

## **Pathophysiology of Heart Failure**

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Prior to this seminar students should visit the following website <http://www.columbia.edu/itc/hs/medical/heartsim> and perform the stimulation based tutorial on the Pressure Volume diagram.

### **Suggested Reading:**

- Heart failure. N Engl J Med. 2003 May 15;348(20):2007-18.
- ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult - J Am Coll Cardiol. 2005 Sep 20;46(6):e1-82
- Hormones and hemodynamics in heart failure. N Engl J Med. 1999 Aug 19;341(8):577-85.
- Pathophysiology of chronic heart failure. Lancet. 1992 Jul 11;340(8811):88-92

### **Learning Objectives:**

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:
  - Insult/injury/remodeling stimuli
  - Neurohormonal activation (RAAS and ANS)
  - Cellular/molecular alterations, hemodynamic alterations (Na retention, volume overload)
  - Remodeling
  - Morbidity and mortality
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

## **I. Definitions - Not a disease but rather a syndrome, with diverse etiologies and several mechanisms**

- A. 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.
- B. 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
- C. 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.

## **II. Epidemiology in United States**

- A. Prevalence: 3.5 million in 1991, 4.7 million in 2000, estimated 10 million by 2037, currently >5 million patients diagnosed with symptomatic HF.
- B. Age dependent prevalence: 1% ages 50--59, >10% over age 80
- C. Incidence: annually there are 550,000 new cases of symptomatic HF diagnosed
- D. 15 million outpatient visits for heart failure per year in U.S.
- E. 1 million hospitalizations and 6.5 million hospital days for heart failure
- F. 2.6 million patients hospitalized with heart failure as a 2° diagnosis
- G. 33% of patients with heart failure as a discharge diagnosis readmitted within 90 days
- H. \$24 billion annually on heart failure in the US
- I. More deaths from HF than from all forms of cancer combined
- J. Most common cause for hospitalization in age >65 (e.g. Medicare Population)

## **III. Heart Failure Paradigms**

- A. A paradigm is a conceptual or methodological model underlying the theories and practices of a science or discipline at a particular time; (hence) a generally accepted world view.
- B. The cardiorenal model was favored in the 1950-1960s when heart failure was predominately an edematous state. This era led to the advent of diuretics and digoxin.
- C. The hemodynamic model was the predominant paradigm from the 1970s through the early 1980s, was focused on the tools available at the time including measures of intra-cardiac pressures and flow. This

paradigm forms the basis for our understanding of heart failure as a hemodynamic disorder and remains a principle method in which we teach the pathophysiology of the syndrome. These first two paradigms have now been largely abandoned in clinical practice of the management of patients with chronic heart failure (e.g. outpatients) and are employed specifically in for the management of decompensated patients in the hospital, where positive inotropic drugs and vasodilators are still widely used.

- D. The neurohormonal hypothesis forms the basis for the modern treatment of chronic heart failure. This paradigm focuses on the neuroendocrine activation that results after the initial insult or stimuli and has been shown chronically to be important in the progression of heart failure. Inhibition of neurohormones has been demonstrated to have long-term benefit with regard to morbidity and mortality and have revolutionized the treatment for chronic heart failure.
- E. Genetic model is on the horizon and will employ newer genetic testing to further characterize the underlying mechanism, develop novel but more targeted therapies, define the natural history of the disease as well as the response to pharamaco-therapy (e.g. pharmacogenomics). Indeed a new classification system has been proposed for cardiomyopathies that is based specifically on genetic etiologies (Circulation. 2006 Apr 11;113(14):1807-16).

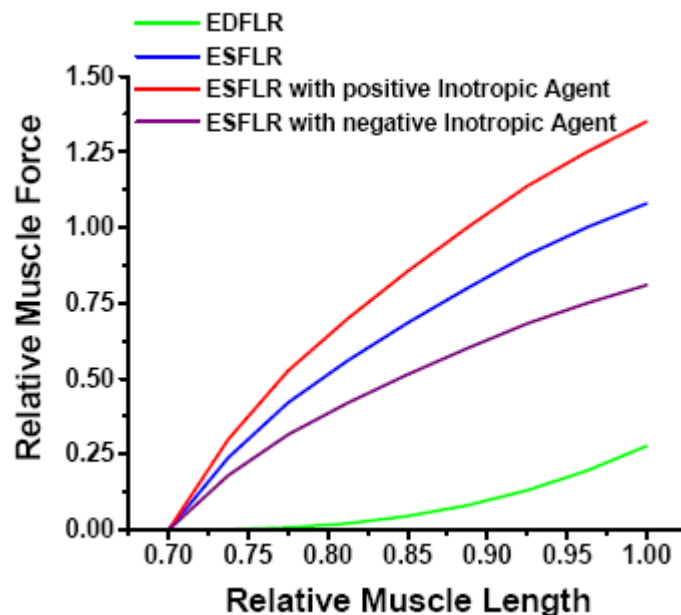
#### **IV. Basic Cardiovascular Parameters**

- A. The heart is a muscular pump connected to the systemic and pulmonary vascular systems. Working together, the principle job of the heart and vasculature is to maintain an adequate supply of nutrients in the form of oxygenated blood and metabolic substrates to all of the tissues of the body under a wide range of conditions. In order to understand the heart as a muscular pump and of the interaction between the heart and the vasculature and how this can become disordered, the concepts of contractility, preload and afterload are paramount.
- B. The ability of the ventricles to generate blood flow and pressure is derived from the ability of individual myocytes to shorten and generate force. Myocytes are tubular structures. During contraction, the muscles does one of two actions, it either shortens and/or generate force.
- C. One can isolate a piece of muscle from the heart, hold the ends and measuring the force developed at different muscle lengths while preventing muscles from shortening (e.g. isometric contractions). As the muscle is stretched from its slack length (the length at which no force is generated), both the resting (end-diastolic) force and the peak (end-systolic) force increase. The end-diastolic (passive) force-length relationship (EDFLR) is nonlinear, exhibiting a shallow slope at low

lengths and a steeper slope at higher lengths which reflects the nonlinear mechanical restraints imposed by the sarcolemma and extracellular matrix that prevent overstretch of the sarcomeres (see figure below and EDFLR in green). End-systolic (peak activated) force increases with increasing muscle length to a much greater degree than does end-diastolic force. End-systolic force decreases to zero at the slack length, which is generally ~70% of the length at which maximum force is generated. The difference in force at any given muscle length between the end-diastolic and end-systolic relations increases as muscle length increases, indicating a greater amount of developed force as the muscle is stretched. This fundamental property of cardiac muscle is referred to as the Frank-Starling Law of the Heart in recognition of its two discoverers.

- D. **Frank Starling law** of the heart delineates that with increasing length of the sarcomere, myocytes or cardiac muscle fibers there is an increasing force generated. **The length of a cardiac muscle fiber prior to the onset of contraction or the volume of the left ventricle prior to the onset of contraction is a measure of cardiac preload.**

For the ventricle, there are several possible measures of preload: 1) EDP, 2) EDV, 3) wall stress at end-diastole and 4) end-diastolic sarcomere length. Sarcomere length probably provides the most meaningful measure of muscle preload, but this is not possible to measure in the intact heart. In the clinical setting, EDP probably provides the most meaningful measure of preload in the ventricle. EDP can be assessed clinically by measuring the pulmonary capillary wedge pressure (PCWP) using a Swan-Ganz catheter that is placed through the right ventricle into the pulmonary artery.



E. **Afterload is the load imposed on the ventricle during ejection.**

This load is usually imposed on the heart by the arterial system, but under pathologic conditions when either the mitral valve is incompetent (i.e., leaky) or the aortic valve is stenotic (i.e., constricted) afterload is determined by factors other than the properties of the arterial system. There are several measures of afterload that are used in different settings (clinical versus basic science settings). Four different measures of afterload include:

1. **Aortic Pressure.** This provides a measure of the pressure that the ventricle must overcome to eject blood. It is simple to measure, but has several shortcomings. First, aortic pressure is not a constant during ejection. Thus, many people use the mean value when considering this as the measure of afterload. Second, aortic pressure is determined by properties of both the arterial system and of the ventricle. For example, if one increases contractility and increases cardiac output, aortic pressure will increase. Thus, mean aortic pressure is not a measure which uniquely indexes arterial system properties.

2. **Total Peripheral Resistance.** The total peripheral resistance (TPR) is the ratio between the mean pressure drop across the arterial system [which is equal to the mean aortic pressure (MAP) minus the central venous pressure (CVP)] and mean flow into the arterial system [which is equal to the cardiac output (CO)]. Unlike aortic pressure by itself, this measure is independent of the functioning of the ventricle. Therefore, it is an index which describes arterial properties. According to its mathematical definition, it can only be used to relate mean flows and pressures through the arterial system.

3. **Arterial Impedance.** This is an analysis of the relationship between pulsatile flow and pressure waves in the arterial system. It is based on the theories of Fourier analysis in which flow and pressure waves are decomposed into their harmonic components and the ratio between the magnitudes of pressure and flow waves are determined on a harmonic-by-harmonic basis. Thus, in simplistic terms, impedance provides a measure of resistance at different driving frequencies. Unlike TPR, impedance allows one to relate instantaneous pressure and flow. It is more difficult to understand, most difficult to measure, but the most comprehensive description of the intrinsic properties of the arterial system as they pertain to understanding the influence of afterload on ventricular performance. It is used primarily in research settings.

4. **Myocardial Peak Wall Stress.** During systole, the muscle contracts and generates force, which is transduced into intraventricular pressure, the amount of pressure being dependent

upon the amount of muscle and the geometry of the chamber. By definition, wall stress ( $\sigma$ ) is the force per unit cross sectional area of muscle and is simplistically interrelated to intraventricular pressure (LVP) using **Laplace's law:  $\sigma=LVP*r/h$** , where r is the internal radius of curvature of the chamber and h is the wall thickness. In terms of the muscle performance, the peak wall stress relates to the amount of force and work the muscle does during a contraction. Therefore, peak wall stress is sometimes used as an index of afterload. While this is a valid approach when trying to explain forces experienced by muscles within the wall of the ventricular chamber, wall stress is mathematically linked to aortic pressure which, as discussed above, does not provide a measure of the arterial properties and therefore is not useful within the context of indexing the afterload of the ventricular chamber.

- F. **Contractility is the force of contraction independent of preload and afterload.** If a drug is administered which increases the amount of calcium released to the myofilaments (for example epinephrine, which belongs to a class called inotropic agents), the end-systolic force-length relationship (ESFLR) will be shifted upwards, indicating that at any given length the muscle can generate more force. Conversely, negative inotropic agents generally decrease the amount of calcium released to the myofilaments and shift the ESFLR downward. Inotropic agents typically do not affect the end-diastolic force-length relationship.

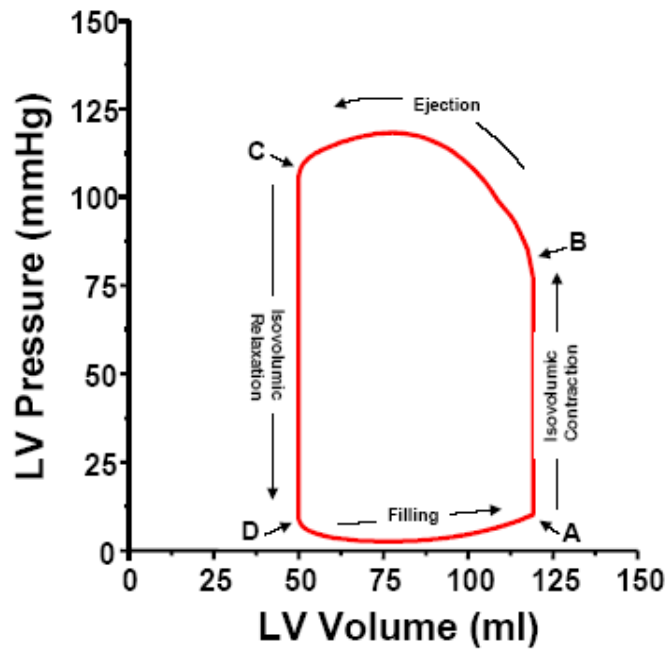
## V. Ventricular-Vascular Coupling Analyzed on the Pressure-Volume Diagram

### A. Pressure Volume Paradigm

#### 1. Basic parameters of the PV loop

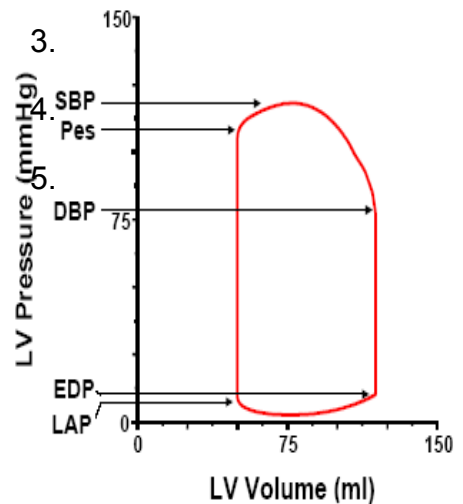
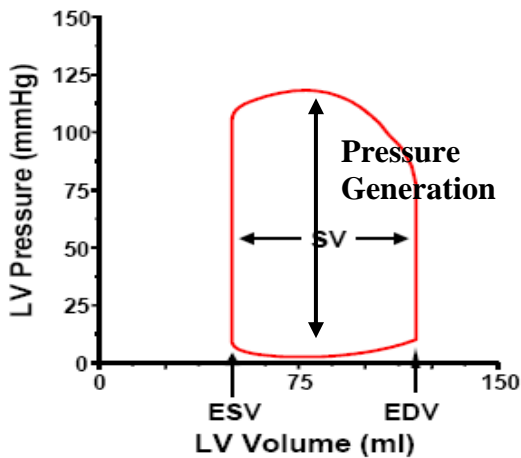
a) During a single cardiac cycle the heart contracts isovolumetrically (points A to B), then ejects blood (points B to C), isovolumetrically relaxes (points C to D) and then passively fills (point D to A) as depicted in the diagram below. Systole is the time between points A to C and

diastole between C to A.



B. Various parameters can be derived from the PV loop as shown below. In general the heart in its role as a hemodynamic pump has two roles:

1. To move blood (e.g. generate a stroke volume, which is the difference between the end diastolic volume [EDV] and the end systolic volume [ESV]).
2. To generate pressure, (e.g. the difference between the EDP and the systolic blood pressure is the pressure generated by the left ventricle).



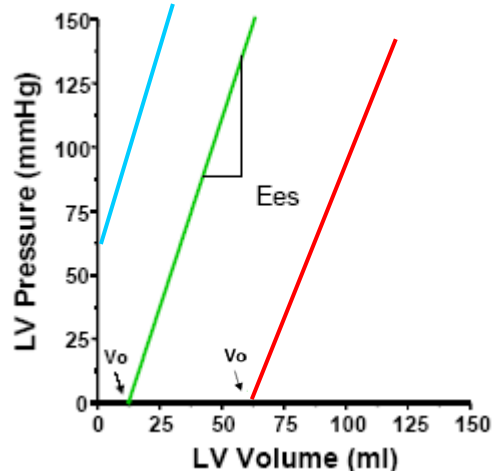
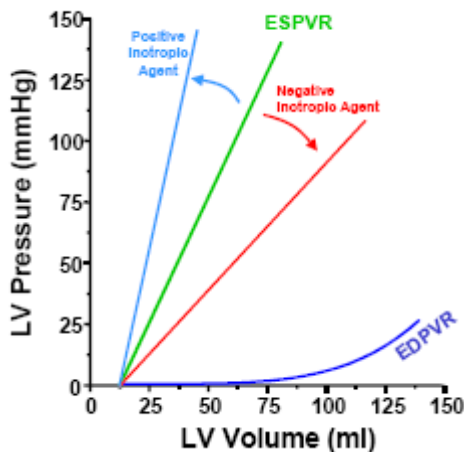
3. The area of the pressure volume loop is a representation of the work that the ventricle is able to do and is called the stroke work, which can be estimated as the stroke volume time the difference between SBP and LVEDP.

### C. ESPVR and EDPVR

1. If one were to place a balloon in the inferior vena cava or a clamp on the inferior vena cava and inflate the balloon or tighten the clamp, venous return would decline and the pressures and volumes of the left ventricle would decline, as shown below.

2. Connecting the end systolic and end-diastolic pressure volume points delineates two measure of ventricular function the ESPVR which is a measure of left ventricular chamber contractility and the EDPVR which is a measure of ventricular filling.

3. The ESPVR is a measure of chamber contractility, which is determined both by its slope and its relative position on the pressure volume plane. For example, one can increase or decrease contractility by administering a positive inotropic agent (e.g. dobutamine) which will shift the ESPVR upward. At any given volume of the ventricle with the higher ESPVR (shown in blue) will generate more pressure than the ventricle with the normal contractility (shown in green) and is therefore considered to be "stronger". Alternatively one can shift the ESPVR downward (shown in red) as occurs with an insult such as a myocardial infarction and the pressure generating capacity of the ventricle will decline. These changes occur without any shift in the  $V_0$ . Alternatively shifts in  $V_0$  also are indicative of changes in contractility.





## D. EDPVR

1. The EDPVR can change for example as the heart grows during childhood or during pathologic situations, such as during the healing from an infarct or during the evolution of a dilated cardiomyopathy.

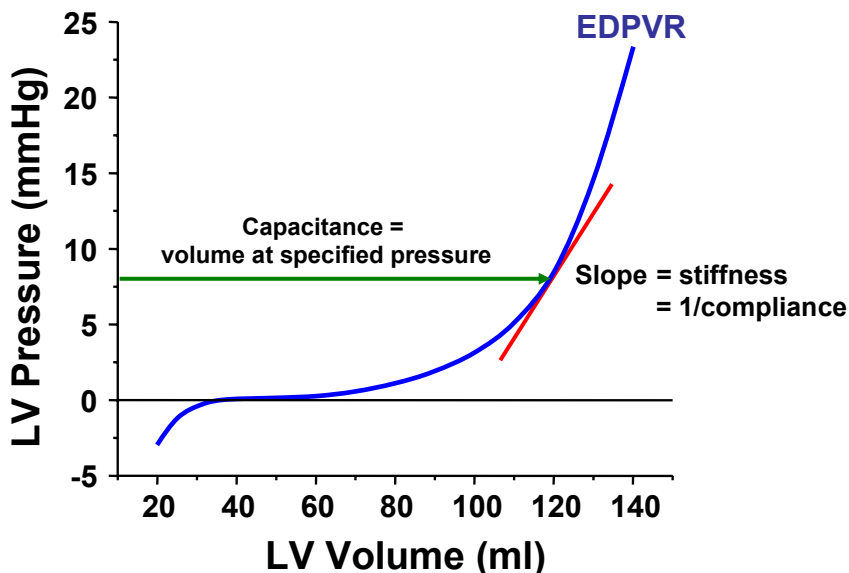
2. Terms used to define changes in the EDPVR are noted below.

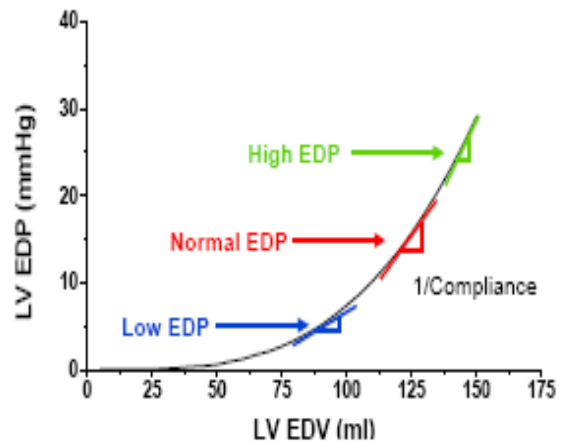
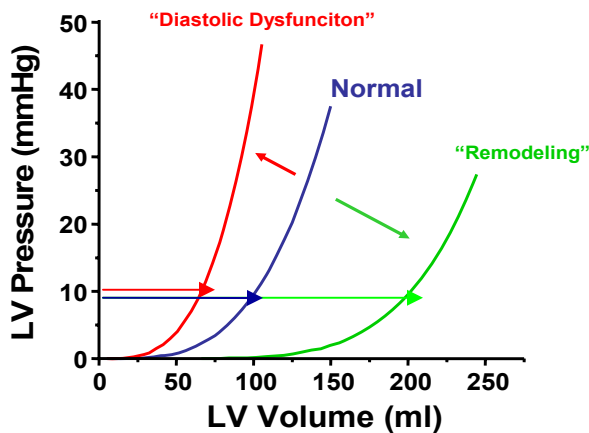
a) *Compliance* is a term which is frequently used in discussions of the end-diastolic ventricular. Technically, *compliance* is the change in volume for a given change in pressure or, expressed in mathematical terms, it is the reciprocal of the derivative of the EDPVR.

b) Since the EDPVR is nonlinear, the compliance varies with volume; compliance is greatest at low volume and smallest at high volumes (see figure below).

c) In the clinical arena, however, *compliance* is used in two different ways. First, it is used to express the idea that the diastolic properties are, in a general way, altered compared to normal; that is, that the EDPVR is either elevated or depressed compared to normal. Second, it is used to express the idea that the heart is working at a point on the EDPVR where its slope is either high or low (this usage is technically more correct).

d) Capacitance is a better term to define shifts in the EDPVR (either to smaller volumes – diastolic dysfunction) or toward larger volumes (remodeling). Capacitance refers to the volume that the ventricle can hold at a given filling pressure.





### E. Arterial properties

1. These can be represented on the PV diagram by looking at a parameter called  $E_a$  (arterial elastance).  $E_a$  is closely related to TPR. Let us start with the definition of TPR:

$$\text{TPR} = [\text{MAP} - \text{CVP}] / \text{CO}$$

where CVP is the central venous pressure and MAP is the mean arterial pressure. Cardiac output (CO) represents the mean flow during the cardiac cycle and can be expressed as:

$$\text{CO} = \text{SV} * \text{HR}$$

where SV is the stroke volume and HR is heart rate. Substituting the second equation into the first we obtain:

$$\text{TPR} = [\text{MAP} - \text{CVP}] / (\text{SV} * \text{HR})$$

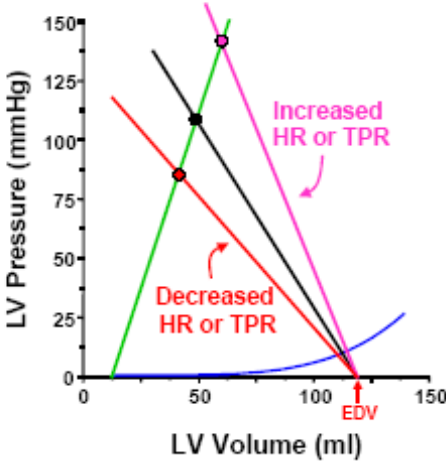
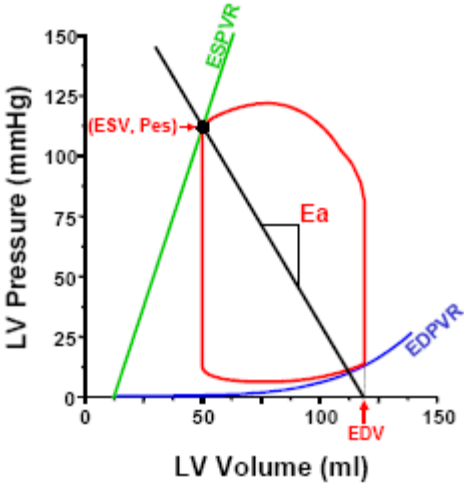
At this point we make two simplifying assumptions. First, we assume that CVP is negligible compared to MAP. This is reasonable under normal conditions, since the CVP is generally around 0-5 mmHg. Second, we will make the assumption that MAP is approximately equal to the end-systolic pressure in the ventricle ( $P_{es}$ ). Making these assumptions, we can rewrite the equation as:

$$\text{TPR} = P_{es} / (\text{SV} * \text{HR})$$

which can be rearranged to:

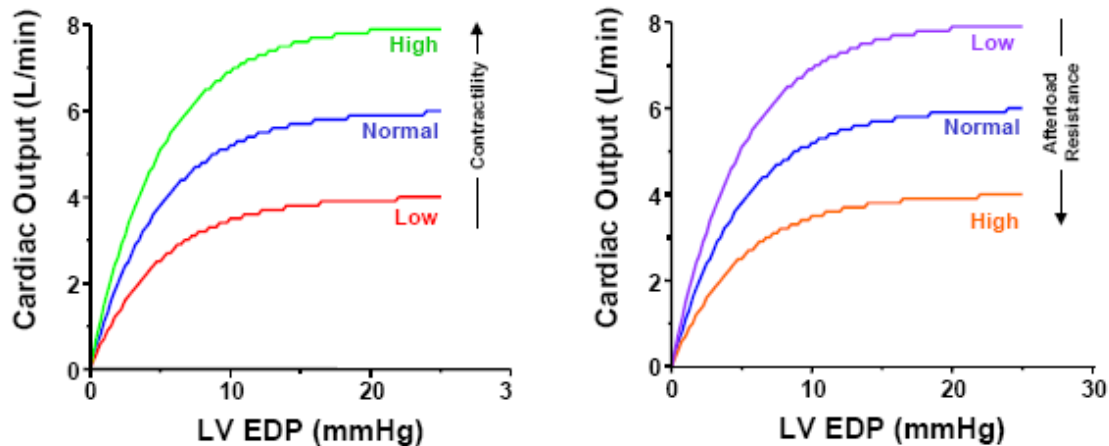
$$\text{TPR} = \text{HR} * P_{es} / \text{SV} .$$

The quantity  $P_{es}/SV$  can be easily ascertained from the pressure volume loop by taking the negative value of the slope of the line connecting the point on the volume-axis equal to the EDV with the end-systolic pressure-volume point.



## VI. Frank Starling Curves

- A. Otto Frank (1899) is credited with the seminal observation that peak ventricular pressure increases as the end-diastolic volume is increased. This observation was made in an isolated frog heart preparation in which ventricular volume could be measured with relative ease. Though of primary importance, the significance may not have been appreciated to the degree it could have been because it was (and remains) difficult to measure ventricular volume in more intact settings (e.g., experimental animals or patients). Thus it was difficult for other investigators to study the relationship between pressure and volume in these more relevant settings.
- B. Around the mid 1910's, Starling and coworkers observed a related phenomenon, which they presented in a manner that was much more useful to physiologists and ultimately to clinicians. They measured the relationship between ventricular filling pressure (related to end-diastolic volume) and cardiac output ( $CO=SV \times HR$ ). They showed that there was a nonlinear relationship between end-diastolic pressure (EDP, also referred to as ventricular filling pressure) and CO as shown below; as filling pressure was increased in the low range there is a marked increase in CO, whereas the slope of this relationship becomes less steep at higher filling pressures.
- C. **The observations of Frank and of Starling form one of the basic concepts of cardiovascular physiology that is referred to as the Frank-Starling Law of the Heart: cardiac performance (its ability to generate pressure or to pump blood) increases as preload is increased.**
- D. However, increases in preload are not without their negative consequences. As pulmonary venous pressure rises there is an increased tendency (Starling Forces) for fluid to leak out of the capillaries and into the interstitial space and alveoli. When this happens, there is impairment of gas exchange across the alveoli and hemoglobin oxygen saturation can be markedly diminished. This phenomenon typically comes into play when pulmonary venous pressure rises above pressures increases above 25-30 mmHg, there can be profound transudation of fluid into the alveoli and pulmonary edema is usually prominent.
- E. Also, factors other than preload are important for determining cardiac performance: ventricular contractility and afterload properties. Both of these factors can influence the Frank-Starling Curves. When ventricular contractile state is increased, CO for a given EDP will increase and when contractile state is depressed, CO will decrease (see below). When arterial resistance is increased, CO will decrease for a given EDP while CO will increase when arterial resistance is decreased (see below). Thus, shifts of the Frank-Starling curve are nonspecific in that they may signify either a change in contractility or a change in afterload. It is for this reason that Starling-Curves are not used as a means of indexing ventricular contractile strength.



## VII. Mechanisms

- A. Since virtually any form of heart disease can lead to heart failure, there can be no single causative mechanism. At the organ and the cellular level, there is likewise no single mechanism that is consistently operative.
- B. It is helpful to employ evolutionary theory in understanding heart failure pathophysiology. In general, cells, organs, and organisms each have evolved adaptive responses to offset hostile environments, thus allowing a survival advantage.
- C. Classically, heart failure begins as an acute injury to the heart, such as an acute myocardial infarction or severe inflammatory myocarditis. Other causes include ischemia, valvular disease, hypertension, inflammation, metabolic derangements, muscular dystrophies, sensitivity and toxic reactions (alcohol, cocaine, chemotherapy), infiltrative disorders (amyloid) or genetic disorders (hypertrophic cardiomyopathy).
- D. The classic pathophysiologic events in the genesis of heart failure are:
  1. Insult/injury/remodeling stimuli  $\Rightarrow$
  2. Neurohormonal activation (RAAS and ANS)  $\Rightarrow$
  3. Cellular/molecular alterations and Hemodynamic alterations (Na retention, volume overload)  $\Rightarrow$
  4. Remodeling  $\Rightarrow$
  5. Morbidity and mortality

E. The heart and its circulatory physiology must somehow “adapt” to this “hostile” new environment. Physiologic adaptations can become pathologic, in some instances enhancing and inducing progression of heart failure. Some of the important adaptations include:

1. **Remodeling** - In response to increased load, whether created by increased pressure or loss of myocytes, hypertrophy occurs and tends to normalize the load per cell.

- a) When the ventricle is called on to deliver an elevated cardiac output for prolonged periods, as in valvular regurgitation, it develops *eccentric hypertrophy*, i.e., cavity dilatation, with an increase in muscle mass so that the ratio between wall thickness and ventricular cavity diameter remains relatively constant early in the process.
- b) With chronic pressure overload, as in valvular aortic stenosis or untreated hypertension, *concentric ventricular hypertrophy* develops; in this condition the ratio between wall thickness and ventricular cavity size increases.
- c) In both eccentric and concentric hypertrophy, wall tension is initially maintained at a normal level and cardiac function may remain stable for many years. However, myocardial function may ultimately deteriorate, leading to HF. Often at this time, the ventricle dilates and the ratio between wall thickness and cavity size declines, leading to increased stress on each unit of myocardium, further dilatation, and a vicious cycle is initiated. Remodeling of the ventricle occurs with a change to a more spherical shape, which increases the hemodynamic stresses on the wall and may cause or intensify mitral regurgitation

2. **Regulation of Body-Fluid Volume-**

- a) The integrity of the arterial circulation, as determined by cardiac output and peripheral arterial resistance, is the primary determinant of renal sodium and water excretion
- b) Specifically, either a primary decrease in cardiac output or arterial vasodilatation (as in the case of high output failure) causes arterial underfilling, which results in the activation of neurohumoral reflexes that stimulate sodium and water retention.
- c) This integrated mechanism explains why plasma volume and blood volume increase in patients with heart failure, whether associated with low or high cardiac output, while their kidneys, which are otherwise normal, continue to retain sodium and water.
- d) The retention of sodium and water may result in pulmonary congestion or peripheral edema and thus cause substantial morbidity and mortality in patients with heart failure.

### 3. The Sympathetic Nervous System

- a) The baroreceptor-mediated increase in sympathetic tone that occurs with ventricular dysfunction has several consequences, including increased myocardial contractility, tachycardia, arterial vasoconstriction and thus increased cardiac afterload, and venoconstriction with increased cardiac preload.
- b) Catecholamines are directly toxic to myocardial cells, an effect mediated through calcium overload, the induction of apoptosis, or both and this can be prevented by chronic use of beta blockers.
- c) Also, by renal mechanisms including renal vasoconstriction, stimulation of the renin–angiotensin–aldosterone system, and direct effects on the proximal convoluted tubule, increased adrenergic activity contributes to the sodium and water retention that occurs in patients with heart failure.
- d) In the past,  $\beta$ -adrenergic blockade was thought to be contraindicated in patients with heart failure. However, if patients can tolerate short-term  $\beta$ -adrenergic blockade, ventricular function subsequently improves.

### 4. The Renin–Angiotensin–Aldosterone System

- a) The activity of the renin–angiotensin–aldosterone (RAAS) system is also increased in most patients with heart failure and the degree of increase in plasma renin activity provides a prognostic index in these patients.
- b) Not only is the activity of the RAAS increased in heart failure, but also the action of aldosterone is more persistent than in normal subjects.
- c) Sodium delivery to the distal tubule and collecting duct tends to decrease in heart failure in part because  $\alpha$ -adrenergic stimulation and angiotensin II increase sodium transport in the proximal tubule, leaving less sodium available for reabsorption in the distal tubule.
- d) This decreased sodium delivery to the collecting duct results in ongoing activation of the RAAS and the persistent aldosterone-mediated sodium retention.

### 5. Nonosmotic Release of Arginine Vasopressin

- a) Water retention in excess of sodium retention may occur in patients with heart failure and lead to hyponatremia. Hyponatremia is a very ominous prognostic indicator in patients with heart failure.
- b) Hyponatremia may be partly due to the increased water intake caused by the increased thirst associated with heart failure. However, increased water intake alone rarely causes

hyponatremia, because the normal renal capacity to excrete solute-free water is substantial (about 10 to 15 liters a day).

- c) In patients with heart failure there are persistently high plasma concentrations of arginine vasopressin which causes an antidiuresis.
- d) Activation of vasopressin ( $V_1$ ) receptors in vascular smooth muscle by arginine vasopressin may contribute to cardiac dysfunction in patients with severe heart failure in that AVP raises blood pressure and increases afterload.

#### 6. Natriuretic Peptides

- a) Atrial natriuretic peptide is a 28-amino-acid peptide that is normally synthesized in the atria and to a lesser extent in the ventricles and is released into the circulation during atrial distention. Brain or B-type natriuretic peptide is a 32-amino-acid peptide that is synthesized primarily in the ventricles, and its release into the circulation is also increased in patients with heart failure
- b) In patients with heart failure, plasma atrial natriuretic peptide concentrations rise as atrial pressures increase.
- c) Because plasma concentrations of brain natriuretic peptide are increased in patients with early heart failure or left ventricular dysfunction, plasma brain natriuretic peptide may be a sensitive diagnostic marker of heart failure.
- d) Atrial natriuretic peptide exerts its effects on the kidney primarily by increasing sodium excretion. Atrial natriuretic peptide also inhibits the secretion of renin and aldosterone.
- e) Finally, the infusion of synthetic brain natriuretic peptide in patients with heart failure decreases pulmonary-capillary wedge pressure, diminishes systemic vascular resistance, and increases cardiac output.

#### 7. Endothelial Hormones/Cytokines

- a) Prostacyclin and prostaglandin E are vasodilating hormones produced from arachidonic acid in many cells. These vasodilatory prostaglandins may thus counterbalance the neurohormone-induced renal vasoconstriction that occurs in heart failure.
- b) Heart failure patients who take aspirin or NSAIDs are because of their inhibitory effects on prostacyclin and prostaglandin production, they can result in renal vasoconstriction and decreased urine output as well as acute renal failure.
- c) Nitric oxide is an even more potent vasodilator than prostacyclin and prostaglandin E.
- d) Endothelin is one of the most potent vasoconstrictors, and plasma endothelin concentrations are increased in some patients with heart failure.



- e) The plasma concentrations of some cytokines, such as tumor necrosis factor, are increased in patients with heart failure.

## VIII. Classifications

### A. Right versus Left

- This classification relates to whether the principal abnormality is initially afflicting the left ventricle or the right ventricle.
- Patients in whom the left ventricle is mechanically overloaded (e.g., excessive afterload in the case of aortic stenosis or excessive preload in the case of excessive intravenous fluids) or weakened (e.g., decreased contractility in the case post myocardial infarction) develop dyspnea and orthopnea as a result of pulmonary congestion, a condition referred to as left sided heart failure.
- In contrast, when the underlying abnormality affects the right ventricle primarily (e.g., pulmonic stenosis or pulmonary hypertension, right ventricular infarction), symptoms resulting from pulmonary congestion such as orthopnea and paroxysmal nocturnal dyspnea are less common, and edema, congestive hepatomegaly, and systemic venous distention, i.e., clinical manifestations of right sided heart failure, are more prominent.
- Most patients with long standing heart failure have evidence of biventricular failure. For example, patients with long standing aortic valve disease or systemic hypertension may have ankle edema, congestive hepatomegaly, and systemic venous distention late in the course of their disease, even though the abnormal hemodynamic burden initially was placed on the left ventricle.

### B. Dilated versus hypertrophic

- This classification relates to whether structural abnormality of the left ventricle is either dilated (enlarged) or hypertrophic (thick walled and non-dilated).
- Typically, pressure overload as would occur in the setting of an increased afterload (e.g. hypertension or aortic stenosis) will result in an increased systolic stress to the ventricle.
- To compensate for this increased systolic wall stress and normalize it, the ventricle will hypertrophy by adding new myofibrils in parallel resulting in a concentrically hypertrophied morphology. This is characterized by an increased wall thickness with either little or no chamber dilation.
- In the case of chronic volume overload, which can occur classically in the setting of aortic insufficiency, mitral regurgitation or left to right

shunts, the augmented preload results in increased diastolic wall stress.

- To compensate for the increased diastolic wall stress, new sarcomeres are added in series resulting in chamber enlargement and an eccentrically hypertrophied ventricle. This is characterized by increased chamber size with a concomitant increase in mass but relatively little wall thickening.

### **C. Systolic versus diastolic**

- This classification relates to whether the principal abnormality is the inability to contract normally and expel sufficient blood (systolic failure) or to relax and fill normally (diastolic failure).
- The major clinical manifestations of systolic failure relate to an inadequate cardiac output with weakness, fatigue, reduced exercise tolerance and other symptoms of hypoperfusion, while in diastolic failure they relate principally to an elevation of filling pressures. In many patients, particularly those who have both ventricular hypertrophy and dilatation, abnormalities of contraction and relaxation coexist.
- Diastolic heart failure may be caused by increased resistance to ventricular inflow and reduced ventricular diastolic capacity (constrictive pericarditis and restrictive, hypertensive, and hypertrophic cardiomyopathy), impaired ventricular relaxation (acute myocardial ischemia, hypertrophic cardiomyopathy), and myocardial fibrosis and infiltration (dilated, chronic ischemic, and restrictive cardiomyopathy).

### **D. *Compensated versus decompensated***

- This profile refers to the clinical presentation of the patient with decompensated patients demonstrating worsening renal function, persistent neurohormonal activation, and progressive deterioration in myocardial function which typically result in hospitalization.
- Decompensation can also occur without a fundamental worsening of underlying cardiac structure or function. Failure to adhere to prescribed medications related to inadequate financial resources, poor compliance, and lack of education or an inadequate medical regimen may lead to hospitalization without a worsening of underlying circulatory function.
- Compensated patients on the other hand are patients who are typically not hospitalized who remain stable or are even improving with regards to functional capacity or cardiac function (e.g. ejection fraction).
- When a patient presents in a decompensated state, clinicians typically utilize the physical examination and history to divide the

decompensated into one of four profiles that guides treatment and provides prognostic information.

- These profiles were based on the presence or absence of congestion (pulmonary capillary wedge pressure [PCWP]  $\geq 18$  mm Hg) and adequacy of perfusion (cardiac index [CI] = 2.2 l/min/m<sup>2</sup>).
  - Profile I represented no congestion or hypoperfusion;
  - Profile II, congestion without hypoperfusion;
  - Profile III, hypoperfusion without congestion; and
  - Profile IV, both congestion and hypoperfusion.
- Evidence for congestion on physical examination includes: orthopnea, elevated JVP, increasing S3, loud pulmonic component of the second heart sound, edema, ascites, rales (uncommon in chronic heart failure), hepatjugular reflux and valsalva square root sign.
- Evidence for low perfusion on physical exam includes: narrow pulse pressure, pulsus alternans, cool extremities, obtundation, hypotension in response to medications, low serum sodium and worsening renal function.

#### **E. High versus Low Output**

- This classification relates to whether the principal abnormality is a low or high cardiac output. Cardiac output is determined by multiplying the stroke volume (end diastolic volume minus end systolic volume) times the heart rate.
- Low output heart failure occurs secondary to ischemic heart disease, dilated cardiomyopathy, some forms of valvular heart disease and pericardial disease and is clinically identified at the bedside by a low blood pressure, narrow pulse pressure (the difference between systolic and diastolic blood pressure), cool extremities and evidence of end organ hypoperfusion (prerenal azotemia).
- High output heart failure occurs in hyperthyroidism, anemia, pregnancy, arteriovenous fistulas, beriberi, and Paget's disease. It is recognized at the bedside by a normal to high blood pressure with a widened pulse pressure and warm extremities.
- In clinical practice, however, low output and high output heart failure cannot always be readily distinguished.

#### **F. Forward versus Backward**

- The concept of backward heart failure contends that in heart failure, one or the other ventricle fails to discharge its contents or fails to fill normally. As a consequence, the pressures in the atrium and venous system behind the failing ventricle rise, and retention of sodium and water occurs as a consequence of the elevation of systemic venous and capillary pressures and the resultant transudation of fluids into the interstitial space.

- The concept of backward failure has fallen out of favor in that physiologists have recognized that the heart does not determine its filling pressure but rather these parameters are determined by the needs of the body and result from the activation of the neurohormonal cascade as well as salt and water retention.
- In contrast, the proponents of the forward heart failure hypothesis maintain that the clinical manifestations of heart failure result directly from an inadequate discharge of blood into the arterial system.
- According to this concept, salt and water retention is a consequence of diminished renal perfusion and excessive proximal tubular sodium reabsorption and of excessive distal tubular reabsorption through activation of the renin-angiotensin-aldosterone system.

### **G. Acute versus Chronic**

- The prototype of acute heart failure is the patient who is entirely well but who suddenly develops a large myocardial infarction or rupture of a cardiac valve.
- Chronic heart failure is typically observed in patients with dilated cardiomyopathy or multivalvular heart disease that develops or progresses slowly over months to years.
- Acute heart failure is usually largely systolic and the sudden reduction in cardiac output often results in systemic hypotension without peripheral edema.
- In chronic heart failure, arterial pressure tends to be well maintained until very late in the course, but there is often accumulation of peripheral edema.

### **H. Cardiac versus non-Cardiac**

- This classification relates to whether the primary or initial insult or remodeling stimuli is cardiac (e.g. valvular dysfunction, myocardial infarction) or whether it resides outside of the heart (hypertension, anemia, renal dysfunction, arteriovenous fistula).
- This classification is relatively new but gaining greater acceptance as we come to appreciate the complex nature of the heart failure state and the impact that extra-cardiac conditions play in the progression of disease.

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## IX. NYHA Class and AHA/ACC Stage

A. New York Heart Association (NYHA) functional classification system relates symptoms to everyday activities and the patient's quality of life. Patient can move from one class to another based on symptom resolution or progression.

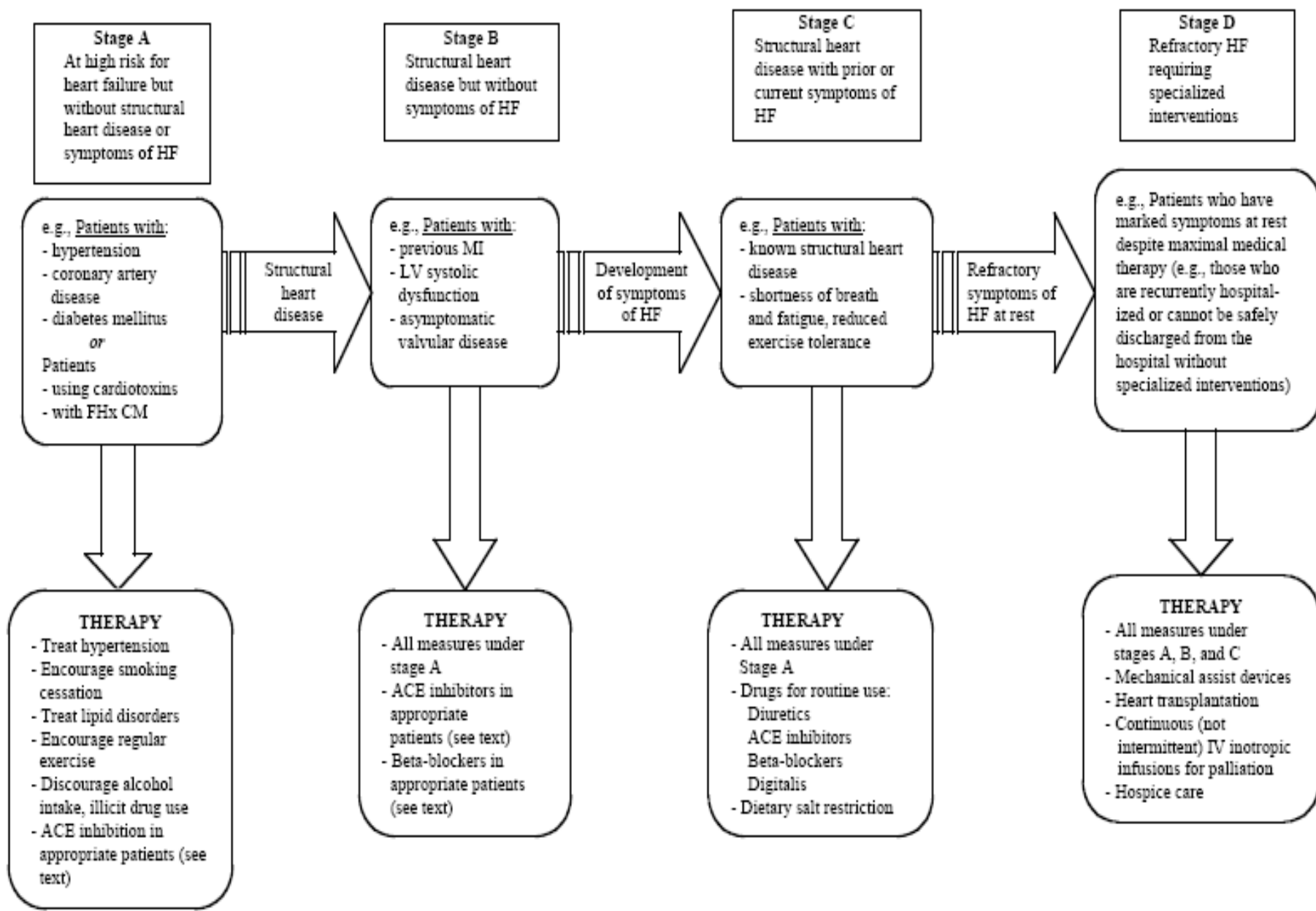
<b>Class</b>	<b>Patient Symptoms</b>
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased

B. Stages of Heart Failure - The new system is different from NYHA classes in that once you are in a stage you stay there. It is like cancer in that even though treatment may make cancer disappear, the patient is still classified as a cancer patient. Patients who develop into stage C always remain in stage C even if they get better and their symptoms disappear. Their functional class would improve to class one but they would remain in stage C anyway.

1. **Stage A:** Patient is at high risk for developing HF but has no structural disorder of the heart. Examples: patients at high risk for developing HF because of high blood pressure, CAD, diabetes, history of drug or alcohol abuse, history of rheumatic fever, family history of cardiomyopathy, etc.
2. **Stage B:** Patient has a structural disorder of the heart but has never developed HF symptoms. Examples: patients with structural heart disease like left heart enlargement, heart fibrosis, valve disease, previous heart attack.
3. **Stage C:** Patient with past or current CHF symptoms *and* underlying structural heart disease.
4. **Stage D:** Patient with end-stage disease who is frequently hospitalized for CHF or who requires special treatments such as LVAD, artificial heart, inotropic infusions, heart transplant or hospice care

## X. Treatment

- A. There are four major goals of treatment:
1. Identification and correction of underlying condition causing heart failure.
  2. Elimination of acute precipitating cause of symptoms.
  3. Modulation of neurohormonal response to prevent progression of disease.
  4. Improve long term survival



## Drugs to Treat Heart Failure

Drug	Initial Dose	Maximum Dose
Loop diuretics*		
Bumetanide	0.5 to 1.0 mg once or twice daily	Titrate to achieve dry weight (up to 10 mg daily)
Furosemide	20 to 40 mg once or twice daily	Titrate to achieve dry weight (up to 400 mg daily)
Torsemide	10 to 20 mg once or twice daily	Titrate to achieve dry weight (up to 200 mg daily)
ACE inhibitors		
Captopril	6.25 mg 3 times daily	50 mg 3 times daily
Enalapril	2.5 mg twice daily	10 to 20 mg twice daily
Fosinopril	5 to 10 mg once daily	40 mg once daily
Lisinopril	2.5 to 5.0 mg once daily	20 to 40 mg once daily
Quinapril	10 mg twice daily	40 mg twice daily
Ramipril	1.25 to 2.5 mg once daily	10 mg once daily
Beta-receptor blockers		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily; 50 mg twice daily for patients more than 85 kg
Metoprolol tartrate	6.25 mg twice daily	75 mg twice daily
Metoprolol succinate extended release+	12.5 to 25 mg daily	200 mg once daily
Digitalis glycosides		
Digoxin	0.125 to 0.25 mg once daily	0.125 to 0.25 mg once daily