MECHANICAL PROPERTIES OF THE HEART

I. INTRODUCTION

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 body tissues of the body under widely varied conditions. The goal of this section in the course is to provide a detailed understanding of the heart as a muscular pump and of the interaction between the heart and the vasculature. The concepts of contractility, preload and afterload are paramount to this understanding and will be the focus and repeating theme throughout the text. A sound understanding of cardiac physiology begins with basic understanding of cardiac anatomy and of the physiology of muscular contraction.

II. ANATOMY OF THE HEART

The normal adult human heart is divided into four distinct muscular chambers, two atria and two ventricles, which are arranged to form functionally separate left and right heart pumps. The left heart, composed of the left atrium and left ventricle, pumps blood from the pulmonary veins to the aorta. The human left ventricle is an axisymmetric, truncated ellipsoid with \( \sim 1 \) cm wall thickness. This structure is constructed from billions of cardiac muscle cells (myocytes) connected end-to-end at their gap junctions to form a network of branching muscle fibers which wrap around the chamber in a highly organized manner. The right heart, composed of right atrium and right ventricle, pumps blood from the vena cavae to the pulmonary arteries. The right ventricle is a roughly crescent shaped structure formed by a 3-to-5 millimeter thick sheet of myocardial fibers (the right ventricular free wall) which interdigititate at the anterior and posterior insertion points with the muscle fibers of the outer layer of the left ventricle. The right and left ventricular chambers share a common wall, the interventricular septum, which divide the chambers. Both right and left atria are thin walled muscular structures which receive blood from low pressure venous systems. Valves (the tricuspid valve in the right heart and the mitral valve in the left heart) separate each atrium from its associated ventricle and are arranged in a manner to ensure one-way flow through the pump by prohibiting backward flow during the forceful contraction of the ventricles. These valves attach to fibrous rings which encircle each valve annulus; the central regions of these valves attach via chordae tendinae to papillary muscles which emerge from the ventricular walls. The predominant factor that determines valve opening and closure is the pressure gradient between the atrium and the ventricle. However, the papillary muscles contract synchronously with the other heart muscles and help maintain proper valve leaflet position, thus helping prevent regurgitant (backward) flow during contraction. A second set of valves, the aortic valve and the pulmonary valve, separate each ventricle from its accompanying arterial connection and ensure unidirectional flow by preventing blood from flowing from the artery back into the ventricle. Pressure gradients across these valves is the major determinant of whether they are open or closed.
The Circulatory Loop.
The cardiovascular system can be thought of as a simple loop comprised of two main fluid pumps and a network of vascular tubes. The loop can be divided into the pulmonary system which contains the right ventricle, the pulmonary arteries, the pulmonary capillaries, and pulmonary veins, and the systemic system which contains the left ventricle, the systemic arteries, the systemic capillaries, and the systemic veins. Each pump provides blood with energy to circulate through its respective vascular network. While these pumps are pulsatile (i.e. blood is delivered into the circulatory system intermittently with each heart beat), the flow of blood in the vasculature becomes more and more steady as it approaches capillary networks.

If all of the blood followed this simple pathway, then the amount of blood ejected by the RV must equal the amount of blood ejected by the LV. Consider that if the cardiac output of the RV exceeded that of the LV, then more blood would be introduced into the pulmonary vasculature than was being removed. (It also would mean that more would be removed from the systemic circulation than was being introduced.) This type of discrepancy, no matter how small, cannot be sustained. Therefore, many factors come into play that ensure appropriate "matching" of right and left ventricular outputs. These factors will be discussed in the section, Determinants of Cardiac Output.
III. CARDIAC MUSCLE PHYSIOLOGY

IIIa. Basic Muscle Anatomy.
The ability of the ventricles to generate blood flow and pressure derives from the ability of individual myocytes to shorten and generate force. Myocytes are tubular structures. During contraction, the muscles shorten and generate force along their long axis. Force production and shortening of cardiac muscle are created by regulated interactions between contractile proteins which are assembled in an ordered and repeating structure called the sarcomere. The lateral boundaries of each sarcomere are defined on both sides by a band of structural proteins into which the so called thin filaments attach. The thick filaments are centered between the Z-disc and are held in register by a strand of proteins at the central M-line. Alternating light and dark bands seen in cardiac muscle under light microscopy result from the alignment of the thick and thin filaments giving cardiac muscle its typical striated appearance.

The thin filaments are composed of linearly arranged globular actin molecules. The thick filaments are composed of bundles of myosin strands with each strand having a tail, a hinge and a head region. The tail regions bind to each other in the central portion of the filament and the strands are aligned along a single axis. The head regions extend out from the thick filament, creating a central bare zone and head-rich zones on both ends of the thick filament. Each actin globule has a binding site for the myosin head. The hinge region allows the myosin head to protrude from the thick filament and make contact with the actin filament. In addition to the actin binding site, the myosin head contains an enzymatic site for cleaving the terminal phosphate molecule of ATP (myosin ATPase) which provides the energy used for repeatedly generating force. Force is produced when myosin binds to actin and, with the hydrolysis of ATP, the head rotates and extends the hinge region. Force generated by a single sarcomere is proportional to the number of actin-myosin bonds and the free energy of ATP hydrolysis. The state of actin-myosin binding following ATP hydrolysis is referred to as the rigor state, because in the absence of additional ATP the actin-myosin bond will persist and maintain high muscle tension. Relaxation requires uncoupling of the actin-myosin bond which occurs when a new ATP molecule binds to the ATPase site on the myosin head.

Actin-myosin interactions are regulated by tropinin and tropomyosin. Tropomyosin is a thin protein strand that sits on the actin strand and, under normal resting conditions, covers the actin-myosin binding site thus inhibiting their interaction and preventing force production. Tropinin is a macromolecule with three subunits: tropominin T bind the tropomin complex to tropomyosin, tropomin C has binding sites for calcium and
troponin I binds to actin. When intracellular calcium concentrations are low, the troponin complex pulls the tropomyosin from its preferred resting state to block the actin-myosin binding sites. When calcium concentrations rises and calcium binds to troponin C, troponin I releases from actin allowing the tropomyosin molecule to be pulled away from the actin-myosin binding site. This eliminates inhibition of actin-myosin interaction and allows force to be produced. This arrangement of proteins provides a means by which variations in intracellular calcium can readily modify instantaneous force production. Calcium rises and falls during each beat and this underlies the cyclic rise and fall of muscle force. The greater the peak calcium the greater the number of potential actin-myosin bonds, the greater the amount of force production.

IIIb. Excitation-contraction coupling.
The sequence of events that lead to myocardial contraction is triggered by electrical depolarization of the cell. Cell depolarization increases the probability of transmembrane calcium channel openings and thus causes calcium influx into the cell into a small cleft next to the sarcoplasmic reticular (SR) terminal cisterne. This rise of local calcium concentration causes release of a larger pool of calcium stored in the SR through calcium release channels (also known as ryanodine receptors). This method whereby local calcium regulates SR calcium dumping is referred to as calcium induced calcium release. The calcium released from the SR diffuses through the myofilament lattice and is available for binding to troponin which dysinhibits actin and myosin interactions and results in force production.

Calcium release is rapid and does not require energy because of the large calcium concentration gradient between the SR and the cytosol during diastole. In contrast, removal of calcium from the cytosol and from troponin occurs up a concentration gradient and is an energy requiring process. Calcium sequestration is primarily accomplished by pumps on the SR membrane that consume ATP (SR Ca\(^{2+}\) ATPase pumps); these pumps are located in the central portions of the SR and are in close proximity to the myofilaments. SR Ca\(^{2+}\) ATPase activity is regulated by the phosphorylation status of another SR protein, phospholamban. In order to maintain calcium homeostasis, an amount of calcium equal to that which entered the cell through the sarcolemmal calcium channels must also exit with each beat. This is accomplished primarily by the sarcolemmal sodium-calcium exchanger, a transmembrane protein which translocates calcium across the membrane against its concentration gradient in exchange for sodium ions moved in the opposite direction. Sodium homeostasis is in turn regulated largely by the ATP requiring sodium-potassium pump on the sarcolemma.

IIIc. Force-Length Relations.
In addition to calcium, cardiac muscle length exerts a major influence on force production. Since each muscle is composed of a linear array of sarcomere bundles from one end of the cell to the other, muscle length is directly proportional to average sarcomere length. Changes in sarcomere length alter the geometric relationship between thick and thin filaments. For myofilaments in general, optimal force is achieved when sarcomere length is about 2.2-2.3 microns, the length which provides optimal overlap of thick and thin filaments. As sarcomere length is decreased below about 2.0 microns, the
tips of apposing thin filaments hit each other, the thick filaments approach the Z-lines and the distance between thick and thin filaments increases. Each of these factors contributes to a reduction in force with decreasing sarcomere length. In skeletal muscle (SM), sarcomeres can be stretched beyond 2.3 microns and this causes a decrease in force because fewer myosin heads can reach and bind with actin; skeletal muscle can typically operate in this so called descending limb of the sarcomere force-length relationship. In cardiac muscle (CM), however, constraints imposed by the sarcolemma prevent myocardial sarcomeres from being stretched beyond ~2.3 microns, even under conditions of severe heart failure when very high stretching pressures are imposed on the heart.

Force-length relationships are conveniently used to characterize systolic and diastolic contractile properties of cardiac muscle. These are measured by holding the ends of an isolated muscle strip and measuring the force developed at different muscle lengths while preventing muscles from shortening (isometric contractions). As the muscle is stretched from its slack length (the length at which no force is generated), both the resting (end-diastolic [green]) force and the peak (end-systolic [red]) force increase. The end-diastolic 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. End-systolic force increases with increasing muscle length to a much greater degree than does end-diastolic force. The difference in force at any given muscle length between the end-diastolic and end-systolic relations (arrows in the Figure) 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. 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 (red-dashed line), indicating that at any given length, the muscle can generate more force. Inotropic agents typically do not affect the end-diastolic force-length relationship. In view of the prominent effect of length on muscle force generation, it is most appropriate that intrinsic strength of cardiac muscle,
commonly referred to as muscle contractility, be indexed by the end-systolic force-length relationship.

**IIIId. From Muscle to Chamber.**
Just as end-systolic and end-diastolic force-length relationships can be used to characterize systolic and diastolic properties of cardiac muscle fibers, so too can end-systolic and end-diastolic pressure-volume relationships (ESPVR [red] and EDPVR [green], respectively) be used to characterize peak systolic and end diastolic properties of the ventricular chambers. Analogous to muscle, the EDPVR is nonlinear, with a shallow incline at low pressures and a steep rise at pressures in excess of 20 mmHg. However, the ESPVR is typically linear and, as for muscle, ventricular pressure-generating capability is increased as ventricular volume is increased. Also analogous to muscle, the ESPVR is used to index ventricular chamber contractility. Because the ESPVR is roughly linear, it can be characterized by a slope and volume axis intercept. The slope of the line indicates the degree of myocardial stiffness or elastance and is called Ees (end-systolic elastance). The volume axis intercept (analogous to slack length of the muscle) is referred to as Vo. When muscle contractility is increased (for example by administration of an inotropic agent), the slope of the ESPVR (Ees) increases [red-dashed line], whereas there is little change in Vo (discussed further below).

**IV. THE CARDIAC CYCLE AND THE PRESSURE-VOLUME LOOP**

**IVa. Pressures and Volumes as a Function of Time During the Cardiac Cycle.**
The heart beats roughly once every second and repeatedly cycles through a sequence of hemodynamic events referred to as the cardiac cycle. The cardiac cycle is broadly divided into two parts: systole and diastole. Systole is the period of time during which the muscle transforms from its totally relaxed state (low intracellular calcium with crossbridges uncoupled) to the instant of maximal mechanical activation (high intracellular calcium and time of maximal crossbridge coupling); this period of time includes the electrical events responsible for initiating the contraction. Diastole is the period of time during which the muscle relaxes from the end-systolic (maximally activated) state back towards its resting state. Systole is considered to start at the onset of electrical activation of the myocardium; systole ends and diastole begins as the activation process of the myofilaments passes through a maximum.
The mechanical events occurring during the cardiac cycle consist of changes in pressure in the ventricle that cause blood to move in and out of the ventricle. Thus, we can characterize the cardiac cycle by tracking changes in pressures and volumes in the ventricle as shown in the Figure, where ventricular volume (LVV), ventricular pressure (LVP), atrial pressure (LAP) and aortic pressure (AoP) are plotted as a function of time.

Shortly prior to the onset of systole (1), LVP and LVV are relatively invariant and AoP is gradually declining. During this time the heart is in its relaxed (diastolic) state; AoP falls as the blood ejected into the arterial system on the previous beat is gradually pushed from the large arteries to the capillary bed, being propelled by the energy stored in the elastic wall of the arteries. At the onset of systole (2), contraction begins and pressure rises inside the chamber. Early after contraction begins, LVP rises to become greater than left atrial pressure and the mitral valve closes. Since LVP is less than AoP, the aortic valve is also closed. Since both valves are closed, no blood can enter or leave the ventricle during this time, and therefore the ventricle is contracting isovolumically (at a constant volume). This period is called isovolumic contraction. Eventually, LVP reaches and slightly exceeds AoP, the aortic valve opens (3) and blood is ejected from the ventricle into the aorta and LVV decreases. The shapes of the aortic pressure wave and LVV waves during this ejection phase are determined by the complex interaction between the ongoing contraction process of the cardiac muscles and the properties of the arterial system and will be discussed further below. As cardiac muscle contraction reaches its maximal effort, ejection slows and ultimately, as the muscles begin to relax, LVP falls below AoP and the aortic valve closes (4). At this point, ejection has ended and the ventricle is at its lowest volume. The relaxation process continues as indicated by the continued decline of LVP, but LVV is constant at its low level because, once again, both mitral and aortic valves are closed. This phase is called isovolumic relaxation. Eventually, LVP falls below the pressure existing in the left atrium and the mitral valve opens (5). Blood flows from the LA into the LV as indicated by the rise of LVV; also note the slight rise in LVP as filling proceeds. This phase is called filling. In general terms, systole includes isovolumic contraction and ejection; diastole includes isovolumic relaxation and filling.
IVb. Echocardiographic images of the cardiac cycle.
The following images are taken from a transesophageal echocardiographic examination and will demonstrate the phases of the cardiac cycle. Some of the terms in the accompanying description may be unfamiliar to you at this point; however, they will be explained subsequently in this section and in the section on electrical properties of the heart.

The endocardium (inner boundary) of the LV chamber is outlined in red. The epicardium (outer boundary) of the LV chamber is outlined in orange. Left atrium is outlined in blue. Note the proximity of the Mitral Valve to the Aortic Valve.

- Corresponds with QRS complex on ECG
- Rising left ventricular pressure (LVP) closes MV
- LVP still less than pressure in Aorta therefore AV remains closed
- Since both valves are closed, there is no change in chamber volume (hence “isovolumic”)
- This portion of the cycle is brief
- Rate of LVP rise (dP/dt) is a measure of Contractility
- LVP is much higher than LA pressure (LAP)
- MV remains closed
- LVP now exceeds Aortic Pressure
- AV is open
- Pressure gradient between LV and Aorta causes blood to move out of chamber
- As blood leaves, chamber gets smaller
- The amount of blood ejected depends on Afterload, Contractility, Preload

- Corresponds to the T-wave on ECG
- Active process of relaxation
- LVP rapidly declines
- LVP lower than Aortic pressure--AV closed
- LVP still higher than LAP--MV closed
- Since both valves are closed, there is no change in chamber volume
- This portion of the cycle is brief
- Rate of LVP decay is a measure of active relaxation

- LVP quickly drops lower than LA pressure
- Rapid establishment of pressure gradient between LA and LV
- MV is open, blood rushes from LA to LV
- The majority of LV filling occurs now

- The movement of blood from LA to LV quickly abolishes pressure gradient
- Flow across MV is greatly diminished (hence the term Diaastasis)
IVc. Ventricular Pressure-Volume Loops.

Whereas the four phases of the cardiac cycle are clearly illustrated on the plots of LVV, LVP and AoP as a function of time, it turns out that there are many advantages (which will soon become clear) to displaying the cardiac cycle by plotting LVP as a function of LVV on a "pressure-volume diagram". This is accomplished simply by plotting the simultaneously measured LVV and LVP on appropriately scaled axes; the resulting pressure-volume diagram corresponding to the curves in the above Figure is shown in this Figure, with volume on the x-axis and pressure on the y-axis. As shown, the plot of pressure versus volume for one cardiac cycle forms a closed loop. This loop is called the pressure-volume loop (abbreviated PV loop). As time proceeds, the PV points go around the loop in a counter clockwise direction. The basic events occurring during the cardiac cycle reviewed above can be identified on the PV loop. The point of maximal volume and minimal pressure (i.e., the bottom right corner of the loop) corresponds with the onset of systole. During the first part of the cycle, pressure rises but volume stays the same (isovolumic contraction). Once LVP rises above AoP, the aortic valve opens, ejection begins and volume decreases. After the ventricle reaches its maximum activated state (upper left corner of PV loop), LVP falls below AoP, the aortic valve closes and iso-volumic relaxation commences. Finally, filling begins with mitral valve opening (bottom left corner). Filling continues until LVP exceeds atrial pressure and the mitral valve closes.
IVd. Physiologic measurements retrievable from the pressure-volume loop.

The ventricular pressure-volume loop displays the instantaneous relationship between intraventricular pressure and volume throughout the cardiac cycle. It turns out that with this representation it is easy to ascertain values of several parameters and variables of physiologic importance.

Consider first the volume axis. The maximum volume of the cardiac cycle can readily be determined. This volume is called the end-diastolic volume (EDV) because this is the ventricular volume at the end of a cardiac cycle. The heart attains its minimum volume at the end of the ejection phase and is termed the end-systolic volume (ESV). The difference between EDV and ESV represents the amount of blood ejected during the cardiac cycle and is called the stroke volume (SV).

Now consider the pressure axis. Near the top right side of the loop we can identify the point at which the ventricle begins to eject (i.e., the point at which the aortic valve opens and volume starts to decrease). This is the point at which ventricular pressure just exceeds aortic pressure and is therefore the aortic pressure at the onset of ejection; this also corresponds with the point of minimum aortic pressure during the cardiac cycle and is called the diastolic blood pressure (DBP). During the ejection phase, aortic and ventricular pressures are essentially equal. Therefore, the point of greatest pressure on the loop also represents the greatest pressure in the aorta, and this is called the systolic blood pressure (SBP). One additional pressure, the end-systolic pressure (Pes) is identified as the pressure of the left upper corner of the loop; the significance of this pressure will be discussed in detail below. Moving to the bottom of the loop, we can reason that the pressure of the left lower corner (the point at which the mitral valve opens and filling begins) is roughly equal to the pressure existing in the left atrium (LAP) at that instant in time (recall that atrial pressure is not a constant, but varies with atrial contraction and instantaneous atrial volume). The pressure of the point at the bottom right corner of the loop is the pressure in the ventricle at the end of the cardiac cycle and is called the end-diastolic pressure (EDP).

V. PRESSURE-VOLUME RELATIONSHIPS

We have reviewed how cardiac muscles contract and relax with each cardiac cycle. With the ventricular chamber composed of billions of cardiac muscle cells contracting nearly synchronously, this causes the chamber wall to stiffen (reaching a maximal stiffness at the end of systole) and become flaccid during the relaxation phase (reaching its minimal
stiffness at end-diastole). The mechanical properties of the ventricle are therefore time-varying and they vary in a cyclical manner with a time period defined by the cardiac cycle. We will now explore one way to represent the time-varying mechanical properties of the heart using the pressure-volume diagram. We will start with a consideration of ventricular properties at the extreme states of maximum and minimum stiffness -- end systole and end diastole -- and then explore the mechanical properties throughout the cardiac cycle.

**Va. End-Diastolic Pressure-Volume Relationship (EDPVR)**

Let us first consider the properties of the ventricle at end-diastole. Imagine the ventricle frozen in time in a state of complete relaxation. The properties of this ventricle with weak, relaxed muscles can be thought of as being similar to those of a floppy balloon. What happens to the pressure inside a floppy balloon when its volume is varied? With no volume inside the balloon, there is no pressure. At first, as the balloon is inflated volume will increase with essentially no change in pressure until a certain point is reached. The point at which pressure starts to rise is referred to as the unstressed volume and is designated Vo. At volumes above this point, pressure rises gradually until a second critical volume is reached when it becomes increasingly difficult to inflate the balloon further. At this point, pressure can increase dramatically with only very small volume increments. This curve is called the end-diastolic pressure-volume relationship (EDPVR).

Under normal conditions, the heart never exists in a frozen state as described above. However, during each contraction there is a period of time during which the mechanical properties of the heart pass through the state described by the EDPVR. Since the EDPVR provides the pressure-volume relation with the heart in its most relaxed state, the EDPVR provides a boundary on which the PV loop must fall at the end of the cardiac cycle.

Under certain circumstances, the EDPVR may change. Physiologically, the EDPVR changes as the heart grows during childhood. Most other changes in the EDPVR accompany pathologic situations; examples include the changes that occur with hypertrophy, the healing of an infarct, and the evolution of a dilated cardiomyopathy.

There is a term that is frequently used in discussions of the end-diastolic ventricular properties: compliance. Technically, compliance is the change in volume for a given change in pressure or, expressed in mathematical terms, it is the reciprocal of the EDPVR derivative ([dP/dV]⁻¹). Since the EDPVR is nonlinear, the compliance varies with volume; compliance is greatest at low volumes and smallest at high volumes. In the
clinical arena, however, compliance is commonly used in two different ways. First, it is used to express the notion 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).

Vb. End-systolic pressure-volume relationship (ESPVR)
Let us now move to the opposite extreme in the cardiac cycle: end-systole. At that instant of the cardiac cycle, the muscles are in their maximally activated state and it is easy to imagine the heart as a much stiffer chamber. As for end diastole, we can construct a pressure-volume relationship at end systole if we imagine the heart frozen in this state of maximal activation. As for the EDPVR, the end-systolic pressure volume relationship (ESPVR) intersects the volume axis at a slightly positive value (Vo), indicating that a finite amount of volume must fill the ventricle before it can generate any pressure. In contrast to the nonlinear EDPVR, the ESPVR has been shown to be reasonably linear over a wide range of conditions, and can therefore be expressed by a simple equation: Pes = Ees (V-Vo), where Pes is the end-systolic pressure, Vo is as defined above, V is the volume of interest and Ees is the slope of the linear relation. Ees stands for end systolic elastance. Elastance means essentially the same thing as stiffness, and is defined as the change in pressure for a given change in volume within a chamber [dP/dV]; the higher the elastance, the stiffer the wall of the chamber.

As discussed above for the EDPVR, the heart would never exist in a frozen state of maximal activation. However, it does pass through this state during each cardiac cycle. The ESPVR provides a line which the PV loop will hit at end-systole, thus providing a boundary for the upper left hand corner of the PV loop.
Vc. Time varying elastance
In the above discussion we have described the pressure-volume relationships at two instances in the cardiac cycle: end diastole and end systole. However, at each instant of time during the cardiac cycle there exists a pressure-volume relationship. In fact, there is a relatively smooth transition from the EDPVR to the ESPVR and back. Therefore, the properties of the ventricle provide specific boundaries within which the PV loop sits; specifically, these are the end-systolic and end-diastolic pressure-volume relations.

VI. CONTRACTILITY

Contractility refers to the intrinsic strength of the ventricle or cardiac muscle. By intrinsic strength we mean those features of the cardiac contraction process that are intrinsic to the ventricle (and cardiac muscle) and are independent of external conditions imposed on it by the vasculature (i.e., by either the preload or afterload, discussed below). How can contractility be changed? Basically, we consider ventricular contractility to be altered when any one or combination of the following events occurs:

1) the amount of calcium released to the myofilaments is changed
2) the affinity of the myofilaments for calcium is changed
3) there is an alteration in the number of myofilaments available to participate in the contraction process.

You will recall that calcium interacts with troponin to trigger a sequence of events which allows actin and myosin to interact and generate force. The more calcium available for this process, the greater the number of actin-myosin interactions. Similarly, the greater troponin's affinity for calcium the greater the amount of calcium bound and the greater the number of actin-myosin interactions. Here we are linking contractility to cellular mechanisms which underly excitation-contraction coupling and thus, changes in ventricular contractility would be the global expression of changes in contractility of the

Isovolumic Contraction  Ejection  Isovolumic Relaxation

Isovolumic Contraction  Ejection  Isovolumic Relaxation
cells that make up the heart. Stated another way, ventricular contractility reflects myocardial contractility (the contractility of individual cardiac cells).

Through the third mechanism, changes in the number of muscle cells, as opposed to the functioning of any given muscle cell, cause changes in the performance of the ventricle as an organ. In acknowledging this as a mechanism through which ventricular contractility can be modified we recognize that ventricular contractility and myocardial contractility are not always linked to each other.

Humoral and pharmacologic agents can modify ventricular contractility by the first two mechanisms. Beta-adrenergic agonists (e.g. epinephrine and norepinephrine) increase the amount of calcium released to the myofilaments and cause an increase in contractility. In contrast, beta-adrenergic antagonists (e.g., propranolol) block the effects of circulating epinephrine and norepinephrine and acutely reduces contractility. Nifedipine is a drug that blocks entry of calcium into the cell and therefore reduces contractility when sufficiently high doses are administered. One example of how ventricular contractility can be modified by the third mechanism mentioned above is the reduction in ventricular contractility following a myocardial infarction where there is loss of myocardial tissue while the unaffected regions of the ventricle function normally.

Experiments have shown that the contractility of the left ventricle can be indexed on the pressure-volume diagram by the slope of the ESPVR relationship. In essence, the stronger the muscle, the stiffer the heart wall becomes at the end of contraction. The stiffer the chamber the greater the slope fo the ESPVR.

VII. PRELOAD

Preload is the hemodynamic load on the ventricle at the end of diastole just before contraction begins. The term was originally coined in studies of isolated strips of cardiac muscle where a weight was hung from the muscle to stretch it to the specified load before (pre-) contraction. For the ventricle, end-diastolic volume most closely reflects the degree to which sarcomeres are stretched prior to initiation of contraction. However, end-diastolic pressure is simple to measure clinically and in the absence of changes in the EDPVR, will also correlate with sarcomere length in a given heart.

VIII. AFTERLOAD

Afterload is the hydraulic load imposed on the ventricle during ejection, usually by the arterial system. Unlike isolated muscle strip experiments where weights hung from one end that are lifted during muscle contraction clearly quantify afterload, characterization of ventricular afterload is not as simple. Aortic pressure is one of the simplest measures of ventricular afterload in that it defines the pressure that the ventricle must overcome to eject blood. Consider the impossible but illustrative situation of an infinite pressure (and hence afterload) in the aorta: The AoV would never open, and all the work that the heart does would go into pressure generation with absolutely no flow of blood out of the heart. Conversely, if the pressure in the aorta were zero, all of the contents of the ventricle
would rush out with little pressure generation in the ventricle. Therefore, it should be obvious that afterload is a major determinant of the volume of blood that remains in the heart at the end of ejection (i.e. all else being equal, if there is great opposition to ejection, little ejection occurs!). The implication is that afterload determines where the pressure-volume loop intersects with the ESPVR line.

While useful in the illustration above, AoP is not, by itself, a measure of afterload. As will become clear below, aortic pressure is determined by properties of both the arterial system and of the ventricle, and thus does not provide a measure that relays information exclusively about the arterial system. Total peripheral resistance (TPR), the ratio between the mean pressure and flow in the arterial system, is independent of the functioning of the ventricle and therefore is an index which describes arterial properties. However, according to its mathematical definition, it can only be used to relate mean flows and pressures through the arterial system. Arterial Impedance is an analysis of the relationship between pulsatile flow and pressure waves in the arterial system; pressure and waves are decomposed into their harmonic components (Fourier Transform) 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 frequencies. Although it is the most comprehensive description of arterial properties as they relate to defining ventricular afterload, it is most difficult to understand and most difficult to measure and is therefore generally used in the context of hemodynamic research, not clinical practice.

IX. UNDERSTANDING THE DETERMINANTS OF VENTRICULAR PERFORMANCE

Two primary measurements of overall cardiovascular performance are the arterial blood pressure and the cardiac output (HR x SV). These measures are also of primary concern in the clinical setting since both an adequate blood pressure and an adequate cardiac output are necessary to maintain life. It is important to appreciate, however, that both of these variables are determined by the interaction between the heart the arterial system (afterload) and the venous system (preload); this is a fundamental concept. Furthermore, it is important to develop an appreciation for how the heart and vasculature interact to determine these indices of performance. This is highlighted by the fact that one major facet of intensive care medicine deals with maintaining adequate blood pressure and cardiac output by manipulating ventricular contractility, arterial resistance and ventricular preload. Two approaches to understanding how these parameters regulate cardiovascular performance will be reviewed: a classical approach, commonly referred to as Frank-Starling Curves, and a more modern approach based upon pressure-volume analyses.

IXa. Frank-Starling Curves

Otto Frank (circa 1890) 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.

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. They showed that there was a nonlinear relationship between end-diastolic pressure (EDP, also referred to as ventricular filling pressure) and CO as shown in Fig. 11; 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.

The observations of Frank and of Starling form one of the basic concepts of cardiovascular physiology: cardiac performance (its ability to generate pressure or to pump blood) increases with preload. There are a few caveats, however. Recall from the anatomy of the cardiovascular system that left ventricular filling pressure is approximately equal to pulmonary venous pressure. 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 marked diminished. This phenomenon typically comes into play when pulmonary venous pressure rises above 20mmHg and becomes increasingly prominent with further increases. When pulmonary venous pressures increase above 25-30 mmHg, there is profound transudation of fluid into the alveoli and pulmonary edema is usually prominent. Therefore, factors extrinsic to the heart dictate a practical limit to how high filling pressure can be increased.

As noted above, 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. However, when arterial resistance is decreased, CO will also increase for a given EDP. 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.
IXb. What can we tell about ventricular performance from the P-V Loop?

*Almost Everything.*

- **Contractility.** Consider that for a given volume, the greater the elastance, the more pressure will be generated. In other words, a stronger ventricle will achieve greater stiffness (i.e. greater maximal elastance) than a weak ventricle. The slope of a line through the end-systolic pressure-volume point (the left upper corner of the P-V loop) is termed End-Systolic Elastance (Ees) and is a measure of ventricular contractility.

- **Diastolic Compliance.** Look at the filling portion of the loop. A healthy ventricle is very compliant during the filling phase, such that there is not a large increase in pressure as it is being filled. Scar tissue, impaired active relaxation, myocardial hypertrophy all cause an upward and leftward shift in this compliance curve. This means that for a given end-diastolic volume, venous pressures would be elevated. Or, for a given venous pressure, there would be less filling.

- **Preload.** The stretch on the sacromeres just prior to contraction is proportional to end-diastolic volume. End-diastolic Pressure reflects the pressure that is required of the venous system to achieve that particular preload volume. The end-diastolic pressure-volume point is the bottom right corner of the P-V loop.

- **Afterload.** This is the most confusing concept. At the least, know that afterload is represented on the P-V diagram by the slope of a line that starts on the volume axis at the end-diastolic volume, and goes through the end-systolic pressure-volume point. This line is called the Arterial Elastance line (Ea). As afterload is increased, this line becomes steeper, and the Ea line would intersect with the Ees line at a higher point (meaning that ESV would be higher and SV would be less). A derivation of this follows in the next (last) section.

- **Stroke Volume.** The difference between end-diastolic volume (EDV) and end-systolic volume (ESV). Obvious as the width of the P-V loop.

- **Ejection Fraction.** This is a common index of contractility used clinically. It is defined as SV/EDV. You can gestalt it from the width of the P-V loop relative to the width of the y-axis to isovolumic contraction line. In the diagram, it’s more than 50%.
• **Arterial Systolic and Diastolic Blood Pressures.** Arterial systolic blood pressure (SBP) is the peak pressure in the arteries. This is the same as peak pressure as in the ventricle and on the P-V loop. The arterial diastolic pressure (DBP) is the pressure at which the aortic valve opens during systole. This can be identified as the right upper corner of the P-V loop.

**Derivation of Arterial Elastance (Ea).** Let’s start with the definition of TPR:

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

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:

$$CO = SV \times HR$$

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

$$TPR = \frac{[MAP - CVP]}{(SV \times HR)}$$

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 (Pes). Making these assumptions, we can rewrite this last equation as:

$$TPR = \frac{Pes}{(SV \times HR)}$$

which can be rearranged to:

$$TPR \times HR = \frac{Pes}{SV} .$$

Note, as shown in the Figure, that the quantity Pes/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. Let us define the slope of this line as Ea:

$$Ea = \frac{Pes}{SV}$$

This term is designated E for "elastance" because the units of this index are mmHg/ml (same as for Ees). The "a" denotes that this term is for the arterial system. Note that this measure is dependent on the TPR and heart rate.