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.

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
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.

Epidemiology Heart Failure: The Problem

- 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.

Heart Failure Paradigms
Heart Failure: Classifications

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

Cardiac Muscle Function

**Preload**

- The length of a cardiac muscle fiber prior to the onset of contraction.
- Frank Starling

**Afterload**

- The force against which a cardiac muscle fiber must shorten.
- Isotonic Contraction

**Contractility**

- The force of contraction independent of preload and afterload.
- Inotropic State

From Muscle to Chamber
The Pressure Volume Loop

- Diastole
- Systole

Volume

Pressure

ESPVR vs Preload

Compliance/Stiffness vs Capacitance
Afterload (Arterial Properties)

Ea (Arterial Elastance)
• If
  – TPR = [MAP - CVP] / CO, and
  – CO = SV * HR
• Substituting the second equation into the first we obtain:
  – TPR = [MAP - CVP] / (SV*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 (Pes).
• Then,
  – TPR = Pes / (SV*HR)
• Which can be rearranged to:
  – Pes = TPR * SV * 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>Wall stress at end systole</td>
<td></td>
</tr>
</tbody>
</table>

Frank Starling Curves
Pathophysiology - PV Loop

Pathophysiology of Heart Failure

Myocardial Insult/Stimuli/Damage

Pump dysfunction

Activation of neurohormones
- Catecholamines
- Angiotensin II
- Cytokines

Remodeling
- Hypertrophy
- Fibrosis
- Apoptosis

RAS, renin-angiotensin system; SNS, sympathetic nervous system.

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

Heart failure symptoms
- Fatigue
- Activity altered
- Fluid retention
- Edema
- Shortness of breath

Morbidity and mortality
- Arrhythmias
- Pump failure
Neurohormonal Activation in Heart Failure

- Angiotensin II
- Norepinephrine

Hypertrophy, apoptosis, ischemia, arrhythmias, remodeling, fibrosis

Morbidity and Mortality

Adrenergic Pathway in Heart Failure Progression

- CNS sympathetic outflow
- Cardiac sympathetic activity
- Vascular sympathetic activity
- Renal sympathetic activity

- Myocyte hypertrophy
- Myocyte injury
- Increased arrhythmias

Disease progression

- Sodium retention
- Vasoconstriction
- β1, β2 activation of RAS

Neurohormonal Balance in Heart Failure

- Endothelin
- Aldosterone
- Angiotensin II
- Epinephrine

- ANP
- BNP

Adapted from: Buechel, IC. / (Buerger, J.P./Getman, L.) 157-163
**Neurohormones in Heart Failure**

- Myocardial Injury → Fall in LV Performance
  - Activation of RAAS and SNS (endothelin, AVP, cytokines)
  - ANP and BNP
  -Peripheral Vasoconstriction
  - Sodium/Water Retention
- Myocardial Toxicity
- Change in Gene Expression
- Peripheral Vasoconstriction
- Sodium/Water Retention
- HF Symptoms

**Pathophysiology of myocardial remodeling:**

- Insult / Remodeling Stimuli
  - Wall Stress
  - Cytokines
  - Neurohormones
  - Oxidative stress
  - Altered calcium handling proteins
  - Myocyte Hypertrophy
  - Altered interstitial matrix
  - Fetal Gene Expression
  - Diastolic Dysfunction
  - Systolic Dysfunction
  - Myocyte Death

**Acute and Chronic Responses – Benefits and Harm**

<table>
<thead>
<tr>
<th>Response</th>
<th>Short-term Effects (mainly adaptive; hemorrhage, acute heart failure)</th>
<th>Long-term Effects (mainly deleterious; chronic heart failure)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salt and water retention</td>
<td>Angiogenesis</td>
<td>Pulmonary congestion, Dice_FLASH</td>
</tr>
<tr>
<td>Vasorelaxation</td>
<td>Maintain perfusion to vital organs (brain, heart)</td>
<td>Decrease pump function, increase cardiac energy expenditure</td>
</tr>
<tr>
<td>Sympathetic stimulation</td>
<td>Increase heart rate and ejection</td>
<td>Increase energy expenditure</td>
</tr>
<tr>
<td>Cytokine activation</td>
<td>Vasodilation</td>
<td>Skeletal muscle catabolism, disorganization of endothelial function, impaired contraction, LV remodeling</td>
</tr>
<tr>
<td>Hypertrophy</td>
<td>Unloads individual muscle fibers</td>
<td>Deterioration and death of cardiac cells; cardiomyopathy of overload</td>
</tr>
<tr>
<td>Increased collagen</td>
<td>May reduce diastole</td>
<td>Injures relaxation</td>
</tr>
</tbody>
</table>

Laplace’s Law

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

Remodeling – Concentric vs. Eccentric

Ventricular Remodeling
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

**Increased Blood Volume**

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>Parameter</th>
<th>Normal</th>
<th>AI</th>
<th>AI + Neurohormones</th>
<th>AI + Remodeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral Regurgitation</td>
<td>BP (mm Hg)</td>
<td>140/75</td>
<td>128/50</td>
<td>130/50</td>
<td>104/45</td>
</tr>
<tr>
<td>Aortic Regurgitation</td>
<td>SV (ml)</td>
<td>84</td>
<td>80</td>
<td>82</td>
<td>62</td>
</tr>
<tr>
<td>Volume Overload</td>
<td>Cardiac Output (L/min)</td>
<td>3.8</td>
<td>3.0</td>
<td>4.3</td>
<td>2.6</td>
</tr>
<tr>
<td>Left to Right Shunts</td>
<td>PCWP (mm Hg)</td>
<td>10</td>
<td>15</td>
<td>25</td>
<td>20</td>
</tr>
</tbody>
</table>

**Increased Afterload**

<table>
<thead>
<tr>
<th>Etiologies</th>
<th>Parameter</th>
<th>Normal</th>
<th>HTN</th>
<th>HTN + DD</th>
<th>HTN + DD + HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Stenosis</td>
<td>BP (mm Hg)</td>
<td>120/70</td>
<td>130/70</td>
<td>140/80</td>
<td>160/100</td>
</tr>
<tr>
<td>Aortic Coarctation</td>
<td>SV (ml)</td>
<td>67</td>
<td>52</td>
<td>49</td>
<td>57</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Cardiac Output (L/min)</td>
<td>4.0</td>
<td>3.6</td>
<td>3.4</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td>PCWP (mm Hg)</td>
<td>10</td>
<td>15</td>
<td>25</td>
<td>23</td>
</tr>
</tbody>
</table>
**Decreased Contractility**

Etiologies
- Ischemic Cardiomyopathy
  - Myocardial Infarction
  - Myocardial Ischemia
- Myosin Defects
- Toxins
  - Anthracycline
  - Alcohol
  - Cocaine

**Decreased Filling**

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

Part II
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

Types of Heart Failure

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>SHF</th>
<th>Diastolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired Contraction</td>
<td>Impaired Filling</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Demographics</th>
<th>All ages</th>
<th>&gt; 60 years</th>
</tr>
</thead>
</table>

| 1° Cause       | Coronary Artery Disease | Hypertension |

Systolic Versus Diastolic Failure

- Systolic Dysfunction
- Normal
- Diastolic Dysfunction

<table>
<thead>
<tr>
<th>Pressure</th>
<th>Volume</th>
<th>Pressure</th>
<th>Volume</th>
<th>Pressure</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Systolic Versus Diastolic Failure

Heart Failure: Classifications

Decompensated Heart Failure
Heart Failure: Classifications

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

Heart Failure: Classifications

- Cardiac vs. Non-cardiac

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
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, familial with autosomal dominant inheritance</td>
</tr>
<tr>
<td>Hypertrophic</td>
<td>Left and/or right ventricular hypertrophy</td>
<td>Ischemic, idiopathic, familial, viral, alcoholic, toxic, 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>Ischemic, idiopathic, familial, viral, alcoholic, toxic, familial with autosomal dominant inheritance, 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>
<tbody>
<tr>
<td>I</td>
<td>No limitation of physical activity</td>
</tr>
<tr>
<td></td>
<td>No undue fatigue, palpitation or dyspnea</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity</td>
</tr>
<tr>
<td></td>
<td>Comfortable at rest</td>
</tr>
<tr>
<td></td>
<td>Less than ordinary activity results in fatigue, palpitation, or dyspnea</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity</td>
</tr>
<tr>
<td></td>
<td>Comfortable at rest</td>
</tr>
<tr>
<td></td>
<td>Less than ordinary activity results in fatigue, palpitation, or dyspnea</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry out any physical activity without discomfort</td>
</tr>
<tr>
<td></td>
<td>Symptoms of cardiac insufficiency at rest</td>
</tr>
<tr>
<td></td>
<td>Physical activity causes increased discomfort</td>
</tr>
</tbody>
</table>

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

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)

Known structural heart disease

Shortness of breath and fatigue

Reduced exercise tolerance

Previous myocardial infarction

Left ventricular systolic dysfunction

Asymptomatic valvular disease

Known structural heart disease

Shortness of breath and fatigue

Reduced exercise tolerance

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)

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 (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, β-blockers, α-β-blockers (carvedilol) diabetics</td>
</tr>
<tr>
<td>B (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 (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 ≤ 35%)</td>
</tr>
<tr>
<td>D (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>
</tr>
<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/