PATHOPHYSIOLOGY OF HEART FAILURE

I. WORKING DEFINITION OF CONGESTIVE HEART FAILURE:
   A. The inability of the heart to pump blood forward at a sufficient rate to meet the metabolic demands of the body (“forward failure”), or
   B. the ability to do so only if the cardiac filling pressures are abnormally high (“backward failure”),
   C. or both.
   D. Syndrome, not a Disease!
   E. At some time during the course of the illness, CHF is the principal manifestation of nearly every form of cardiac disease.
   F. Causes of acute heart failure can differ from chronic heart failure
   G. Treatment of acute heart failure can differ from chronic heart failure

II. REVIEW - MAJOR DETERMINANTS OF CARDIAC PERFORMANCE
   A. Heart Rate - single most important determinant of cardiac output
   B. “Preload”
      1. The ventricular wall tension at the end of diastole
      2. In mechanical terms, the stretch on the muscle fibers prior to contraction
      3. Often approximated clinically as the LV end-diastolic pressure (LVEDP)
   C. “Afterload”
      1. Ventricular wall tension during systole (aortic impedance)
      2. In mechanical terms, the stress on the muscle fibers during contraction
      3. Approximated clinically as Systemic Vascular Resistance (SVR)
   D. “Contractility” (“Inotropy”)
      1. A measure of the magnitude of contractile force at any given resting fiber length
      2. Approximated by the slope of endsystolic pressure-volume relationship (ESPVR) in the intact heart
      3. Alterations in [Ca^{2+}] and myofilament Ca^{2+} sensitivity can have profound effects on myocardial contractility.

III. REVIEW – ISOLATED CARDIAC MUSCLE MECHANICS [not in PPT presentation]
   A. Just “passive stretch” of the muscle increases developed tension during an isometric contraction.
B. Following “inotropic” stimulation (for example, sympathetic stimulation), isometric tension development at any given length (preload) increases tension (i.e., there is increased “contractility”).

C. If the muscle is allowed to shorten against a fixed load (i.e., an isotonic contraction with constant afterload), then increasing muscle length (increasing preload) causes the muscle to shorten a greater distance (ΔLc vs. ΔLa).

D. If the muscle is allowed to shorten against a fixed load, the presence of an inotrope causes greater fiber shortening and a smaller final muscle length compared to a contraction in the absence of the inotrope (a→c vs. a→b).
IV. REVIEW - REGULATION OF CARDIAC CONTRACTILITY [not in ppt presentation]

A. Central Role of Calcium in Regulating Excitation-Contraction Coupling

B. Calcium Gradient

1. *Extracellular* free $\text{Ca}^{2+}$ concentration ($[\text{Ca}^{2+}]_o$) = 1-2mM

2. *Intracellular* free $\text{Ca}^{2+}$ concentration ($[\text{Ca}^{2+}]_i$) during diastole = 100nM

3. $[\text{Ca}^{2+}]_i$ rises to 1-2 $\alpha$M systole.

C. Calcium Trigger

1. Calcium enters during plateau phase of the action potential largely via voltage-gated, L-type $\text{Ca}^{2+}$ channels

2. Calcium entry triggers $\text{Ca}^{2+}$ release from intracellular storage pool within the Sarcoplasmic Reticulum (SR)

3. $\text{Ca}^{2+}$ Release Channel (Ryanodine Receptor)- Ligand-operated channel, where the ligand is $\text{Ca}^{2+}$

4. Calcium-induced calcium release (CICR) allows for the explosive release of calcium needed for muscle contraction

D. Myofibrillar Proteins and Contraction

1. $\text{Ca}^{2+}$ interacts with troponin C within the thin filament of the cardiac sarcomere

2. Troponin complex alters conformation of tropomyosin, which “de-inhibits” actin-myosin interaction (myofibrillar ATPase)

3. Thick filament (myosin) slides over thin filament (actin) to produce muscle contraction at the expense of cellular ATP

E. Relaxation

1. $\text{Ca}^{2+}$ ions are re-sequestered into the SR by action of the SR $\text{Ca}^{2+}$ ATPase (SR $\text{Ca}^{2+}$ Pump, or SERCA2a)

2. Activity of the SR $\text{Ca}^{2+}$ pump is regulated by the phosphoprotein *Phospholamban*.

3. Activator $\text{Ca}^{2+}$ extruded from cell by $\text{Na}^+/\text{Ca}^{2+}$ Exchanger, and sarcolemmal $\text{Ca}^{2+}$ ATPase (SL $\text{Ca}^{2+}$ Pump).

4. Removal of $\text{Ca}^{2+}$ from myofilaments terminates actin-myosin crossbridge formation, leading to muscle relaxation.

5. Restoring forces return sarcomeres to their resting length

V. REVIEW - Pressure-Volume Loops and Left Ventricular Performance (Frank-Starling) Curves

A. Cardiac Output: Volume of blood ejected from the ventricle per minute

B. Cardiac Output (liters per minute) = Stroke Volume x Heart Rate (C.O. = SV x HR)

C. Normal Values at rest:

C.O. $\approx$ 5L/min

Heart Rate $\approx$ 70 beats per minute

LV End-Diastolic Volume (LVEDV) $\approx$ 120 ml

LV End-Systolic Volume (LVESV) $\approx$ 50 ml
Mechanisms of Human Disease
Pathophysiology of Heart Failure
Thursday Sept 27, 2018 Max Liebo M.D.

Stroke Volume (SV) = LVEDV - LVESV \approx 70 \text{ ml}
LV Ejection Fraction = (SV/LVEDV) \times 100 \approx 60\%

D. Cardiac Output can increase 4-5 fold with EXERCISE!!

E. Pressure-Volume Loops Relate Pressure and Volume
  During a Single Cardiac Cycle

F. Increasing Preload (A), Decreasing Afterload (B), and
  Increasing Contractility (C) all increase stroke volume
  in the normal heart (see below).

G. Frank-Starling Curves relate Cardiac Output to Preload, as measured by the LV End-Diastolic Pressure
1. P-V loops are not used clinically because of inability to measure volume accurately.
2. However, cardiac output and LVEDP can be readily estimated (Swan-Ganz catheter)
3. Both increasing preload (A→B), and increasing contractility (A→C) can increase cardiac output in the intact heart.
4. Decreasing afterload has a similar effect as increasing contractility on the Frank-starling curve
5. Key to understanding how various drugs are used to increase cardiac output in CHF.
VI. PATHOPHYSIOLOGY OF CONGESTIVE HEART FAILURE

A. Congestive Heart Failure (CHF) may result from a variety of causes (it’s a syndrome, not a disease!)

B. Causes of CHF can be generally grouped into 3 broad categories:
   1. Disorders of impaired contractility (ex., myocardial infarction, chronic volume overload, dilated cardiomyopathies, etc.);
   2. Disorders with markedly increased afterload (ex., severe aortic stenosis, uncontrolled hypertension);
   3. Disorders with impaired ventricular relaxation and/or reduced filling (ex., restrictive cardiomyopathies; hypertrophic cardiomyopathy; pericardial constriction/tamponade)

C. SYSTOLIC Heart Failure - results from decreased ventricular emptying (decreased contractility, increased afterload) – Manifested as a HF with Reduced Ejection Fraction

D. DIASTOLIC Heart Failure - results from decreased ventricular filling or reduced relaxation – Manifested as HF with normal (or near-normal) EF

E. Patients with symptoms and signs of CHF are approximately EQUALLY divided between Systolic and Diastolic HF.

F. Many patients manifest BOTH.

VII. HEART FAILURE WITH REDUCED EF (HFrEF)

A. Systolic dysfunction of either ventricle due to impaired contractility or pressure overload

B. Loss of contractility can result from destruction of cardiomyocytes (ex. acute MI) or abnormal myocyte function (ex. alcohol-induced cardiomyopathy)

C. Effect of impaired systolic function on P-V loop and Frank-Starling Curve

1. ESPVR is shifted down and to the right, so that systolic emptying ceases at a greater end-systolic volume.
2. The reduced systolic emptying causes an increase in end-diastolic volume and pressure, causing an increase in left atrial pressure
3. Increased left atrial pressure is transmitted back into the pulmonary venous circulation, resulting in pulmonary congestion.
4. Thus, reduced stroke volume and increased backward pressure results in a downward shift in the Frank-Starling Curve.
5. Thus, for any given LVEDP, cardiac output is reduced.
VIII. HEART FAILURE WITH PRESERVED EF (HFpEF)

A. Diastolic dysfunction of either ventricle due to impaired relaxation or reduced filling
B. Reduced compliance can result from LV hypertrophy, ischemia, fibrosis, or restrictive cardiomyopathy (ex. amyloidosis)
C. Effect of impaired diastolic function on P-V loop and Frank-Starling Curve
   1. EDPVR is shifted upward and to the left, so that diastolic filling is reduced.
   2. ESPVR is preserved so ventricular empties at same end-systolic volume
   3. Increased EDP is transmitted back to left atrium and pulmonary venous circulation, resulting in pulmonary congestion.
   4. Stroke volume is reduced, but EF is relatively preserved, as EDV is also reduced (EF=SV/EDV x 100)
   5. Reduced stroke volume and increased backward pressure also leads to a downward shift in the Frank-Starling Curve.
   6. Thus, for any given LVEDP, cardiac output is reduced.

IX. PATHOPHYSIOLOGY OF RIGHT-SIDED HEART FAILURE

A. Same physiological principles can be applied to both Left and Right Ventricular Failure
B. However, Right Ventricle (RV) is much more compliant, but generates much less pressure
C. RV can tolerate much larger changes in filling without changes in pressure, but does not tolerate changes in afterload nearly as well as the LV
D. RV is very susceptible to acute changes in pulmonary vascular resistance
E. Causes of RV Failure:
   1. Cardiac Causes
      a. LV Failure (****most common cause****)
      b. Pulmonic Stenosis
      c. Acute MI with RV Infarction
   2. Pulmonary parenchymal diseases
      a. COPD
      b. Interstitial lung diseases (silicosis, interstitial pulmonary fibrosis, etc.)
      c. ARDS
3. Pulmonary Vascular Diseases
   a. Pulmonary embolism
   b. Primary pulmonary hypertension

X. COMPENSATORY MECHANISMS ACTIVATED DURING HF PROGRESSION
A. Frank-Starling Mechanism
   1. Rapid response (seconds)
   2. LV dysfunction Decreased stroke volume (SV) Increased LVEDV
      Increased fiber stretch tends to restore SV
B. Autonomic Nervous System Effects
   1. Rapid response (seconds)
   2. LV dysfunction Decreased SV Decreased C.O. Baroreceptor
      Reflex Sympathetic stimulation and withdrawal of parasympathetic tone
      Increased heart rate and contractility tends to restore SV and increase C.O.
C. Renin-Angiotensin-Aldosterone System (RAAS)
   1. Rapid response (seconds – minutes)
   2. LV dysfunction Decreased SV Decreased C.O. Decreased Renal Perfusion

Production Increased Na and Water Retention Increased preload tends to restore increase SV and C.O.

D. Other Hormones
   1. Vasopressin
   2. Endothelin-1
   3. Natriuretic Peptides

E. Compensatory Mechanisms Are Acutely Beneficial, but Can Ultimately Lead to Worsening Ventricular Performance!

XI. CARDIAC HYPERTROPHY AND VENTRICULAR REMODELING
A. 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.”

   Samarel: Hypertrophy and dilatation of noninfarcted segments occurring weeks to years after acute MI.

B. Ventricular Remodeling in other forms of Heart Disease
   1. Chronic pressure overload – concentric left ventricular hypertrophy
   2. Volume overload – eccentric left ventricular hypertrophy
C. Role of Increased Wall Stress in Ventricular Remodeling
D. Ventricular Remodeling is initially beneficial, but can ultimately lead to **worsening** Ventricular Performance!

1. Chronic sympathetic stimulation leads to:
   a) Increased afterload (Norepinephrine-induced vasoconstriction)
   b) Beta-1 receptor down-regulation (decreased response to $\beta_1$-stimulation)
   c) Myocardial injury, apoptosis, and fibrosis
   d) Myocardial adrenergic receptor activation and “pathological hypertrophy”

2. Chronic renin-angiotensin-aldosterone activation leads to:
   a) Increased afterload (AngII is a very potent vasoconstrictor)
   b) Pulmonary congestion (Na and water retention)
   c) Myocardial angiotensin II receptor activation and “pathological hypertrophy”/fibrosis

3. Chronic mechanical overload itself leads to:
   a) “Pathological” hypertrophy via mechanotransduction as well as autocrine/paracrine release of AngII, endothelin-1, and other growth factors
   b) Abnormal cardiomyocyte Ca$^{2+}$ handling (decreased SERCA2)
   c) Chamber dilatation (fiber slippage)
   d) Cytoskeletal alterations - reduced cell compliance

E. Risk Factors for the Development of Post-MI Ventricular Remodeling

1. Infarct Size
2. Decreased ejection fraction (EF) in the peri-infarct period
3. Anterior vs. inferior wall MI
4. Reduced stroke volume in the peri-infarct period
5. Total occlusion of the infarct-related artery

F. Early Recognition and Treatment of Ventricular Dysfunction

1. Structural changes in the ventricular myocardium **represent** a disease process.
2. Remodeling often **PRECEDES** the development of symptoms of CHF (dyspnea, PND, edema, etc.) by months to years.
3. Remodeling is predominantly a **growth-mediated** response, and results from an interplay between mechanical factors, and systemic and locally derived neurohormonal factors.

4. **Efforts directed at preventing or slowing the progression of ventricular remodeling will prevent or delay the development of CHF.**

XII. CLINICAL MANIFESTATIONS OF CONGESTIVE HEART FAILURE

A. Symptoms of Left-Sided CHF

1. Dyspnea on Exertion (DOE)
2. Orthopnea (Inability to lie flat in bed)
3. Paroxysmal Nocturnal Dyspnea (awaken SOB due to mobilization of fluid)
4. Fatigue

B. Symptoms of Right-Sided CHF

1. Peripheral edema
2. RUQ Abdominal Discomfort (hepatic congestion)

C. Signs of Left-Sided CHF

1. Diaphoresis
2. Tachycardia
3. Tachypnea
4. Pulmonary rales
5. S3 gallop (in systolic dysfunction)
6. S4 gallop (in diastolic dysfunction)

D. Signs of Right-Sided CHF
1. Jugular venous distension
2. Hepatomegaly
3. Peripheral edema (pretibial, sacral)

XIII. REVIEW QUESTIONS

1. How does an increase in ventricular afterload reduce cardiac output?

2. How does an increase in ventricular preload increase cardiac output?

3. How does sympathetic stimulation increase cardiac output in the normal heart? In the failing heart?

4. What is the pathophysiological basis for HFrEF? For HFpEF?

5. What are the common symptoms of left-sided congestive heart failure? How do they relate to the pathophysiology of CHF?

6. How is the Renin-Angiotensin II-Aldosterone System (RAAS) acutely beneficial in maintaining cardiac output? Why does RAAS activation ultimately prove deleterious?

7. What is meant by the term “ventricular remodeling”?