**Learning Objectives**

- Review the determinants of cardiac performance in isolated cardiac muscle and in the normal intact heart
- Discuss the compensatory mechanisms activated in response to myocardial dysfunction
  - Frank-Starling Mechanism
  - Neurohormonal Alterations
  - Ventricular Hypertrophy and Remodeling
- Discuss the pathophysiology of Heart Failure
  - with Reduced Ejection Fraction (HFrEF)
  - with Preserved Ejection Fraction (HFpEF)
- Discuss the clinical manifestations of heart failure

**Braunwald’s Working Definition of Congestive Heart Failure**

The inability of the heart to pump blood forward at a sufficient rate to meet the metabolic demands of the body ("forward failure")

-or-

the ability to do so only if the cardiac filling pressures are abnormally high ("backward failure")

-or-

both
**Scope of the problem**

- ~6 million people have HF
- >500,000 new cases per year
- Most common discharge diagnosis of hospitalized patients >65yo (1 million annually)

**Why?**
- We are better at treating coronary disease and have better treatments to keep people alive (prevalence)
- There is more hypertension and diabetes (incidence)
- Our population is aging (prevalence)

**Major Determinants of Cardiac Performance**

- HEART RATE
- PRELOAD
- AFTERLOAD
- CONTRACTILITY

**Preload**

- The tension or “wall stress” in the ventricle at the end of diastole
- Related to the amount of circulating blood volume, venous return, and intrinsic compliance of ventricular myocardium
Afterload

- The tension or “wall stress” in the ventricle during contraction
- The end load against which the ventricle contracts
  - LV → aortic pressure (or aortic valve when significant aortic stenosis is present)
  - RV → pulmonary artery pressure

Contractility

- Innate ability of the heart to contract
- Frank-Starling contractility curve describes the relationship of myocyte/ventricular stretch to the pressure generated during systole

Pressure and Volume During a Single Cardiac Contraction (P-V Loop)

- Cardiac Output = SV x HR
- Heart Rate = 70 beats/min
- Stroke Volume (SV) = 70ml
- SV = 120ml – 50ml
- EF = 58%
Effects of Changing Preload, Afterload, and Contractility on Stroke Volume of Normal Heart

A. Increasing Preload
B. Decreasing Afterload
C. Increasing Contractility

Ventricular Performance Curve (a.k.a. Frank-Starling Curve)

The syndrome of heart failure

Inciting event → Compensatory changes → Response (good and bad)
**Causes of the “inciting event”**

- Disorders of Impaired Contractility
  - Myocardial Infarction (MI) / Ischemic Cardiomyopathy
  - Chronic Aortic or Mitral Regurgitation
  - Dilated Cardiomyopathy

- Disorders of Markedly Increased Afterload
  - Severe Aortic Stenosis
  - Uncontrolled Hypertension
  - Aortic coarctation

- Disorders with Impaired Ventricular Relaxation/Decreased Filling
  - Restrictive Cardiomyopathy
  - Acquired or Familial Hypertrophic Cardiomyopathy
  - Infiltrative diseases (i.e. amyloidosis)
  - Constrictive Pericarditis

**Compensatory Mechanisms to Maintain Cardiac Output in HF**

- Frank-Starling Mechanism - seconds
  (Length-Dependent Activation)

- Autonomic Nervous System - seconds
  (Baroreceptor Response)

- Renal Compensation – seconds to hours
  (Renin-Angiotensin-Aldosterone System)

- Ventricular Remodeling – weeks to years
  (Myocardial hypertrophy and/or dilation)

*These adaptive mechanisms may be adequate to maintain pumping performance; however, their capacity to sustain cardiac performance may ultimately be exceeded.

**Neurohormonal Model**

![Neurohormonal Model Diagram](image-url)
**Sympathetic Nervous System**

- “Flight or fight”
- ↓ Cardiac output →
  - ↑ sympathetic
  - ↓ parasympathetic tone
- ↑ Norepinephrine [NE], β1 activation →
  - ↑ contractility
  - ↑ HR

  This is good, right?

**Negative effect of chronic NE stimulation**

- Ischemia
- Arrhythmia

- Increase Renin
- Increase sodium reabsorption
- Increase in peripheral vascular resistance (afterload)

**Renin**

- Released in response to decrease in cardiac output
  - Decreased stretch of the glomerular afferent arteriole
  - Reduced delivery of chloride to the macula densa
  - Increased beta-1 adrenergic activity
**RAAS**

![Diagram showing RAAS components: Renin, Angiotensin I, Angiotensin II, Vasconstrictor, ↑ Afterload, ↑ Preload.](image)

**Angiotensin II & Aldosterone**

**REMODELING**
- Myocyte hypertrophy
- Re-expression of fetal isoforms
- Myocyte apoptosis
- Changes in the interstitial matrix

→ Worsening cardiac performance due to progressive hypertrophy and/or dilation

**Compensatory Mechanisms Are Acutely Beneficial, but Can Ultimately Lead to Worsening Ventricular Performance!**
**Ventricular Remodeling**

- Post-MI (infarct expansion with regional hypertrophy/dilation of noninfarcted segments)
  - Myocardial Injury
  - Myocardial Infarction
- Pressure-Overload LVH (Concentric LVH)
  - Aortic Stenosis
  - Systemic Hypertension
- Volume-Overload LVH (Eccentric LVH)
  - Mitr al Regurgitation
  - Aortic Insufficiency
  - AV Fistula
  - Hyperthyroidism

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**Role of Increased Wall Stress in Ventricular Remodeling**

- Volume Overload
- Pressure Overload
- Post-MI Segmental Dysfunction
  - Systolic or Diastolic Wall Stress
  - (+) Myocardial Hypertrophy
  - (-) Myocardial Dysfunction

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**Post-MI Regional Wall Stress**

Wall Stress = Pressure \times \text{Radius} / \text{Wall Thickness}
Ventricular Remodeling

- Cardiac Myocyte Hypertrophy
- Cardiac Fibroblast Hyperplasia
- Perivascular and Interstitial Fibrosis
- Vascular Remodeling and Angiogenesis
- Cardiac Myocyte Apoptosis

Early Recognition and Treatment of Ventricular Dysfunction—“ANTI-REMODELING Rx”

- Structural changes in the ventricular myocardium represent the disease process.
- Remodeling often PRECEDES the development of symptoms of HEART FAILURE by months to years.
- Remodeling is predominantly a growth-mediated response, and results from an interplay between mechanical factors, and systemic and locally derived neurohormonal factors.
- Efforts directed at preventing or slowing the progression of ventricular remodeling will prevent or delay the development of congestive heart failure.

Drugs That Prevent or Slow the Progression of Ventricular Remodeling

- Prevent Ventricular Remodeling
  - ACEI/ARB/ARNI
  - Beta Blockers
  - Aldosterone Antagonists

- Prolong Survival
  - ACEI/ARB/ARNI
  - Hydralazine + Nitrates
  - Beta Blockers (carvedilol, metoprolol, bisoprolol)
  - Aldosterone antagonists (spironolactone, eplerenone)
Heart Failure – Clinical Presentations

• "Forward" Failure vs. "Backward" Failure
• LV, RV, and Biventricular Failure
• Systolic vs. Diastolic Failure
• HF with reduced Ejection Fraction (HFrEF)
• HF with preserved Ejection Fraction (HFpEF)

Heart Failure with Reduced Ejection Fraction (Systolic Heart Failure)

Heart Failure with Preserved Ejection Fraction (Diastolic Heart Failure)
Pathophysiology of Left vs Right-Sided Heart Failure

- Same physiological principles can be applied to both Left and Right-Sided HF
- RV is much more "compliant" than LV
  - Wall Thickness
  - RV Developed Pressure << LV Developed Pressure
  - Pulmonary Vascular Resistance << Systemic Vascular Resistance
- RV can tolerate much larger changes in filling without a major change in pressure
- RV is very susceptible to acute changes in Pulmonary Vascular Resistance

Causes of Right-Sided Heart Failure

- Cardiac Causes
  - LV Failure of any cause
  - Mitrail Stenosis/Regurgitation
  - Acute MI with RV Infarction
  - Pulmonic Stenosis
- Pulmonary Parenchymal Diseases
  - COPD
  - Interstitial Lung Diseases (silicosis, pulmonary fibrosis, etc.)
  - ARDS
- Pulmonary Vascular Diseases
  - Pulmonary Embolism
  - Primary Pulmonary Hypertension

Clinical Manifestations of Heart Failure

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Physical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left-Sided HF</td>
<td>Left-Sided HF</td>
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<tr>
<td>Dyspnea</td>
<td>Diaphoresis</td>
</tr>
<tr>
<td>Orthopnea</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Paroxysmal nocturnal dyspnea</td>
<td>Tachypnea</td>
</tr>
<tr>
<td>Cough</td>
<td>Pulmonary rales</td>
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<tr>
<td>Fatigue</td>
<td>Loud P2</td>
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<td></td>
<td>S3 Gallop (Systolic dysfunction)</td>
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<tr>
<td>Right-Sided HF</td>
<td>Right-Sided HF</td>
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<tr>
<td>Peripheral edema</td>
<td>Jugular venous distension</td>
</tr>
<tr>
<td>RUQ discomfort</td>
<td>Peripheral edema</td>
</tr>
<tr>
<td></td>
<td>Hepatomegaly</td>
</tr>
</tbody>
</table>
Sample question 1

Heart failure is
A. a disease that always leads to fluid congestion in the lungs
B. the most common reason for children to be hospitalized in the Units States
C. decreasing in prevalence due to recent medical advances
D. increasing in prevalence due to aging population and increasing incidence of HTN and DM

Sample question 2

A 65 yr old male presents to the hospital with chest pain and is diagnosed with an MI. The following day his echocardiogram shows an ejection fraction of 20%, however, he is devoid of any signs or symptoms of heart failure.

What compensatory mechanism takes weeks to years to develop?
A. Frank Starling mechanism
B. Neurohormonal activation
C. Renal compensation
D. Ventricular remodeling

Sample question 3

A 65 year old female presents to the hospital with subacute onset of dyspnea, orthopnea, and PND, and an echocardiogram reveals dilated cardiomyopathy with EF 25%.

Which of the following is associated with eccentric hypertrophy?
A. Aortic Stenosis
B. Hypertension
C. Mitral Regurgitation
D. Aortic Coarctation
Sample question 4

A 75 year old female with longstanding history of HTN presents to clinic with new dyspnea, orthopnea, and bilateral lower extremity edema. An echocardiogram is ordered and reveals concentric thickening of the myocardium with ejection fraction (EF) 55% and abnormal diastolic function.

Which of the following is true in Heart Failure with preserved EF?

A. Stroke volume is increased due to the increase in preload
B. Stroke volume is decreased due to a reduction in contractility
C. Stroke volume is decreased due to an increase in diastolic compliance
D. End diastolic volume is increased due to a decrease in diastolic compliance
E. EF is preserved because the decrease in stroke volume is offset by the decrease in end diastolic volume

Thank You

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Extra slides
Physiology of Normal Cardiac Muscle Segments During Isometric and Isotonic Contractions

Role of Ca²⁺ in Cardiomyocyte Contractility

Post-MI Ventricular Remodeling

- Mitchell and Pfeffer: “LV enlargement and distortion of regional and global ventricular geometry occurring after myocardial infarction.”

- Whittaker and Kloner: “Any architectural or structural change that occurs after myocardial infarction in either the infarcted or noninfarcted regions of the heart.”
**Post-MI Ventricular Remodeling**

- A - Reversible Injury
- B - Irreversible Injury
- C - Infarct Expansion
- D - Remodeling of noninfarcted muscle
- E - Early reperfusion
- F - Late reperfusion
- G - “Remodeling” Rx

**Alterations in Ventricular Shape and Size Following Acute MI**

- Acute alterations in ventricular dimensions (seconds)
- Infarct expansion (hours - weeks)
- Hypertrophy/dilatation of noninfarcted segments (weeks-years)

**Ventricular Remodeling – Concentric vs. Eccentric Hypertrophy**