

26

²New York Heart Association classification.

^{*}Risk factors include hypertension, myocardial infarct, diabetes.

For selected populations, eg, African American.



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Diuretics

Only for congestive symptoms:

Do not C.O..... may Co

Can be used alone initiallyIV

May be used in combination with digitalis or others.

Cause

○K+ Loss, PP,....etc.

Can be reduceduni Gharaiben, MD, PhD, MHPEAWN

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

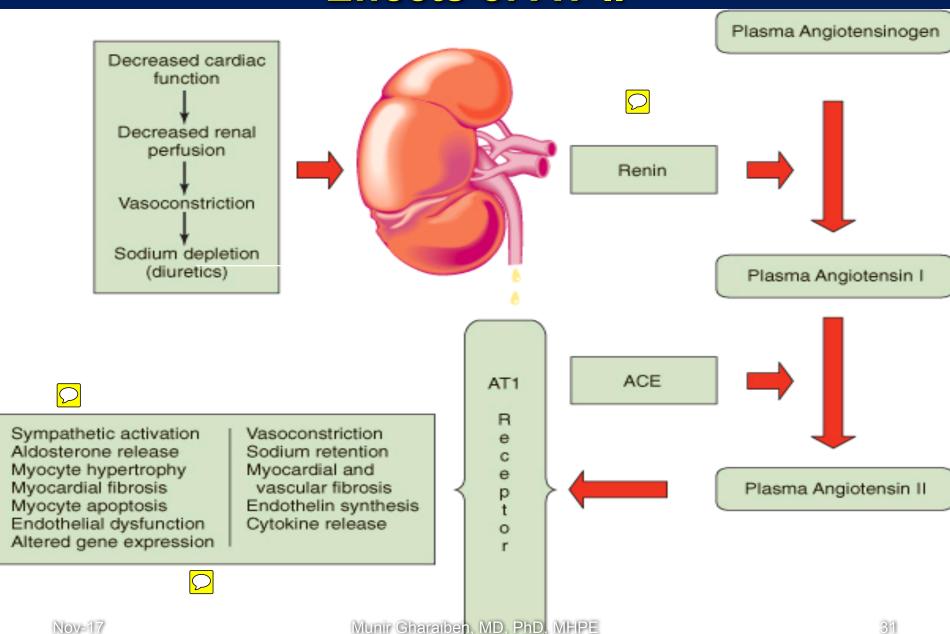
*Nonsteroidal anti-inflammatory drugs

*Primary renal pathology

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

 The Relationship between the Renin-Angiotensin-Aldosterone System and Heart Failure

Effects of AT-II



Potential Roles of Aldosterone in the Pathophysiology of Heart Failure



PATHOPHYSIOLOGICAL EFFECT

Increased Na⁺ and water retention

Edema, elevated cardiac filling pressures

K⁺ and Mg²⁺ 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

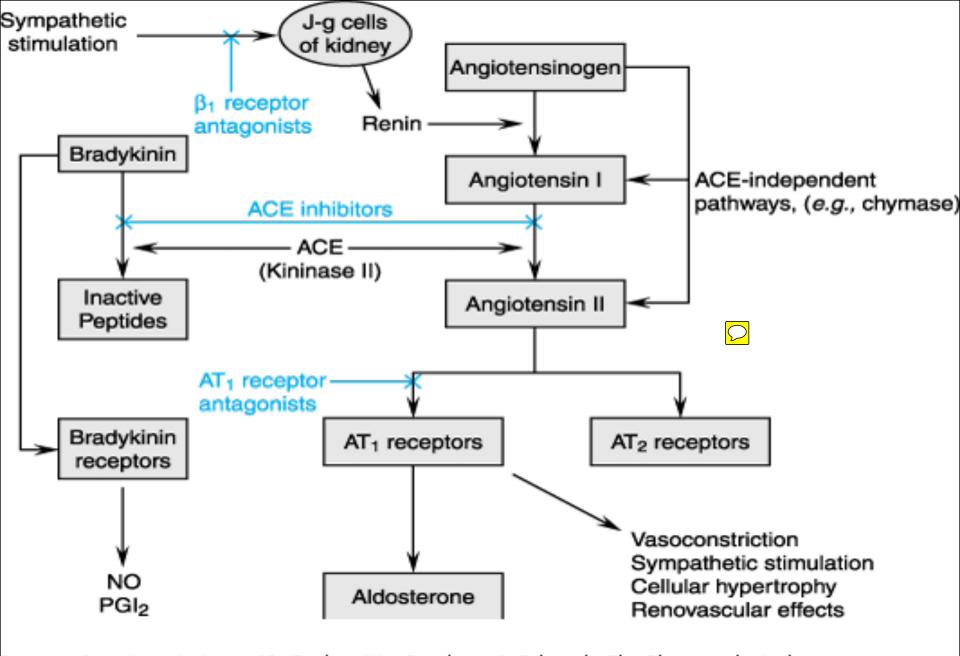
Alterations in Na⁺ channel expression

Increased excitability and contractility of cardiac myocytes

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Angiotensin Converting Enzyme Inhibitors "ACEI"

- Pharmacological Actions:
- Blockade of ACE
- Reduce angiotensin II levels.
- Increase bradykinin.
- Inhibit SNS, leading to decreased NE release and upregulation of β1 receptors.
- Balanced vasodilators causing reduction of both afterload and preload
- Reduce myocyte & fibroblast growth factors causing reduced cardiac remodeling.
- Decrease aldosterone causing decreased fluid retention, decreased K+ loss, and consequently reduced



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

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Therapeutic Values of ACEI

- Nowadays drugs of choice.
- No tolerance.
- Retard progression of HF.
- Decrease arrhythmias.
- Proved to 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 D

Angiotensin (AT1) Receptor Blockers ARBs

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

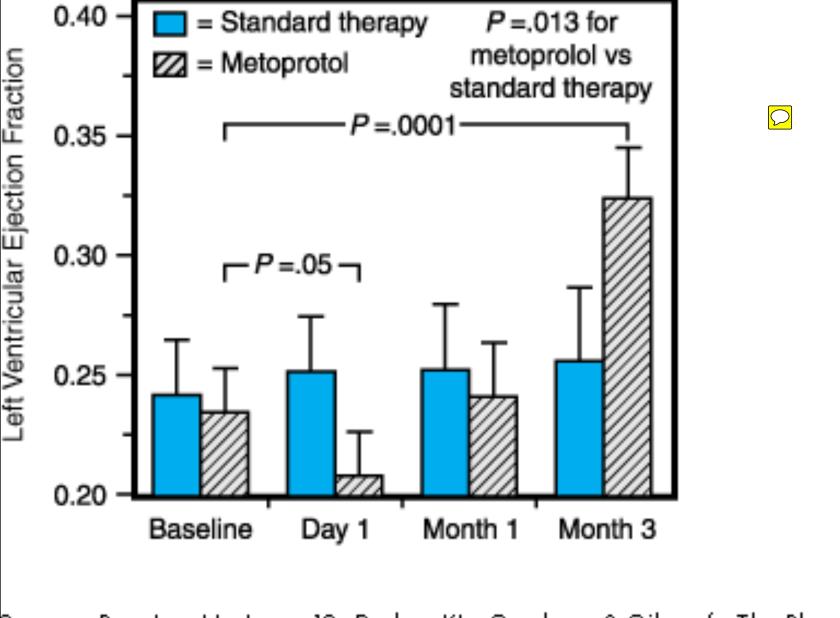
Not superior to ACEIs, but may be useful for patients who can not tolerate ACEIs because of cough.

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 O₂ consumption and enhanced efficiency.
- This would lessen the frequency of ischemic events and arrhythmias.

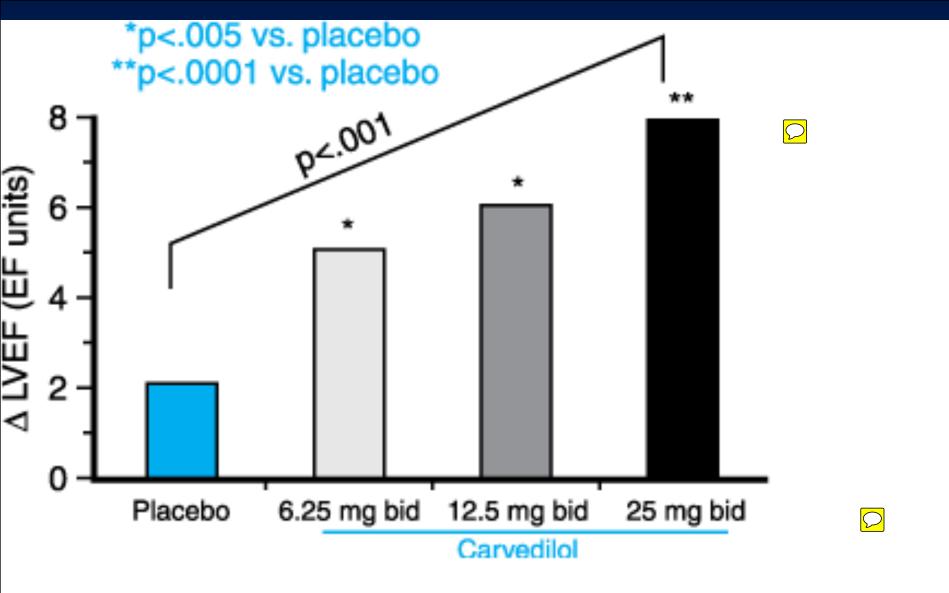
Beta blockers

- 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 treated with these drugs.
- This does not mean that other older agents are not effective.
- Contraindicated in sever, refractory, unstable cases.



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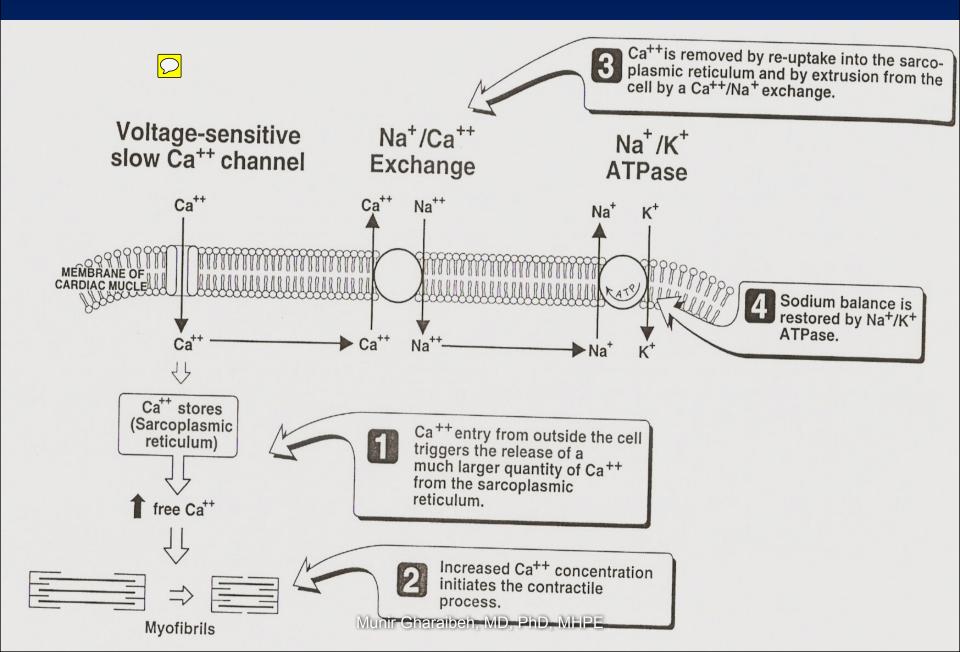


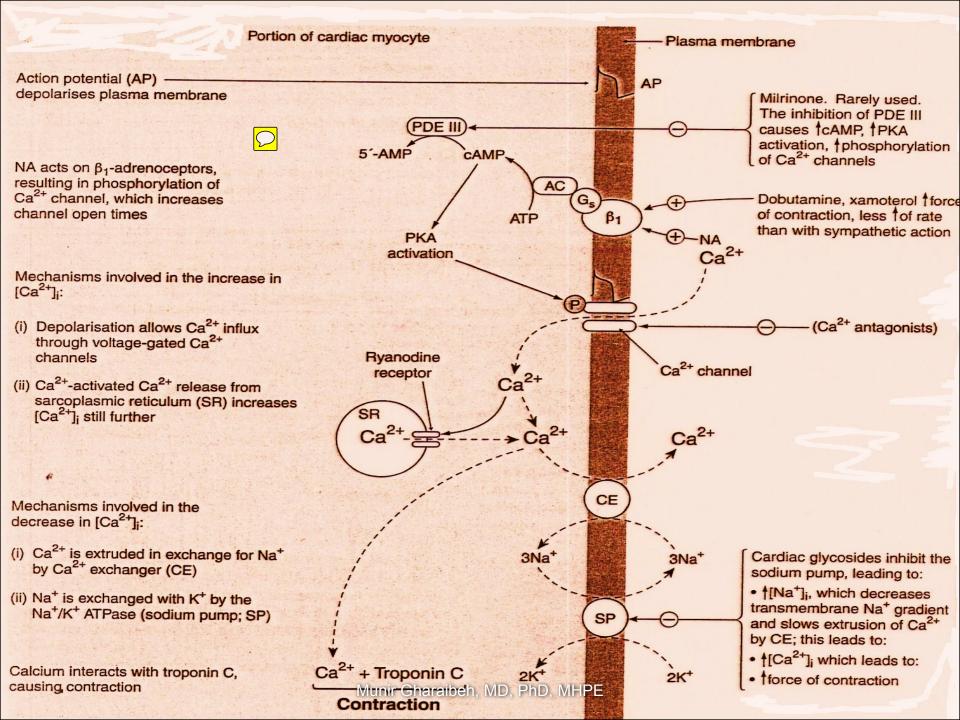
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- Logically will improve cardiac function.
- These drugs increase force of contraction by increasing intracellular cardiac Ca⁺⁺ concentration.
- Cyclic AMP Independent Agents: Digitalis
 - **Pimobendan**
- Cyclic AMP Dependant Agents:
 - **β-adrenergic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

Role of Calcium and Sodium in Myocardial contraction





Cyclic AMP Independent Agents:

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

Digitalis Glycosides

History:

- Egyptians -----
- Chinese

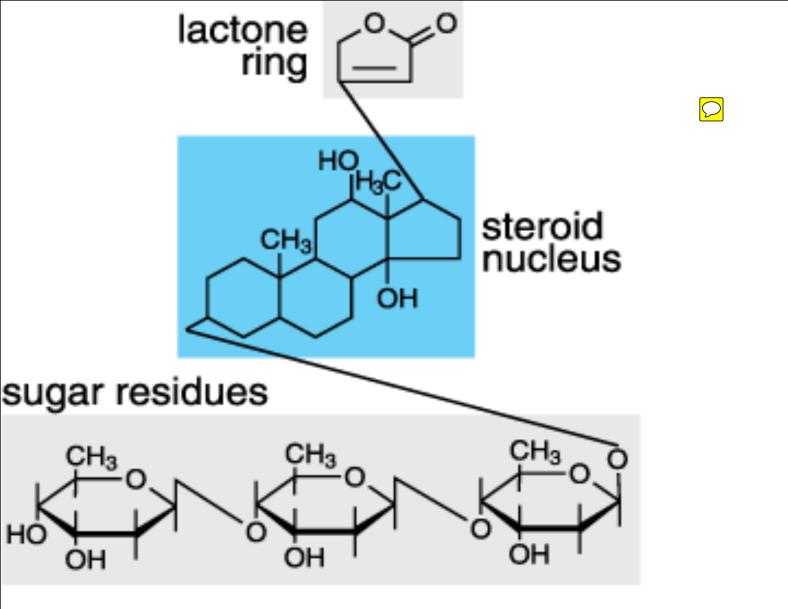
العنصل)Squill

Toad skin

William Withering ---- Foxglove 1785

- Digitalis purpura
- Digitalis lanata
- Strophanthus





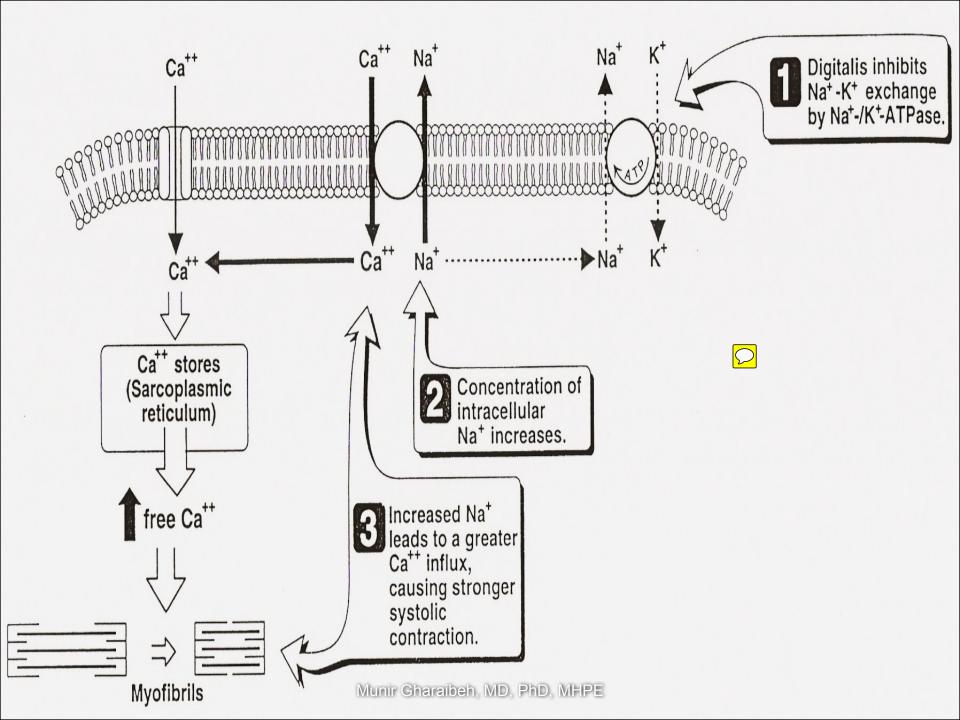
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Digitalis Glycosides

Mechanism:

Inhibition of Na+/K+ ATPase



Digitalis Glycosides

Actions:

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

Digitalis



Contractility

(Heart and Vascular Muscle)

Normal

Failure









Effects of Digoxin on the Electrical Properties of Cardiac Tissues.

Tissue or	
Variable	

Effects at Therapeutic Doses(vagal Stimulation)

Effects at Toxic Doses

Sinus node

Rate

⁺ Rate

Atrial muscle

Refractory period
 Refractory pe

[→] Refractory period, arrhythmias

Atrioventricular node

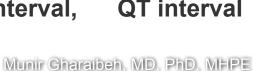
Conduction velocity, refractory period

 Refractory period, arrhythmias Extrasystoles,

Purkinje system, Slight | refractory period ventricular muscle

Electrocardiogram

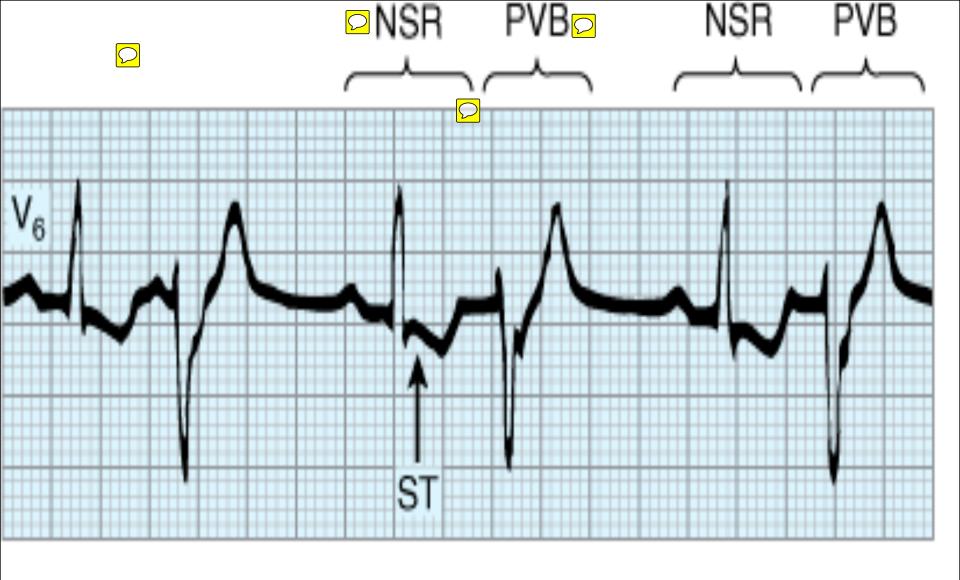
QT interval → PR interval,



tachycardia, fibrillation 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, only useful in CCHF with supraventricular arrhythmia
 - Might decrease morbidity
 - ? Withdrawal D
 - ? 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.

Cyclic AMP Dependent Agents:

β-adrenergic Agonists: □

NE

Dopamine

Dobutamine

Phosphodiesterase Inhibitors:

Amrinone

Inamrinone

Milrinone

Vesanirone

Sildenafi

Cyclic AMP Dependent Agents:

β-adrenergic Agonists:

All increase myocardial oxygen consumption, so not helpful for chronic use, may be used (IV) for short term or in acute heart failure.

NE:

Was used in cardiogenic shock, but caused severe vasospasm and gangrene.



Still used in cardiac arrest, by intracardiac injection.

Dopamine:

Widely used in cardiogenic shock.

Low doses: stimulate DA₁ 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.

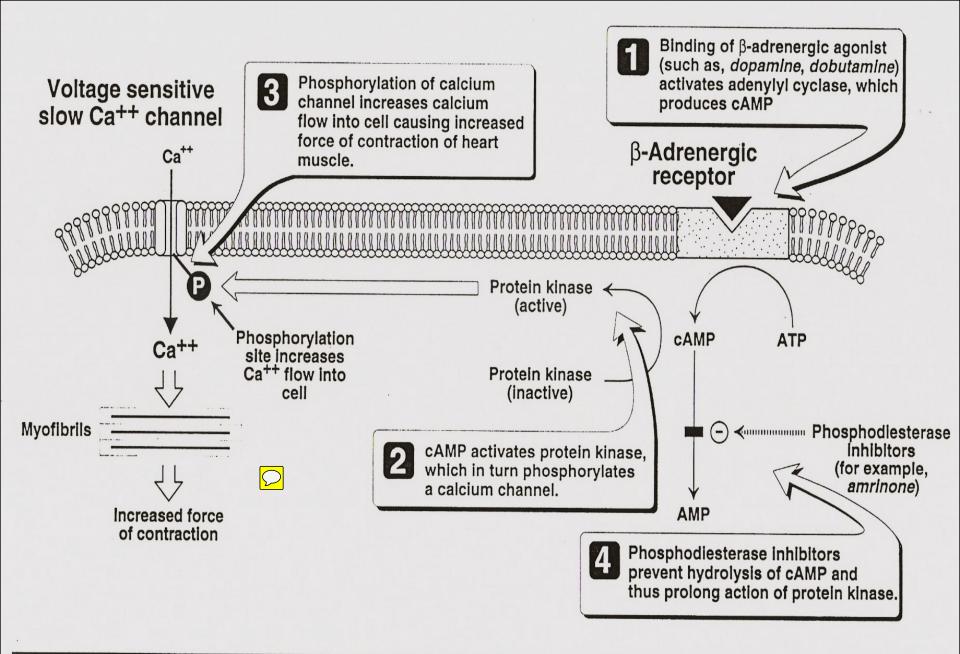


Figure 16.11

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

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)

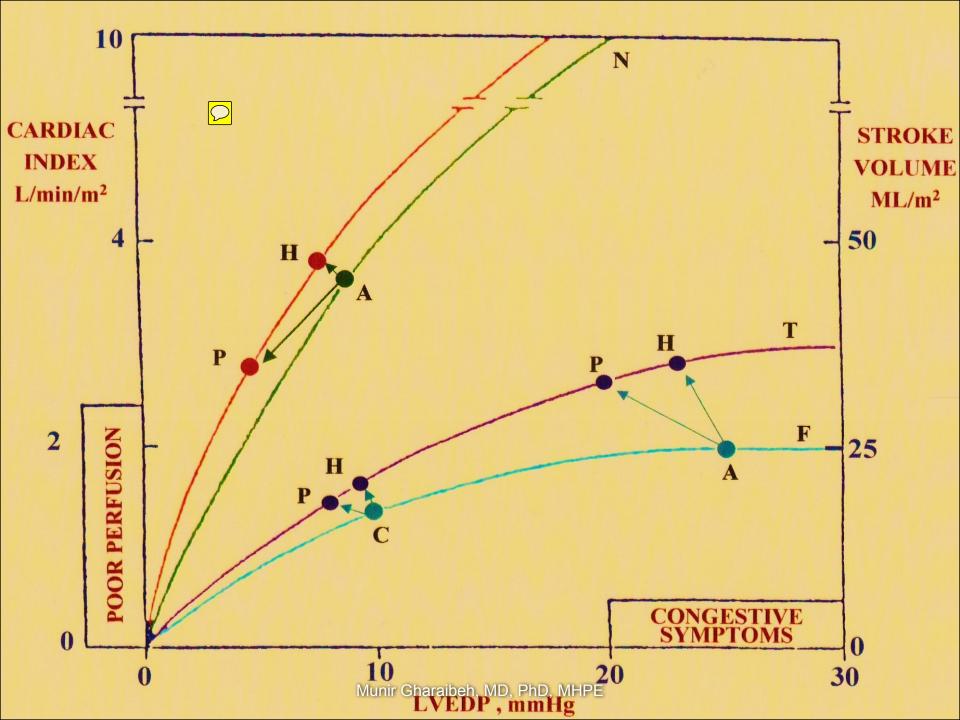
Sildenafil (PDE-5) Munir Gharaibeh, MD, PhD, MHPE

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.

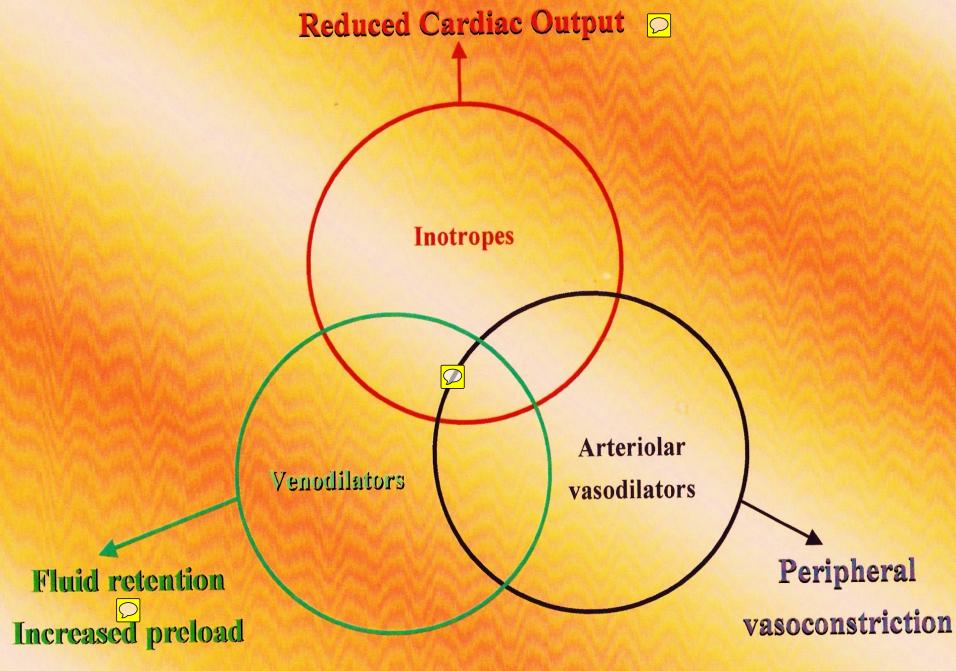


Venous Dilators	Mixed Action	Arterial Dilators
Nitroglycerin	Nitroprusside	Hydralazine
Isosorbide dinitrate	Captopril	Minoxidil
	Enalapril 🖸	
MANUALITY	Hydralazine + Nitrate	
MINITED BY		
LVEDV	LVEDV	LVEDV
↓ LVEDV ↓ MVO2 — CO	↓ LVEDV ↓ MVO2 ↑ CO	— LVEDV↓ MVO2↑ CO
	Munir Gharaibeh, MD, PhD, MHPE	



Vasodilator Drugs Used to Treat Heart Failure

vasodi	lator Drug	s Usea to Trea	it Heart F	allure
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 adren ergic antagonists	Phentolamine	Nonselective adrenergic receptor blockade	+++	+++
Vasodilating β / 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	nir Gharaibeh, MD, PhD, MHPE Stimulation of vascular ₂	+	++



(BNP)-Niseritide

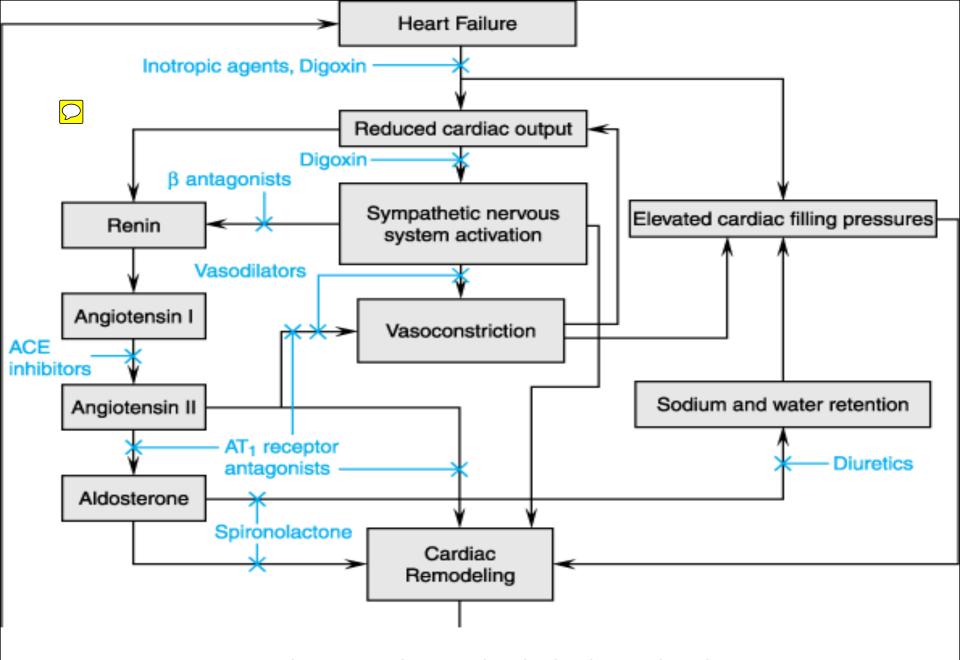
- Brain (B-type) natriuretic peptide (BNP) is secreted constitutively by ventricular myocytes in response to stretch.
- BNP binds to receptors in the vasculature, kidney, and other organs, producing potent vasodilation with rapid onset and offset of action by increasing levels of cGMP.
- Niseritide is 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.

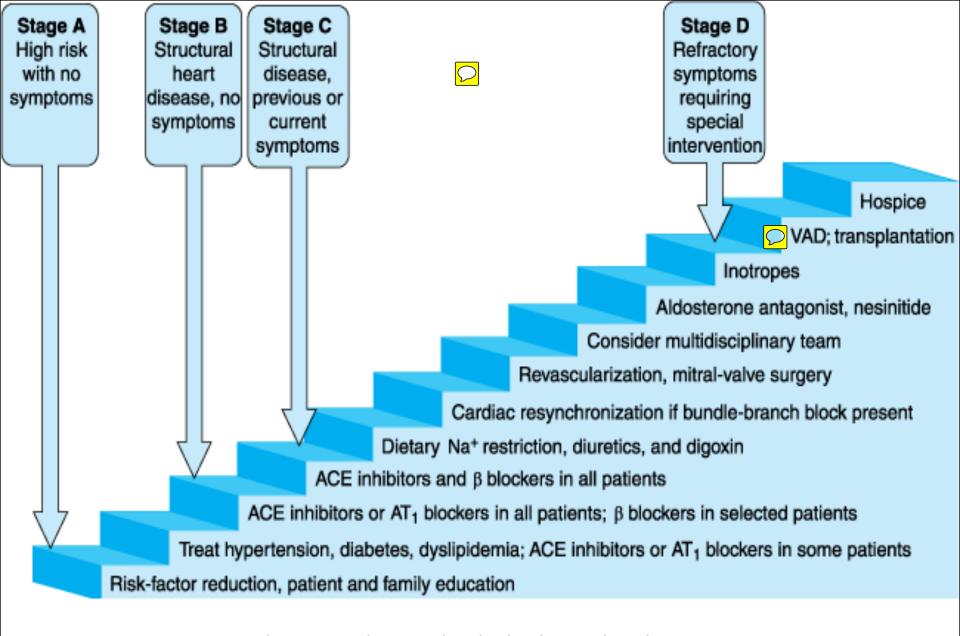
Effective in HF because of reduction in preload and afterload.

Hypotension is the main side effect.



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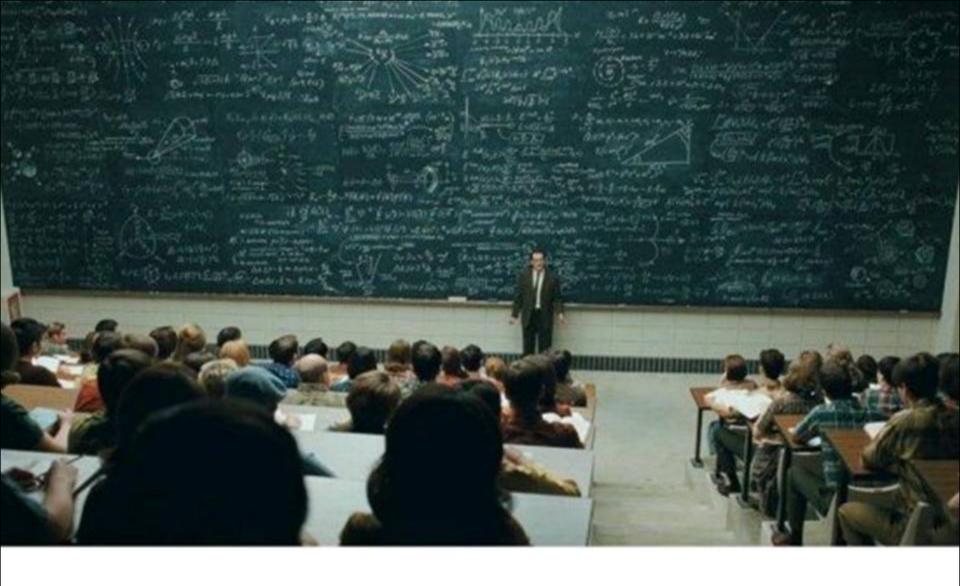
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Steps in the Prevention and Treatment of Chronic Heart Failure.

ACC/AHA Stage	Step ¹	Intervention
A, B	1	Control hypertension, hyperlipidemia, glucose metabolism (diabetes), obesity
С	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 beta blockers to patients with stable class II–IV heart failure
	8	Give aldosterone antagonist
	9	Give vasodilators
D	10 M	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 مفهوم لو اعيدلكم الدرس Munir Gharaibeh, MD, PhD, MHPE

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