Pathophysiology Of Heart Failure

A. Bagherzadeh, M.D.

Certified Board on Cardiology

Fellowship of Interventional Electrophysiology and Pacemaker

Assistant professor of Tehran University of Medical Sciences

Introduction

- Heart failure (HF) is a clinical syndrome comprised of symptoms and signs associated with congestion and/or hypoperfusion.
- It can result from any structural or functional cardiac disorder that impairs the ability of the ventricles to eject blood (systolic dysfunction), to fill properly (diastolic dysfunction), or both.

Epidemiology

- Heart failure is a worldwide pandemic.
- More than 6% of the population older than 65 years of age have HF, and the incidence and prevalence are increasing.
- In the United States, HF accounts for approximately 900,000 hospitalizations and represents the single largest expense for Medicare.
- It afflicts approximately 22 million individuals worldwide and 5 million people in the United States, with 2 million and 550,000, respectively, new cases annually.

Epidemiology

- Heart failure causes or contributes to up to 300,000 deaths per year.
- The five-year mortality rate is as high as 50% as a result of progressive pump failure or sudden death.

Two systems of stratifying patients with HF have been developed:

- **New York Heart Association (NYHA) functional classification** – which describes the degree of physical disability imposed on the patient.
- **AHA/ACC Guidelines** – which describes stages of Heart Failure.

AHA/ACC Guidelines – Stages of Heart Failure

Stage	Description
A	Patients at high risk of developing HF because of the presence of conditions that are strongly associated with the development of HF. Such patients have no identified structural or functional abnormalities of the pericardium, myocardium, or cardiac valves and have never shown signs or symptoms of HF.
B	Patients who have developed structural heart disease that is strongly associated with the development of HF but who have never shown signs or symptoms of HF.
C	Patients who have current or prior symptoms of HF associated with underlying structural heart disease.
D	Patients with advanced structural heart disease and marked symptoms of HF at rest despite maximal medical therapy and who require specialized interventions.

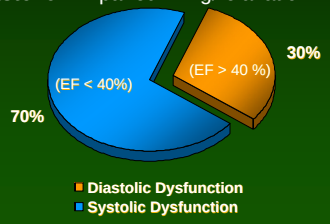
Etiology of Heart Failure

What causes heart failure?

- The loss of a critical quantity of functioning myocardial cells after injury to the heart due to:
  - Ischemic Heart Disease
  - Hypertension
  - Idiopathic Cardiomyopathy
  - Infections (e.g., viral myocarditis, Chagas' disease)
  - Toxins (e.g., alcohol or cytotoxic drugs)
  - Valvular Disease
  - Prolonged Arrhythmias

Left Ventricular Dysfunction

- **Systolic:** Impaired contractility/ejection
  - Approximately two-thirds of heart failure patients have systolic dysfunction[1]
- **Diastolic:** Impaired filling/relaxation



1 Lilly, L. Pathophysiology of Heart Disease. Second Edition p 200

Systolic vs Diastolic HF

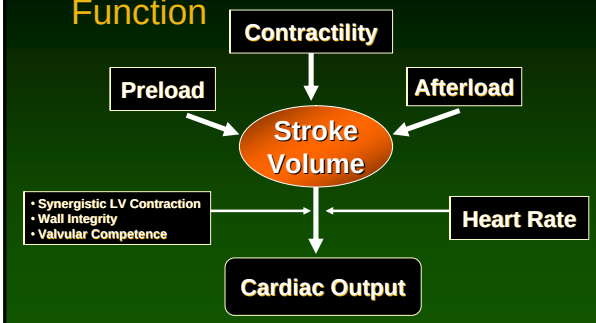
- The manifestations of systolic failure relate to an inadequate cardiac output with weakness, fatigue, reduced exercise tolerance, and other symptoms of hypoperfusion, while in diastolic HF the manifestations relate principally to the elevation of filling pressures in the left and/or right ventricles.
- Diastolic HF is usually defined as HF in patients with an ejection >50%. and may be caused by constrictive pericarditis and restrictive, hypertensive, and hypertrophic cardiomyopathy, impaired ventricular relaxation (acute myocardial ischemia), and myocardial fibrosis and infiltration (restrictive cardiomyopathy). Diastolic HF occurs more frequently in women than men, especially elderly women with hypertension.
- In most patients with HF, abnormalities both of contraction and relaxation coexist.

Cardiac Output

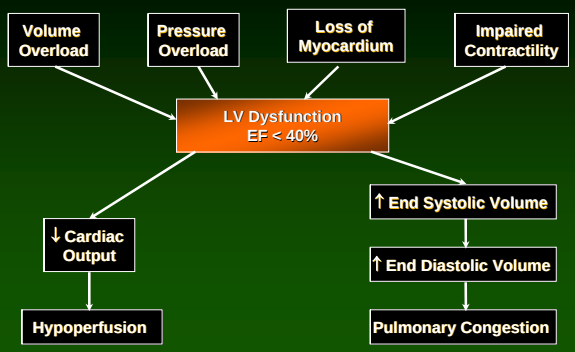
- Cardiac output is the amount of blood that the ventricle ejects per minute

Cardiac Output = HR x SV

Determinants of Ventricular Function



Left Ventricular Dysfunction



Consequences of Decreased Mean Arterial Pressure

↓ Mean Arterial Pressure (BP)

=

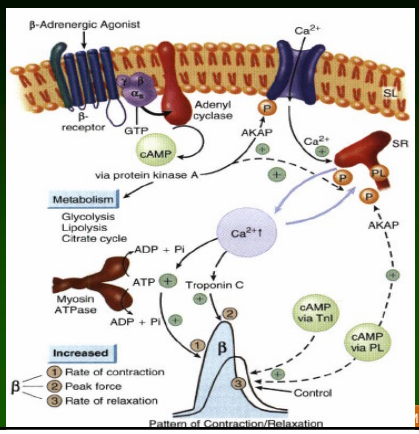
↓ Cardiac Output

x

Total Peripheral Resistance

Low-output vs High-output HF

- *Low-output HF* occurs secondary to ischemic heart disease, hypertension, dilated cardiomyopathy, and valvular and pericardial disease, while *high-output HF* occurs in patients with reduced systemic vascular resistance, i.e., hyperthyroidism, anemia, pregnancy, arteriovenous fistulas, beriberi, and Paget's disease.



Frank-starling mechanism

- At any level of contractility, the performance of the myocardium is influenced profoundly by ventricular end-diastolic fiber length and therefore by diastolic ventricular volume i.e., by operation of the Frank-Starling mechanism

determinants of ventricular preload

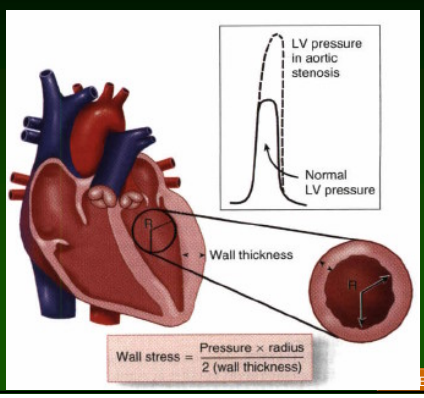
- Total Blood volume
- Distribution of Blood volume
  - 1. *Body position.*
  - 2. *Intrathoracic pressure.*
  - 3. *Intrapericardial pressure.*
  - 4. *Venous tone.*
  - 5. *The pumping action of skeletal muscle.*
- Atrial contraction

Determinants of ventricular contractility

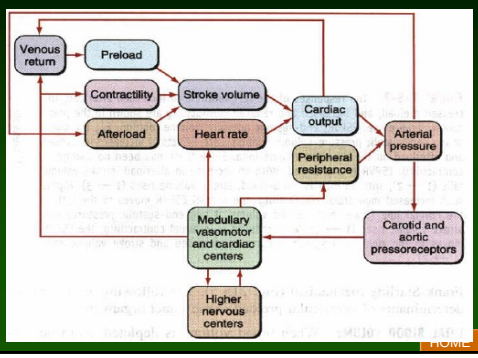
- Adrenergic Activity
- Circulating Catheculamines
- Exogenous inotropic agents
- Force-Frequency relationship
- Physiologic depressants: hypoxia, ischemia, acidosis.
- Pharmacologic depressants: procainamide and disopyramide; calcium antagonists such as verapamil; ,B-adrenergic blockers; and large doses of barbiturates, alcohol, and general anesthetics

Determinants of Afterload

- In the intact heart, as in isolated cardiac muscle, the extent (and velocity) of shortening of ventricular muscle fibers at any level of preload and of myocardial contractility are inversely related to afterload .
- Afterload may be defined as the tension or stress developed in the ventricular wall during ejection. It is determined by the aortic pressure as well as by the volume and thickness of the ventricular cavity.
- Laplace's law indicates that the tension of the myocardial fiber is a function of the product of the intracavitary ventricular pressure and ventricular radius divided by the wall thickness.



- Elevations of both preload and contractility increase myocardial fiber shortening, while increases in afterload reduce it. The extent of myocardial fiber shortening and left ventricular size are the determinants of stroke volume.
- Arterial pressure, in turn, is related to the product of cardiac output and systemic vascular resistance, while afterload is a function of left ventricular volume, wall thickness, and arterial pressure.



Assessment of Cardiac function

- A sensitive index is the ejection fraction, i.e., the ratio of stroke volume to end-diastolic volume (normal value = 67 + 8%).
- Alternatively, the abnormally elevated ventricular end-diastolic volume or end-systolic volume signify impairment of left ventricular systolic function. A limitation of measuring cardiac output, ejection fraction, and ventricular volumes is that these variables are influenced strongly by ventricular loading conditions. Thus, a depressed ejection fraction and lowered cardiac output may be observed in patients with normal ventricular function but reduced preload, as occurs in hypovolemia, or with increased afterload, as occurs in acutely elevated arterial pressure.

TABLE 215-1 *Short-Term and Long-Term Responses to Impaired Cardiac Performance*

Response	Short-term Effects (mainly adaptive; hemorrhage, acute heart failure)	Long-term Effects (mainly deleterious; chronic heart failure)
Salt and water retention	Augments preload	Pulmonary congestion, anasarca
Vasoconstriction	Maintains pressure for perfusion of vital organs (brain, heart)	Exacerbates pump dysfunction, increases cardiac energy expenditure
Sympathetic stimulation	Increases heart rate and ejection	Increases energy expenditure
Cytokine activation	Vasodilatation	Skeletal muscle catabolism, deterioration of endothelial function, impaired contraction, LV remodeling.
Hypertrophy	Unloads individual muscle fibers	Deterioration and death of cardiac cells: cardiomyopathy of overload
Increased collagen	May reduce dilatation	Impairs relaxation

Compensatory Mechanisms

- Frank-Starling Mechanism
- Compensatory Hypertrophy
- Redistribution
- Neurohormonal Activation
  - Sympathetic Nervous system
  - RAAS
- Ventricular Remodeling

Adaptive Mechanisms :Frank-Starling law

- The *Frank-Starling mechanism* operates through an increase in preload. An increase in the end-diastolic volume of the ventricle is associated with stretching of the sarcomeres, which increases the interaction between actin and myosin filaments and their sensitivity to Ca2+. thereby enhancing contraction.
- However, ventricular dilatation may become maladaptive when it becomes excessive, as may occur in severe valvular regurgitation, dilatation increases wall stress through the operation of Laplace's law and thereby reduces shortening.

Frank-starling mechanism

- At any level of contractility, the performance of the myocardium is influenced profoundly by ventricular end-diastolic fiber length and therefore by diastolic ventricular volume i.e., by operation of the Frank-Starling mechanism

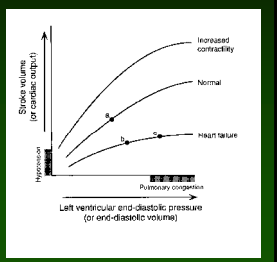
Compensatory Mechanisms

Frank-Starling Mechanism

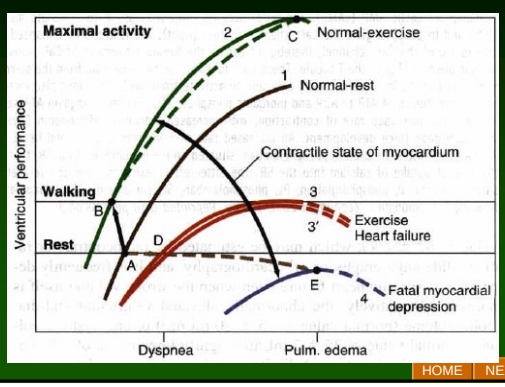
a. At rest, no HF

b. HF due to LV systolic dysfunction

c. Advanced HF

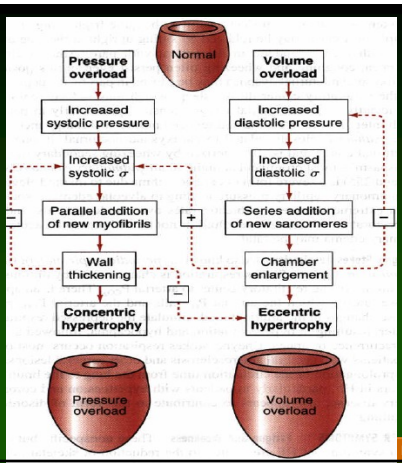


Frank-starling mechanism



Adaptive Mechanisms : Compensatory Hypertrophy

- *Adaptive Mechanisms* occurs in hemodynamic overload, which in turn restores elevated ventricular wall stress to normal .If the hypertrophy is insufficient to restore wall stress to normal, the ventricle dilates and this increases wall stress further, leading to a vicious circle. Also, severe ventricular hypertrophy may impair ventricular filling and cause myocardial ischemia.



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Adaptive Mechanisms : Redistribution

- *Redistribution of a subnormal cardiac output* away from the skin, skeletal muscle, and kidneys with maintenance of blood flow to the most vital organs, i.e., the brain and the heart, occurs. The vasoconstriction, however, may increase afterload, thereby reducing cardiac output further.

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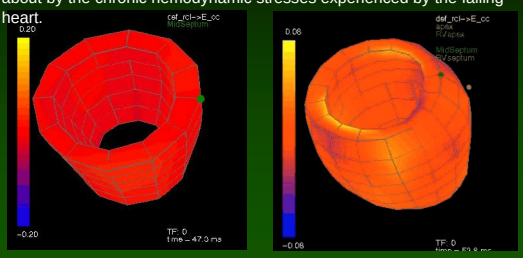
Ventricular Remodeling

Alterations in the heart's size, shape, structure, and function brought about by the chronic hemodynamic stresses experienced by the failing heart.



Curry CW, et al. Mechanical dyssynchrony in dilated cardiomyopathy with intraventricular conduction delay as depicted by 3D tagged magnetic resonance imaging. Circulation 2000 Jan 4;101(1):E2.

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TABLE 215-2 *Factors that Lead to the Progressive Remodeling of the Left Ventricle*

Mechanism of Progressive Remodeling and Heart Failure			
Cell Growth	Fibrosis	Apoptosis	Counter-regulatory Factors
Angiotensin II	Angiotensin II	TNF-α	ANP
Catecholamines	Endothelin	*Fas* ligand	Bradykinin
Endothelin	Aldosterone		Nitric oxide
TNF-α	TGF-β		BNP
Growth hormone			
IGF			
Cardiotrophin-1			
Mechanical stretch			

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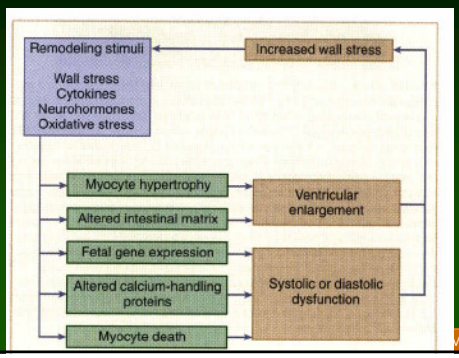
Ventricular remodeling



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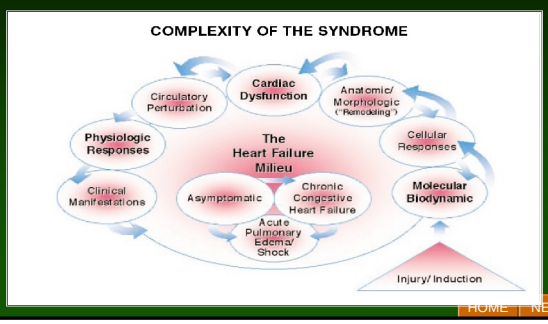
The Facets of Heart Failure

Depiction of the complex interplay of the various pathophysiologic mechanisms of HF



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Compensatory Mechanisms

Neurohormonal Activation

Many different hormone systems are involved in maintaining normal cardiovascular homeostasis, including:

- Sympathetic nervous system (SNS)
- Renin-angiotensin-aldosterone system (RAAS)
- Vasopressin (antidiuretic hormone, ADH)

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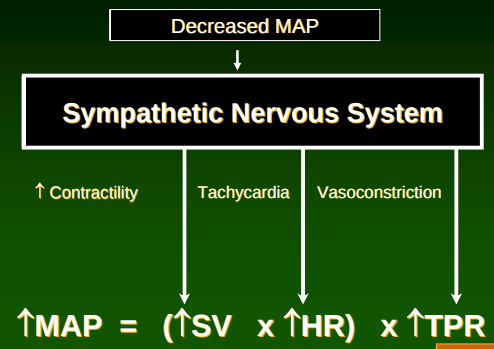
Compensatory Mechanisms: Sympathetic Nervous System



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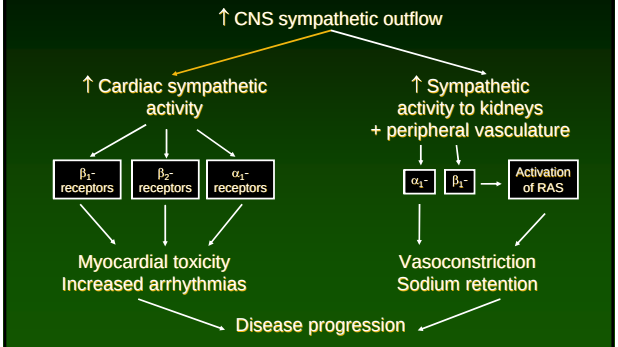
Sympathetic Activation in Heart Failure



Packer. Progr Cardiovasc Dis. 1998;39(suppl I):39-52.

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TABLE 23–10 Biological Responses Mediated by Adrenergic Receptors in the Human Heart

Biological Response	Adrenergic Receptor Mediation
Positive inotropic response	β_1, β_2, α_1 (minimal)
Positive chronotropic response	β_1, β_2
Myocyte toxicity	$\beta_1 >> \beta_2$
Myocyte apoptosis	β_1
Cardiac myocyte growth	$\beta_1 >> \beta_2$, α_1
Fetal gene induction	$\beta_1 >> \beta_2$, α_1
Proarrhythmic	β_1, β_2, α_1

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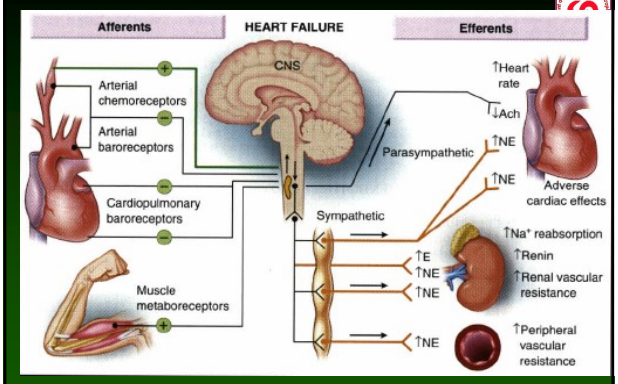

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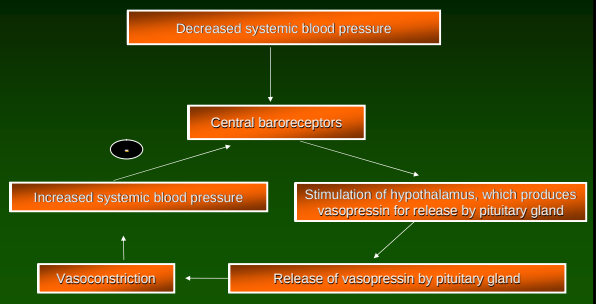
Compensatory Mechanisms: Neurohormonal Activation – Vasopressin



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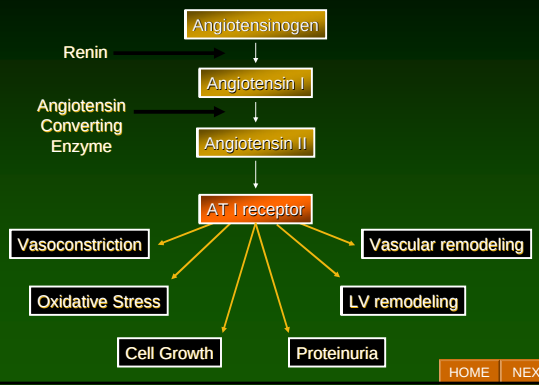
Renin-Angiotensin-Aldosterone (RAAS)



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Renin-Angiotensin-Aldosterone (RAAS)

Renin-Angiotensin-Aldosterone (↓ renal perfusion)

Salt-water retention
Thirst

Sympathetic augmentation

Vasoconstriction

↑MAP = (↑SV x ↑HR) x ↑TPR

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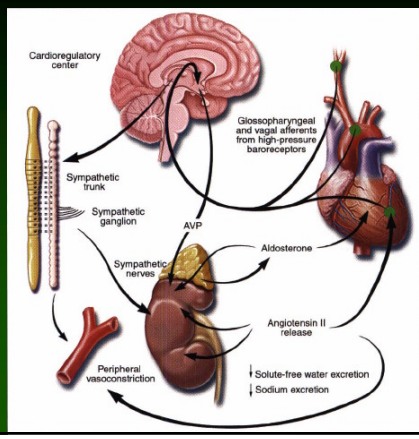
TABLE 23–6 Biological Responses Mediated by Angiotensin II Receptors in the Human Cardiovascular System

Biologic Response	Receptor Mediation
Cardiac myocyte growth	AT_1
Positive inotropic response (minimal)	AT_1
Myocyte apoptosis	AT_1, AT_2
Aldosterone release	AT_1
Norepinephrine release	AT_1
Cardiac myocyte toxicity	Beta-adrenergic via norepinephrine release
Fibroblast proliferation	AT_1
Smooth muscle proliferation	AT_1
Vasoconstriction	AT_1



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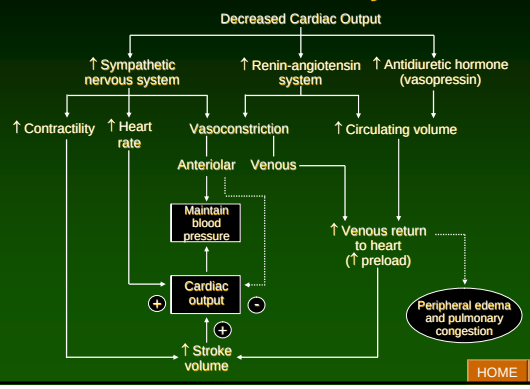
Compensatory Neurohormonal Stimulation: Summary



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Other Neurohormones

- Natriuretic Peptides: Three known types
  - Atrial Natriuretic Peptide (ANP)
    - Predominantly found in the atria
    - Diuretic and vasodilatory properties
  - Brain Natriuretic Peptide (hBNP)
    - Predominantly found in the cardiac ventricles
    - Diuretic and vasodilatory properties
  - C-type Natriuretic Peptide (CNP)
    - Predominantly found in the central nervous system
    - Limited natriuretic and vasodilatory properties

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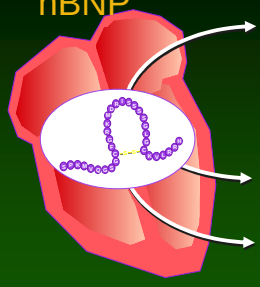
Pharmacological Actions of hBNP



Hemodynamic
(balanced vasodilation)
- veins
- arteries
- coronary arteries

Neurohormonal
- ↓ aldosterone
- ↓ norepinephrine

Renal
- ↑ diuresis & natriuresis

Abraham WT and Schrier RW, 1994

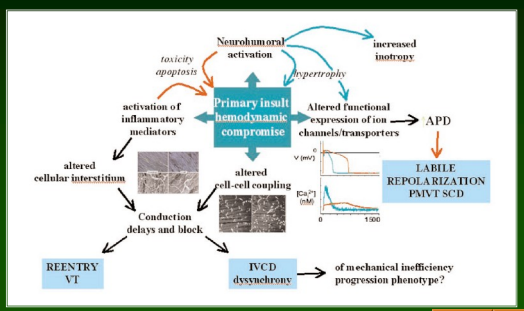
Endothelium-Derived Vasoactive Substances

Produced by a thin lining of cells within the arteries and veins called the endothelium

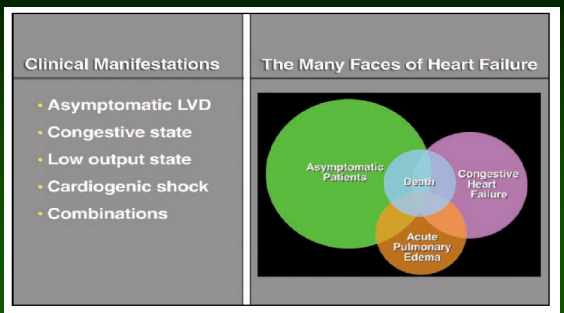
Endothelium-derived relaxing factors (EDRF) – Vasodilators:
- Nitric Oxide (NO)
- Bradykinin
- Prostacyclin

Endothelium-derived constricting factors (EDCF) – Vasoconstrictors:
- Endothelin I

Mechanisms and Consequences of Electrical Remodeling in HF



Clinical Manifestations of Heart Failure



Typical presentations of heart failure

1. Syndrome of decrease exercise tolerance
2. Syndrome of fluid retention
3. No symptoms but incidental discovery of LV dysfunction

Hemodynamic Basis for Heart Failure Symptoms

LVEDP ↑

Left Atrial Pressure ↑

Pulmonary Capillary Pressure ↑

Pulmonary Congestion

Left Ventricular Dysfunction

- Symptoms
  - Dyspnea on Exertion
  - Paroxysmal Nocturnal Dyspnea
  - Tachycardia
  - Cough
  - Hemoptysis
- Physical Signs
  - Basilar Rales
  - Pulmonary Edema
  - S3 Gallop
  - Pleural Effusion
  - Cheyne-Stokes Respiration

Right Ventricular Failure

- Symptoms
  - Abdominal Pain
  - Anorexia
  - Nausea
  - Bloating
  - Swelling
- Physical Signs
  - Peripheral Edema
  - Jugular Venous Distention
  - Abdominal-Jugular Reflux
  - Hepatomegaly

TABLE 216-1 *Framingham Criteria for Diagnosis of Congestive Heart Failure*[a]

MAJOR CRITERIA
Paroxysmal nocturnal dyspnea
Neck vein distention
Rales
Cardiomegaly
Acute pulmonary edema
S_3 gallop
Increased venous pressure (>16 cmH_2O)
Positive hepatojugular reflux
MINOR CRITERIA
Extremity edema
Night cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion
Vital capacity reduced by one-third from normal
Tachycardia (≥120 bpm)
MAJOR OR MINOR
Weight loss ≥4.5 kg over 5 days' treatment

[a] To establish a clinical diagnosis of congestive heart failure by these criteria, at least one major and two minor criteria are required.

Clinical manifestations: Dyspnea

- In early HF. Dyspnea is observed only during exertion, when it may simply represent an aggravation of the breathlessness that occurs normally. As HF advances, dyspnea occurs with progressively less strenuous activity and ultimately it is present even at rest. Cardiac dyspnea is observed most frequently in patients with elevations of pulmonary venous and capillary pressures who have engorged pulmonary vessels and interstitial accumulation of interstitial fluid. The activation of receptors in the lungs results in the rapid, shallow breathing characteristic of cardiac dyspnea. The oxygen cost of breathing is increased by the excessive work of the respiratory muscles required to move air into and out of the congested lungs. This is coupled with the diminiuted delivery of oxygen to these muscles, a consequence of a reduced cardiac output. This imbalance may contribute to fatigue of the respiratory muscles and the sensation of shortness of breath.

Clinical manifestations: Orthopnea

- This symptom, i.e., dyspnea in the recumbent position, is usually a later manifestation of HF than exertional dyspnea. Orthopnea results from the redistribution of fluid from the abdomen and lower extremities into the chest during recumbency, which increases the pulmonary capillary pressure, combined with elevation of the diaphragm. Patients with orthopnea must elevate their head on several pillows at night and frequently awaken short of breath and/or coughing if their head slips off the pillows. Orthopnea is usually relieved by sitting upright, and some patients report that they find relief from sitting in front of an open window. In advanced HF, patients cannot lie down at all and must spend the entire night in a sitting position.

Clinical manifestations: Paroxysmal Nocturnal Dyspnea

- refers to attacks of severe shortness of breath and coughing that generally occur at night, usually awaken the patient from sleep, and may be quite frightening. Though simple orthopnea may be relieved by sitting upright at the side of the bed with legs dependent, in the patient with paroxysmal nocturnal dyspnea, coughing and wheezing often persist even in this position.
- Paroxysmal nocturnal dyspnea may be caused in part by the depression of the respiratory center during sleep, which may reduce ventilation sufficiently to lower arterial oxygen tension, particularly in patients with interstitial lung edema and reduced pulmonary compliance.

Clinical manifestations: *Acute pulmonary edema*

- *Cardiac asthma* is closely related to paroxysmal nocturnal dyspnea and nocturnal cough and is characterized by wheezing secondary to bronchospasm most prominent at night.
- *Acute pulmonary edema* is a severe form of cardiac asthma due to marked elevation of pulmonary capillary pressure leading to alveolar edema, associate with extreme shortness of breath, rales over the lung fields, and the expectoration of blood-tinged fluid. If not treated promptly, acute pulmonary edema may be fatal.

Cheyne-Stokes respiration

- Also known as *periodic respiration* or *cyclic respiration,* Cheyne-Stokes respiration is characterized by diminished sensitivity of the respiratory center to arterial PC02' There is an apneic phase, during which the arterial P02 falls and the arterialPCO2 rises. These changes in the arterial blood stimulate the depressed respiratory center, resulting in hyperventilation and hypocapnia, followed in turnby recurrence of apnea. Cheyne-Stokes respiration occurs most often in patients with cerebral atherosclerosis and other cerebral lesions, but the prolongation of the circulation time from the lung to the brain that occurs in HF, particularly in patients with hypertension and coronary artery disease, also appears to contribute to this form of disordered breathing.

fatigue and Weakness

- These nonspecific but common symptoms of HF are related to the reduction of skeletal muscle perfusion. Exercise capacity is reduced by the limited ability of the failing heart to increase its output and deliver oxygen to the exercising muscles.

Abdominal Symptoms

- Anorexia and nausea associated with abdominal pain and fullness are frequent complaints and may be related to the congested liver and portal venous system.

Cerebral Symptoms

- Patients with severe HF, particularly elderly patients with cerebral arteriosclerosis, reduced cerebral perfusion, and arterial hypoxemia, may develop alterations in the mental state characterized by confusion, difficulty in concentration, impairment of memory, headache, insomnia, and anxiety.

Physical findings

- In mild or moderately severe HF, the patient appears in no distress at rest except feeling uncomfortable when lying flat for more than a few minutes.
- In severe HF, the pulse pressure may be diminished, reflecting a reduction in stroke volume, and the diastolic arterial pressure may be elevated as a consequence of generalized vasoconstriction.
- In severe acute HF, systolic hypotension may be present, with cool, diaphoretic extremities, and Cheyne- Stokes respiration. There may be cyanosis of the lips and nail beds and sinus tachycardia.
- *Systemic venous pressure* is often abnormally elevated, and this may be reflected in distention of the jugular veins. In the early stages of HF, the venous pressure may be normal at rest but may become abnormally elevated, with sustained pressure on the abdomen (positive abdominojugular reflux).

Physical findings

- Third and fourth heart sounds are often audible but are not specific for HF
- P*ulsus alternans,* i.e., a regular rhythm with alternation of strong and weak cardiac contractions and therefore alternation in the strength of the peripheral pulses, may be present. This sign of severe HF may be detected by sphygmomanometry and in more severe cases even by palpation; it frequently follows an extrasystole and is observed most commonly in patients with cardiomyopathy, hypertensive, or ischemic heart disease.

Diastolic heart failure

- In *diastolic heart failure* the principal abnormality is impaired relaxation and filling of the ventricle, which leads to an el. evation of ventricular diastolic pressure at any given diastolic volume . Failure of relaxation can be functional and transient, as during ischemia, which reduces the ATP required for the SR pump to lower cytoplasmic [Ca2+]
- Typical conditions in which diastolic HF occurs are restrictive cardiomyopathy secondary to infiltrative conditions, such as amyloidosis or hemochromatosis, and hypertrophic cardiomyopathy . The concentric hypertrophy associated with chronic hypertension can also impair ventricular filling. In many patients with cardiac hypertrophy and dilatation, systolic and diastolic HF coexist; the left ventricle both empties and fills abnormally.

Diastolic Dysfunction

- 20-40% of presenting CHF syndrome
- Risk of death lower than systolic dysfunction
- Dx: doppler echocardiography
- Lack of clear-cut definition = lack of trial data
- Treat symptomatically and prevent reversible causes

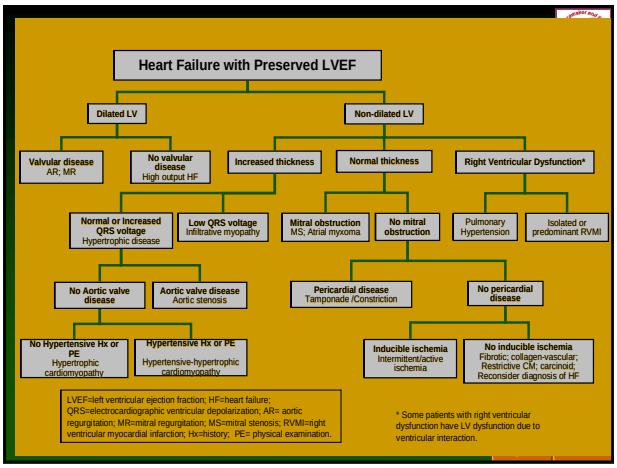
TABLE 22–3 Systolic Versus Diastolic Heart Failure*

Parameters	Systolic	Diastolic
History		
Coronary artery disease	+++†	++
Hypertension	++	++++
Diabetes	++	++
Valvular heart disease	++++	+
Paroxysmal dyspnea	++	+++
Physical Examination		
Cardiomegaly	+++	+
Soft heart sounds	++++	+
S_3 gallop	+++	+
S_4 gallop	+	+++
Hypertension	++	++++
Mitral regurgitation	+++	+
Rales	++	+
Edema	+++	+
Jugular venous distention	+++	+
Chest Radiograph		
Cardiomegaly	+++	+
Pulmonary congestion	+++	+++
Electrocardiogram		
Left ventricular hypertrophy	++	++++
Q waves	++	+
Low voltage	+++	–
Echocardiogram		
Left ventricular hypertrophy	++	++++
Left ventricular dilation	++	–
Left atrial enlargement	++	++
Reduced ejection fraction	++++	–

CHF with preserved systolic function

Differential Diagnosis

- Wrong Dx
- Inaccurate measument of LVEF
- Primary valvular disease
- Restrictive (infiltrative) cardiomyopathies
- Pericardial contriction
- Episodic/reversible LV systolic dysfunction
- High output failure (AVF, Thyroid, anemia)
- Pulmonary disease w/ RVF
- Atrial myxoma
- Diastolic dysfunction



Assessing Heart Failure

- Patient History
- Physical Examination
- Laboratory and Diagnostic Tests

Diagnostic Evaluation of New Onset Heart Failure

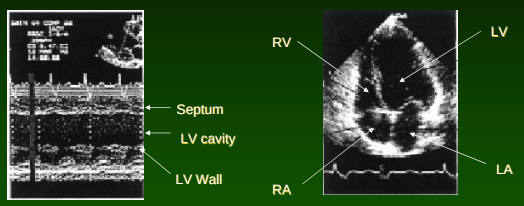
- Determine the type of cardiac dysfunction (systolic vs. diastolic)
- Determine Etiology
- Define prognosis
- Guide therapy

Diagnostic Evaluation of New Onset Heart Failure

Initial Work-up:

- ECG
- Chest x-ray
- Blood work
- Echocardiography

Diagnostic Evaluation of New Onset Heart Failure

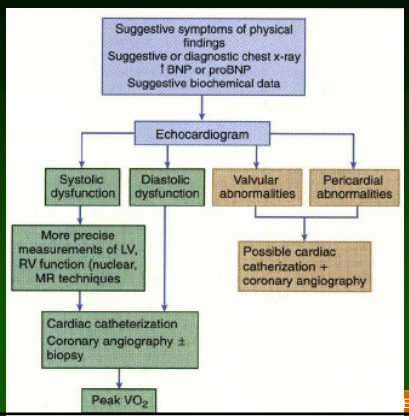


M-Mode Echo

2D Echo

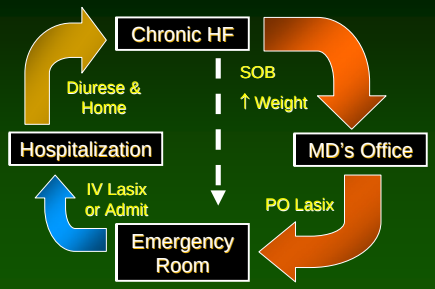
Diagnostic Work-up

- In all cases
  - History, exam, ekg
  - Echo
    - etiology
    - MR? LVEDD, RV fxn
  - Labs
    - TSH, ferritin, Na, Cr
  - Exercise testing
    - Prognosis, VO2Max
  - Assessment of CAD
    - One of few reversible causes
- In selected cases
  - Labs
    - Metanephrines
  - Catheterization
    - CAD
    - Hemodynamics
  - Endomyocardial biopsy
    - If infiltrative disease considered



Current Treatment of Heart Failure

The Vicious Cycle of Heart Failure Management



Aims for therapy

- Reduce symptoms & improve QOL
- Reduce hospitalization
- Reduce mortality
  - Pump failure
  - Sudden cardiac death

General Measures

Lifestyle Modifications:

- Weight reduction
- Discontinue smoking
- Avoid alcohol and other cardiotoxic substances
- Exercise

Medical Considerations:

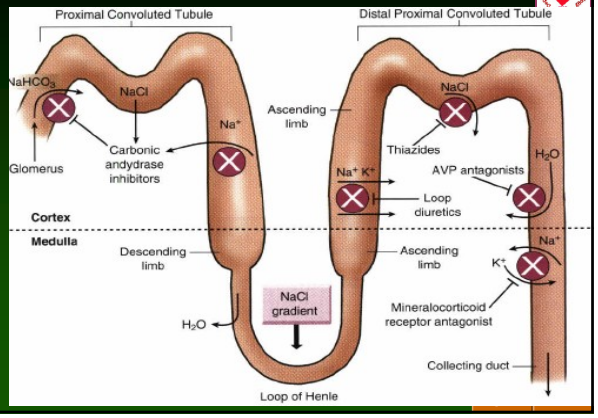
- Treat HTN, hyperlipidemia, diabetes, arrhythmias
- Coronary revascularization
- Anticoagulation
- Immunization
- Sodium restriction
- Daily weights
- Close outpatient monitoring

Diuretics

- Used to relieve fluid retention
- Improve exercise tolerance
- Facilitate the use of other drugs indicated for heart failure
- Patients can be taught to adjust their diuretic dose based on changes in body weight
- Electrolyte depletion a frequent complication
- Should never be used alone to treat heart failure
- Higher doses of diuretics are associated with increased mortality

Drug Class	Use
Diuretics "Loop" diuretics ($Na^+/K^+/2Cl^-$ cotransporter inhibitors)	DHF (IV); CSHF (PO) stage 2-4
Thiazides (Na^+/Cl^- cotransporter inhibitors)	DHF (IV); CSHF (PO) stage 2-4
K^+ sparing (epithelial Na^+ channel inhibitors)	CSHF (PO) stage 2-4
Type I (mineralocorticoid) receptor antagonists	CSHF (PO) stage 3, 4
Carbonic anhydrase inhibitors (acetazolamide)	DHF (IV)

Diuretic	Brand Name	Principal Site and Mechanism of Action	Effects on Urinary Electrolytes	Effects on Blood Electrolytes and Acid-Base Balance	Extrarenal Effects	Usual Dosage*	Drug Interactions
Loop Diuretics ($Na^+/K^+/2Cl^-$ Cotransporter Inhibitors)							
Furosemide Bumetanide Piretanide†	Lasix Bumex Arelix, Diumex, Dranir	Thick ascending limb of the loop of Henle; inhibition of the $Na^+/K^+/2Cl^-$ cotransporter	↑Na^+ ↑Cl^- ↑K^+	Hypochloremic alkalosis ↑HCO_3^- ↓K^+, ↓Na^+ ↓Cl^- ↑Uric acid	Acute: ↑venous capacitance ↑Systemic vascular resistance when given IV, secondary to neurohormonal activation Chronic: ↓cardiac preload, ototoxicity	10-360 mg/d 0.5-20 mg/d 6-20 mg/d	Tubular secretion delayed by competing organic acids (renal failure) and some drugs Effectiveness reduced by prostaglandin inhibitors Additive ototoxicity with aminoglycosides Longer duration of action than furosemide
Ethacrynic acid Torsemide	Edecrin Demadex					50-200 mg/d 2.5-200 mg/d	
Thiazide and Thiazide-like Diuretics (Na^+/Cl^- Cotransporter Inhibitors)							
Chlorothiazide Hydrochlorothiazide Trichlormethiazide Chlorthalidone Metolazone Quinethazone Indapamide	Diuril HydroDIURIL Metahydrin Hygroton Mykrox, Zaroxolyn Hydromox Lozol	Distal tubule; inhibits Na^+/Cl^- cotransporter	↑Na^+, ↑Cl^-, ↑K^+ ↑Mg^{2+}, ↓Ca^{2+}	↓Na^+, particularly in elderly patients ↑HCO_3^- (mild alkalosis) ↑Uric acid, ↑Ca^{2+} ↓K^+, ↓Mg^{2+}	↑Glucose ↑LDL/triglycerides (may be dose related) Extrarenal effects less marked with indapamide	50-100 mg/d 25-50 mg/d 2-8 mg/d 25-100 mg/d 0.5-10 mg/d 5-10 mg/d 50-200 mg/d 2.5-5 mg/d	Efficacy reduced by prostaglandin inhibitors Reduces renal lithium clearance Additive effect on NaCl and K^+ excretion with loop diuretics
K^+-Sparing Diuretics (Epithelial Na^+ Channel Inhibitors)							
Triamterene Amiloride	Dyrenium Midamor	Collecting duct; inhibits apical membrane Na^+ conductance	↓K^+ ↑Na^+	Metabolic acidosis ↑Mg^{2+}		100-300 mg/d 5-10 mg/d	Useful when used with K^+ wasting diuretics; may induce hyperkalemia with ACE inhibitors/ARBs
Type I Mineralocorticoid Receptor Antagonists (also K^+-Sparing Diuretics)							
Spironolactone Eplerenone	Aldactone Inspra	Collecting duct; aldosterone antagonists	↓K^+, ↑Na^+, ↑Cl^-	↑K^+; metabolic acidosis	Gynecomastia for spironolactone, not for eplerenone	12.5-25 mg/d 25-50 mg/d	Useful adjunct to K^+ wasting diuretics; ↑K^+ may be worse in presence of other RAAS inhibitors
Carbonic Anhydrase Inhibitors							
Acetazolamide Dichlorphenamide Methazolamide	Diamox Daranide Neptazane	Proximal tubule Carbonic anhydrase inhibition	↑Na^+, ↑K^+; ↑HCO_3^-	Metabolic acidosis	↑Ventilatory drive ↓Intraocular pressure	250-500 mg/d 10-20 mg/d 25-100 mg/d	May be useful in alkalemia related to other diuretics; may cause severe K^+ wasting



ACE Inhibitors

- Blocks the conversion of angiotensin I to angiotensin II; prevents functional deterioration
- Recommended for all heart failure patients
- Relieves symptoms and improves exercise tolerance
- Reduces risk of death and decreases disease progression and need for hospitalization

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ACE Inhibitors

- These beneficial effects are related only in part to the salutary hemodynamic effects, ie., the reduction of preload and afterload.
- The major effect of ACE inhibitors appears to be on inhibition of local (tissue) renin-angiotensin systems.
- Once begun and an optimal dose has been reached an ACE inbibitor should be maintained indefinitely.
- Benefits may not be apparent for 1-2 months after initiation
- ACE inhibition should *not* be used in hypotensive patients.

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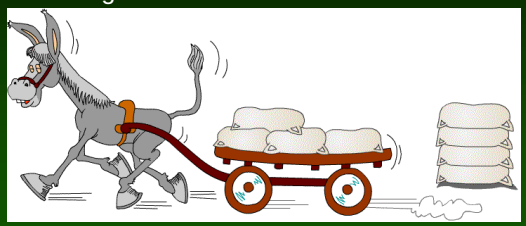
Diuretics, ACE Inhibitors

Reduce the number of sacks on the wagon



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Aldosterone Antagonists

- Generally well-tolerated
- Shown to reduce heart failure-related morbidity and mortality
- Generally reserved for patients with NYHA Class III-IV HF
- Side effects include hyperkalemia and gynecomastia. Potassium and creatinine levels should be closely monitored

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Angiotensin Receptor Blocker

- In patients who cannot tolerate ACE inhibitors because of cough, angioneurotic edema, leukopenia, an angiotensin II receptor blocker antagonist may be used instead and appears to be equally effective.

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Angiotensin Receptor Blockers (ARBs)

- Block AT_1 receptors, which bind circulating angiotensin II
- Examples: valsartan, candesartan, losartan
- Should not be considered equivalent or superior to ACE inhibitors
- In clinical practice, ARBs should be used to treat patients who are ACE intolerant due to intractable cough or who develop angioedema

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Beta-Blockers

- Cardioprotective effects due to blockade of excessive SNS stimulation
- In the short-term, beta blocker decreases myocardial contractility; increase in EF after 1-3 months of use
- Long-term, placebo-controlled trials have shown symptomatic improvement in patients treated with certain beta-blockers[1]
- When combined with conventional HF therapy, beta-blockers reduce the combined risk of morbidity and mortality, or disease progression[1]

1 Hunt, SA, et al ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2001 p. 20.

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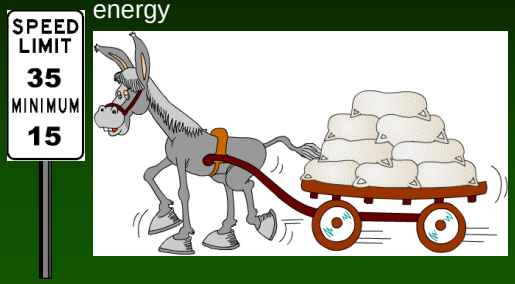
Beta-Blockers

Limit the donkey's speed, thus saving energy



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Digoxin

- Reduces activation of SNS and RAAS
- Enhances inotropy of cardiac muscle
- Controlled trials have shown long-term digoxin therapy:
  - Reduces symptoms
  - Increases exercise tolerance
  - Improves hemodynamics
  - Decreases risk of HF progression
  - Reduces hospitalization rates for decompensated HF
  - Does not improve survival

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Digitalis Compounds

Like the carrot placed in front of the donkey

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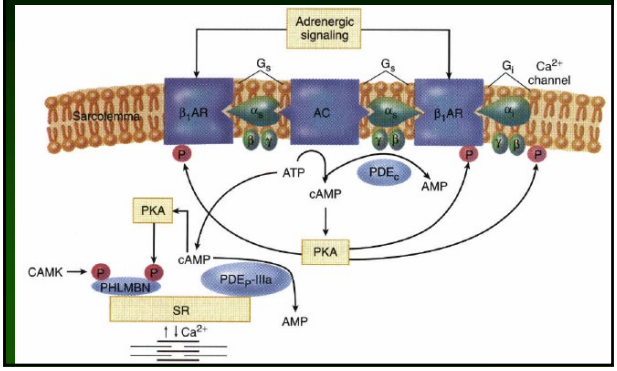
Sympathomimetic Amines

- Sympathomimetic Amines Improve myocardial contractility and are effective in the management of Pulmonary edema and severe acute HF.
- They must be administered by constant intravenous infusion and can be given for several days to patients with intractable, severe HF, particularly those with a reversible component, such as exists in patients who have undergone cardiac surgery, as well as to patients with acute myocardial infarction and shock or pulmonary edema and they may be used in patients with refractory HF as a "bridge" to cardiac transplantation.



Phosphodiesterase Inhibitors

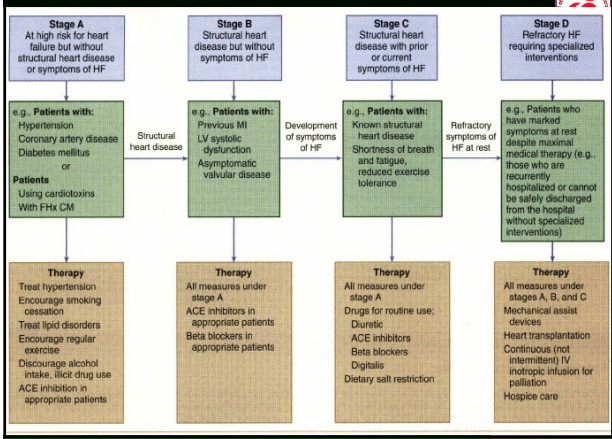
- These noncatecholamine, nonglycoside agents that exert both *positive* inotropic and vasodilator actions by inhibiting phosphodiesterase III, an enzyme that breaks down intracytoplasmic cyclic AMP, the second messenger which is critical to adrenergic stimulation.
- Amrinone and milrinone may be administered for the same conditions in which dopamine or dobutamine are useful; they may be employed together with and potentiate the sympathomimetics.
- If treatment of a patient on a beta blocker with a positive inotropic agent is required, a phosphodiesterase III inhibitor should be used.

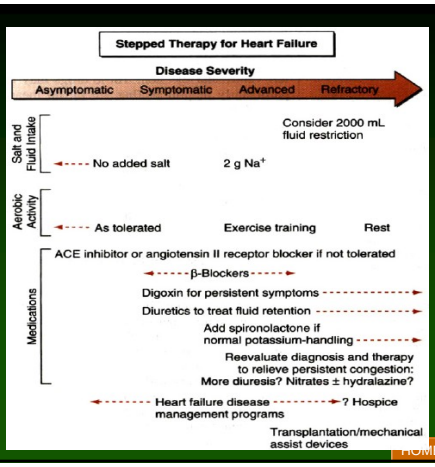
Vasodilators

- Direct vasodilators may be useful in patients with severe, acute HF who demonstrate systemic vasoconstriction despite ACE inhibitor therapy.
- The ideal vasodilator for the treatment of *acute* HF should have a rapid onset and brief duration of action when administered by intravenous infusion; sodium nitroprusside qualifies as such a drug, but its use requires careful monitoring of the arterial pressure and, if possible, of the pulmonary artery wedge pressure.

TABLE 23–3 Profile of Various Vasodilator Classes for Producing Venous or Arteriolar Dilation

Class/Compound	Venodilation	Arteriolar Dilation
Nitrovasodilators	+++	+
Direct acting (hydralazine)	+	+++
Flosequinan	++	+++
Calcium channel blockers	+	+++
K^+ channel activators (e.g., diazoxide, minoxidil)	++	+++
Vasodilator prostaglandins (prostacyclin)	+++	++
Natriuretic peptides (BNP)	+++	+
ACEIs, ARBs	++	+





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Ventricular Dysynchrony

- Abnormal ventricular conduction resulting in a mechanical delay
  - Wide QRS (IVCD); typically LBBB morphology

ECG depicting interventricular conduction delay

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Animation – Ventricular Dysynchrony

Click to Start/Stop

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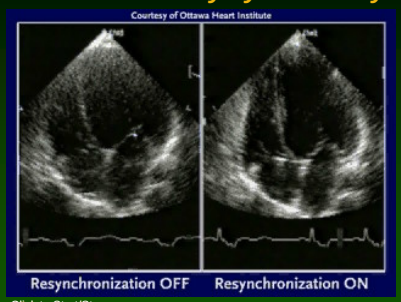
Clinical Consequences of Ventricular Dysynchrony



Click to Start/Stop

- Abnormal interventricular septal wall motion[1]
- Reduced dP/dt[3]
- Reduced diastolic filling time[1,2]
- Prolonged MR duration[1,2]

[1] Grines CL, Bashore TM, Boudoulas H, et al. *Circulation* 1989;79:845-853.
[2] Xiao, HB, Lee CH, Gibson DG. *Br Heart J* 1991;66:443-447.
[3] Xiao HB, Brecker SJD, Gibson DG. *Br Heart J* 1992;68:403-407.

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Cardiac Resynchronization Therapy

Goals

- Improve hemodynamics
- Improve Quality of Life

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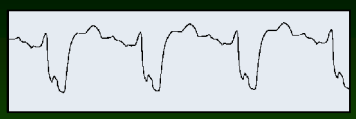
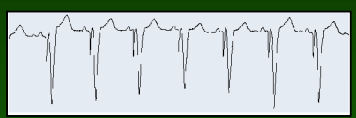
Cardiac Resynchronization Therapy

- Cardiac resynchronization, in association with an optimized AV delay, improves hemodynamic performance by forcing the left ventricle to complete contraction and begin relaxation earlier, allowing an increase in ventricular filling time.
- Coordinate activation of the ventricles and septum.



ECG depicting IVCD



ECG depicting cardiac resynchronization

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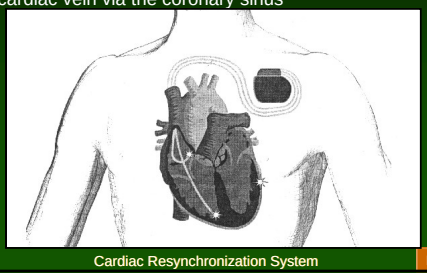
Achieving Cardiac Resynchronization

- Transvenous Approach
  - Standard pacing leads in RA and RV
  - Specially designed left heart lead placed in a left ventricular cardiac vein via the coronary sinus



Cardiac Resynchronization System

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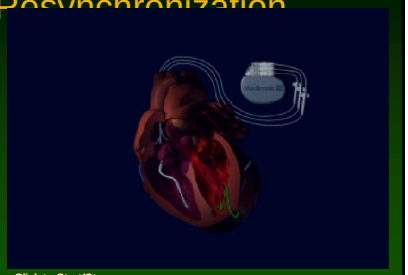
Proposed Mechanisms of Cardiac Resynchronization

- **Improved Contraction Pattern**
- **AV Interval Optimization**



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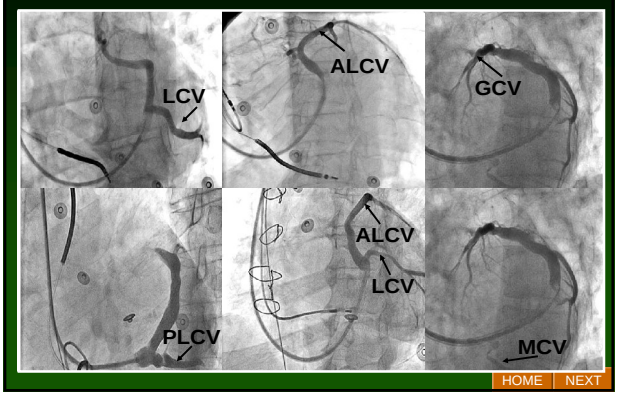
Coronary sinus venous anatomy



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Cardiac Resynchronization Therapy

Increase the donkey's (heart) efficiency

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Prognosis

- The prognosis in patients with HF depends primarily on the nature of the underlying heart disease and on the presence or absence of a precipitating factor that can be treated.
- When one of the latter can be identified and removed, the outlook for immediate survival is far better than if HF occurs without any obvious precipitating cause.
- The long term prognosis is more favorable when the underlying form of heart disease, e.g., valvular heart disease, can be treated effectively.
- When this is not possible, the prognosis can be estimated by observing the response to treatment. When patients can be rendered free of congestion, survival may be 80% at two years. Survival may be as low as 50% at six months in patients with refractory symptoms .

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Prognosis

- Other factors that have been shown to be associated with a poor prognosis include a severely depressed ejection fraction <15%), a reduced maximal O2 uptake (<10 ml/kg/min), the inability to walk on a level and at a normal pace for more than 3 min, reduced serum Na-concentration < 133mEqlL),reducedserumK <3 meqlL), a markedly elevated (>500 pg/mL) BNP, as well as frequent ventricular extrasystoles. .

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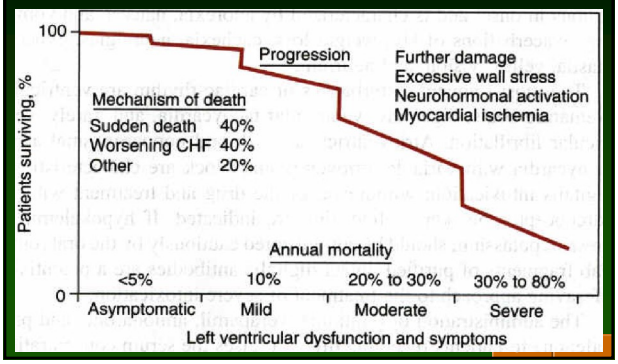
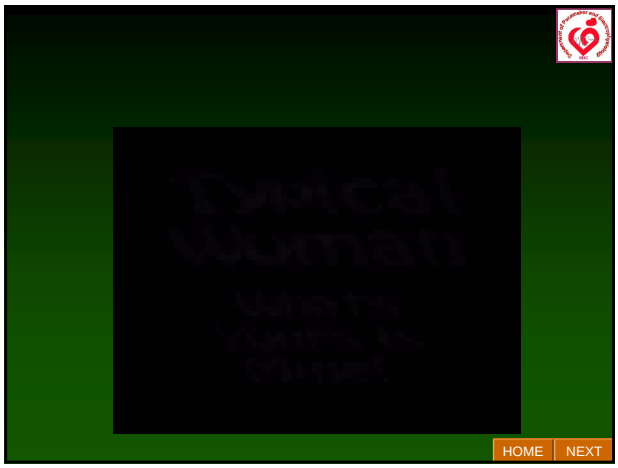

100
0
Patients surviving, %
Progression
Further damage
Excessive wall stress
Neurohormonal activation
Myocardial ischemia
Mechanism of death
Sudden death 40%
Worsening CHF 40%
Other 20%
Annual mortality
<5%
10%
20% to 30%
30% to 80%
Asymptomatic
Mild
Moderate
Severe
Left ventricular dysfunction and symptoms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