**Pathophysiology: Heart Failure**

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**Objectives**

At the conclusion of this seminar, learners will be able to:

1. Define heart failure as a clinical syndrome
2. Define and employ the terms preload, afterload, contractility, remodeling, diastolic dysfunction, compliance, stiffness and capacitance.
3. Describe the classic pathophysiologic steps in the development of heart failure.
4. Delineate four basic mechanisms underlying the development of heart failure.
5. Interpret pressure volume loops / Starling curves and identify contributing mechanisms for heart failure state.
6. Understand the common methods employed for classifying patients with heart failure.
7. Employ the classes and stages of heart failure in describing a clinical scenario.

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**Heart Failure Definitions**

- An inability of the heart to pump blood at a sufficient rate to meet the metabolic demands of the body (e.g. oxygen and cell nutrients) at rest and during effort or to do so only if the cardiac filling pressures are abnormally high.
- A complex clinical syndrome characterized by abnormalities in cardiac function and neurohormonal regulation, which are accompanied by effort intolerance, fluid retention and a reduced longevity.
- A complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood.

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**Epidemiology Heart Failure: The Problem**

- 3.5 million in 1991, 4.7 million in 2000, estimated 10 million in 2037
- Incidence: 550,000 new cases/year
- Prevalence: 1% ages 50--59, >10% over age 80
- More deaths from HF than from all forms of cancer combined
- Most common cause for hospitalization in age >65

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**Heart Failure**

- Not a disease
- A syndrome
  - From "syn" meaning "together" and "dromos" meaning "a running".
  - A group of signs and symptoms that occur together and characterize a particular abnormality.
- Diverse etiologies
- Several mechanisms

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**Heart Failure Paradigms**

- Cardiorenal model
- Hemodynamic model
- Neurohumoral model
- Genetic model

1950 → 2000
Heart Failure: Classifications

- Systolic vs. Diastolic
- Right vs. Left Sided
- Cardiac vs. Non-cardiac
- Dilated vs. Hypertrophic vs. Restrictive
- Compensated vs. Decompensated
- Acute vs. Chronic
- Forward vs. Backward
- High vs. Low Output
- Cardiac vs. Non-cardiac

Cardiac Muscle Function

- **Preload**
  - Muscle Length (mm)
  - The length of a cardiac muscle fiber prior to the onset of contraction.
  - Frank Starling

- **Afterload**
  - Muscle Length (mm)
  - The force against which a cardiac muscle fiber must shorten.
  - Isotonic Contraction

- **Contractility**
  - Muscle Length (mm)
  - The force of contraction independent of preload and afterload.
  - Inotropic State

The Pressure Volume Loop

- **Compliance/Stiffness vs Capacitance**
  - LV Pressure (mmHg)
  - LV Volume (ml)

From Muscle to Chamber

- LV Pressure vs. LV Volume
- LV Pressure vs. LV Volume

The Pressure Volume Loop

- LV Pressure vs. LV Volume
- LV Pressure vs. LV Volume
**Afterload (Arterial Properties)**

**Ea (Arterial Elastance)**
- If
  - \( TPR = \frac{MAP - CVP}{CO} \)
  - \( CO = SV \times HR \)
- Substituting the second equation into the first we obtain:
  - \( TPR = \frac{MAP - CVP}{SV \times HR} \)
- Making two simplifying assumptions.
  1. CVP is negligible compared to MAP.
  2. MAP is approximately equal to the end-systolic pressure in the ventricle (\( P_{es} \)).
- Then,
  - \( TPR = \frac{P_{es}}{SV \times HR} \)
- Which can be rearranged to:
  - \( \frac{P_{es}}{SV} \approx TPR \times HR \).

**Cardiac Chamber Function**

<table>
<thead>
<tr>
<th>Preload</th>
<th>Afterload</th>
<th>Contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDV</td>
<td>Aortic Pressure</td>
<td>Pressure generated at given volume.</td>
</tr>
<tr>
<td>EDP</td>
<td>Total peripheral resistance</td>
<td>Inotropic State</td>
</tr>
<tr>
<td>Wall stress at end diastole</td>
<td>Arterial impedance</td>
<td>Wall stress at end systole</td>
</tr>
</tbody>
</table>

**Pathophysiology of Heart Failure**

**Myocardial Insult/Stimuli/Damage**
- Pump dysfunction
  - Activation of neurohormones
    - Catecholamines
    - Angiotensin II
    - Cytokines
  - Remodeling
    - Hypertrophy
    - Fibrosis
    - Apoptosis

**Frank Starling Curves**

**Pathophysiology - PV Loop**

**Neurohormonal Activation in Heart Failure**

Myocardial injury to the heart (CAD, HTN, CMP, valvular disease)
- Initial fall in LV performance, ↑ wall stress
  - Activation of RAS and SNS
    - Remodeling and progressive worsening of LV function
      - Fibrosis, apoptosis, hypertrophy, cellular molecular alterations, myotoxicity
    - Peripheral vasoconstriction
      - Sodium retention
      - Hemodynamic alterations
  - Morbidity and mortality
    - Arrhythmias
    - Pump failure
  - Heart failure symptoms
    - Fatigue
    - Activity altered
    - Chest congestion
    - Edema
    - Shortness of breath

RAS, renin-angiotensin system; SNS, sympathetic nervous system.
Neurohormonal Activation in Heart Failure

Angiotensin II  
Norepinephrine

Hypertrophy, apoptosis, ischemia, arrhythmias, remodeling, fibrosis

Morbidity and Mortality

Neurohormones in Heart Failure

Myocardial Injury  
Fall in LV Performance

Activation of RAAS and SNS (endothelin, AVP, cytokines)

Myocardial Toxicity  
Change in Gene Expression

↑ ANP  
↑ BNP

Peripheral Vasodilation  
Sodium/Water Retention

Morbidty and Mortality


Adrenergic Pathway in Heart Failure Progression

↑ CNS sympathetic outflow

↑ Cardiac sympathetic activity

Myocyte hypertrophy

Myocyte injury

Increased arrhythmias

Vasoconstriction

Increased Wall Stress

Increased Wall Stress  
Increased Wall Stress

Myocyte Hyper trophy  
Altered interstitial matrix

Ventricular Enlargement  
Diastolic Dysfunction

Altered calcium handling proteins

Myocyte Death

Pathophysiology of myocardial remodeling:

Insult / Remodeling Stimuli

Increased Wall Stress

Vasoconstriction

Sodium retention

Increased Wall Stress

Neurohormonal Balance in Heart Failure

Endothelin  
Aldosterone  
Angiotensin II  
Epinephrine

ANP  
BNP

Acute and Chronic Responses – Benefits and Harm

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  | Vasoconstriction  | Skeletal muscle catabolism, deteriation 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  | Improves relaxation

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**Laplace’s Law**

Where \( P = \) ventricular pressure, \( r = \) ventricular chamber radius and \( h = \) ventricular wall thickness

**Pathophysiology of Heart Failure**

Four Basic Mechanisms
1. Increased Blood Volume (Excessive Preload)
2. Increased Resistant to Blood Flow (Excessive Afterload)
3. Decreased contractility
4. Decreased Filling

**Remodeling – Concentric vs. Eccentric**

**Increased Blood Volume**

- **Aortic Regurgitation**
  - Na Retention
  - Vasoconstriction
- **AI + Neurohormones**
- **AI + Remodeling**

**Increased Afterload**

- **Hypertension**
- **HTN + DD**
- **HTN + DD + HF**

**Ventricular Remodeling**
Decreased Contractility

Etiologies
- Ischemic Cardiomyopathy
  - Myocardial Infarction
  - Myocardial Ischemia
- Myocarditis
- Toxins
  - Anthracycline
  - Alcohol
  - Cocaine

Parameter | Normal | MI | MI + Neurohormones | MI + Remodeling
--- | --- | --- | --- | ---
SV (ml) | 80 | 62 | 46 | 46
Cardiac Output (L/min) | 4.2 | 3.0 | 5.2 | 3.2
PCWP (mm Hg) | 12 | 17 | 25 | 25

Decreased Filling

Etiologies
- Mitral Stenosis
- Constriction
- Restrictive Cardiomyopathy
- Cardiac Tamponade
- Hypertrophic Cardiomyopathy
- Infiltrative Cardiomyopathy

Parameter | Normal | HCM | HCM + HF
--- | --- | --- | ---
SV (ml) | 124/81 | 95/47 | 105/53
Cardiac Output (L/min) | 63 | 50 | 55
PCWP (mm Hg) | 4.4 | 3.5 | 3.8

Heart Failure: Classifications

Heart Failure
- Right vs. Left Sided
- Cardiac vs. Non-cardiac
- Systolic vs. Diastolic
- Dilated vs. Hypertrophic vs. Restrictive
- Acute vs. Chronic
- Forward vs. Backward
- High vs. Low Output

Types of Heart Failure

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Impaired Contraction</th>
<th>Impaired filling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>All ages</td>
<td>&gt; 60 years</td>
</tr>
<tr>
<td>1° Cause</td>
<td>Coronary Artery Disease</td>
<td>Hypertension</td>
</tr>
</tbody>
</table>

Systolic Versus Diastolic Failure

Part II
Systolic Versus Diastolic Failure

Heart Failure: Classifications

Heart Failure
- Right vs. Left Sided
- Cardiac vs. Non-cardiac
- Systolic vs. Diastolic

Dilated vs. Hypertrophic vs. Restrictive

Acute vs. Chronic Forward vs. Backward

High vs. Low Output
- Compensated vs. Decompensated

Heart Failure: Classifications

High vs. Low Output Failure

• Causes:
  - Anemia
  - Systemic arteriovenous fistulas
  - Hyperthyroidism
  - Beriberi heart disease
  - Paget disease of bone
  - Glomerulonephritis
  - Polycythemia vera
  - Carcinoid syndrome
  - Obesity
  - Anemia
  - Multiple myeloma
  - Pregnancy
  - Cor pulmonale
  - Polycythemia vera

Decompensated Heart Failure

Heart Failure: Classifications

Right vs. Left Sided
- Cardiac vs. Non-cardiac
- Systolic vs. Diastolic

Dilated vs. Hypertrophic vs. Restrictive

Acute vs. Chronic Forward vs. Backward

High vs. Low Output
- Compensated vs. Decompensated
### Dilated vs. Hypertrophic vs. Restrictive

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
<th>Sample Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated</td>
<td>Dilated left/both ventricle(s) with impaired contraction</td>
<td>Ischemic, idiopathic, familial, viral, alcoholic, toxic, valvular</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>Left and/or right ventricular hypertrophy</td>
<td>Familial with autosomal dominant inheritance</td>
</tr>
<tr>
<td>Restrictive</td>
<td>Restrictive filling and reduced diastolic filling of one/both ventricles, Normal near normal systolic function</td>
<td>Idiopathic, amyloidosis, endomyocardial fibrosis</td>
</tr>
</tbody>
</table>

### Clinical Manifestations

**Symptoms**
- Reduced exercise tolerance
- Shortness of breath
- Congestion
- Fluid retention
- Difficulty in sleeping
- Weight loss

### Diagnosis of heart failure

- Physical examination
- Chest X-ray
- EKG
- Echocardiogram
- Blood tests: Na, BUN, Creatinine, BNP
- Exercise test
- MRI
- Cardiac catheterization

### NYHA Classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Patient Symptoms</th>
</tr>
</thead>
</table>
| I     | Mild | No limitation of physical activity
|       |     | No undue fatigue, palpitation or dyspnea |
| II    | Mild | Slight limitation of physical activity
|       |     | Comfortable at rest
|       |     | Less than ordinary activity results in fatigue, palpitation, or dyspnea |
| III   | Moderate | Marked limitation of physical activity |
|       |     | Comfortable at rest |
|       |     | Less than ordinary activity results in fatigue, palpitation, or dyspnea |
| IV    | Severe | Unable to carry out any physical activity without discomfort |
|       |     | Symptoms of cardiac insufficiency at rest |
|       |     | Physical activity causes increased discomfort |

### ACC/AHA Staging System

- **STAGE A** High risk for developing HF
- **STAGE B** Asymptomatic LV dysfunction
- **STAGE C** Past or current symptoms of HF
- **STAGE D** End-stage HF

ACC/AHA Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High risk for developing heart failure</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td>Family history of cardiomyopathy</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic heart failure</td>
</tr>
<tr>
<td></td>
<td>Previous myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Left ventricular systolic dysfunction</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic valvular disease</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic heart failure</td>
</tr>
<tr>
<td></td>
<td>Known structural heart disease</td>
</tr>
<tr>
<td></td>
<td>Shortness of breath and fatigue</td>
</tr>
<tr>
<td></td>
<td>Reduced exercise tolerance</td>
</tr>
<tr>
<td>D</td>
<td>Refractory end-stage heart failure</td>
</tr>
<tr>
<td></td>
<td>Marked symptoms at rest despite maximal medical therapy (e.g., those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)</td>
</tr>
</tbody>
</table>

Goals of Treatment

1. Identification and correction of underlying condition causing heart failure.
2. Elimination of acute precipitating cause of symptoms.
4. Improve long term survival.

Etiologies

- Ischemic cardiomyopathy
- Valvular cardiomyopathy
- Hypertensive cardiomyopathy
- Inflammatory cardiomyopathy
- Metabolic cardiomyopathy
- General system disease
- Muscular dystrophies.
- Neuromuscular disorders.
- Sensitivity and toxic reactions.
- Peripartal cardiomyopathy

Percipients /Associated Factors

- Inappropriate reduction in the intensity of treatment, including
  - Dietary sodium restriction,
  - Physical activity reduction,
  - Drug regimen reduction, or,
  - most commonly, a combination of these measures.
- Ischemia
- Hypertension
- Anemia
- Volume Overload
- Increased Metabolic Demand
  - Infection
  - Thyroid Disease
- Arrhythmia
- Asthma/COPD

Targets of Treatment

Standard Pharmacological Therapy

- ACE inhibitors
- Angiotensin Receptor Blockers
- Beta Blockers
- Diuretics
- Aldosterone Antagonists
- Statins
- Vasodilators
- Inotropes

Treatment

<table>
<thead>
<tr>
<th>Stage</th>
<th>Patient Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High risk for developing heart failure</td>
</tr>
<tr>
<td></td>
<td>Optimal pharmacologic therapy (OPT)</td>
</tr>
<tr>
<td></td>
<td>Aspirin, ACE inhibitors, statins, b-blockers, a-b-blockers (carvedilol) diabetic therapy</td>
</tr>
<tr>
<td>B</td>
<td>Asymptomatic heart failure</td>
</tr>
<tr>
<td></td>
<td>OPT</td>
</tr>
<tr>
<td></td>
<td>ICD if left ventricular (LV) dysfunction (systolic) present</td>
</tr>
<tr>
<td>C</td>
<td>Symptomatic heart failure</td>
</tr>
<tr>
<td></td>
<td>OPT</td>
</tr>
<tr>
<td></td>
<td>ICD if LV dysfunction (systolic) present</td>
</tr>
<tr>
<td></td>
<td>CRT if QRS wide, LVEF&lt;35%</td>
</tr>
<tr>
<td>D</td>
<td>Refractory end-stage heart failure</td>
</tr>
<tr>
<td></td>
<td>OPT</td>
</tr>
<tr>
<td></td>
<td>Intermittent IV inotropes</td>
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<tr>
<td></td>
<td>ICD as a bridge to transplantation</td>
</tr>
<tr>
<td></td>
<td>CRT</td>
</tr>
<tr>
<td></td>
<td>Other devices (LVAD, pericardial restraint)</td>
</tr>
</tbody>
</table>
Treatment of Acute Heart Failure

ACC/AHA Staging System

Summary

- Complex Clinical Syndrome
- Multiple Etiologies and Classification Systems
- Physiologic Understanding Essential

http://www.columbia.edu/itc/hs/medical/heartsim/