HEMODİMANİK

Hidrodinamiğin konusu akış halindeki sıvılar olduğu dikkate alındığında, Hemodinamiğin konusununda esas olarak akış halindeki kan olduğu hatırlanmalıdır. Ayrıca kan ile birlikte hareket halindeki diğer vücut sıvılarının da davranışını açıklayabilmek için belirli fizik yasalarını bilmek gerekir. Bu fizik ilkeleri çeperleri sert borular içinde akan visköz (Newtonian) sıvılar için geçerlidir. Fakat çoğu durumlarda bazı yaklaşımlarla kanın ve damarların bu koşullara uydukları kabul edilir.

Akiş Hızı ve Debi Kavramları: Bir akışkanın aktığı boru içinde birim zamanda aldığı yola akış hızı denir ve hız birimi ile belirtilir (m/s, cm/s gibi). Akış borusunun kesit alanı her yerde aynı değilse akış hızı kesit alanı ile değişir ve farklı iki kesit alanı için (A_1 ve A_2 gibi) hız değişimi

$$A_1 v_1 = A_2 v_2$$

bağıntısı ile belirlidir. Bu ilişki akış borusu esnek olmayan sert çeperli bir boru ve akışkan sıkıştırılamayan bir sıvı (su gibi) olduğu kabul edilerek elde edilebilir.

Dolaşım sisteminde bir ağacın dalları gibi kalından inceye sayıları hızla artan arteriyollerin toplam kesit alanı arterlerinkinden çok daha büyüktür. Bu nedenle kan arteriyol ağında arterlerde olduğundan çok daha yavaş hareket eder.

Akışkanın birim zamanda bir kesitten geçen hacmine akışkanın debisi denir. Debinin birimi (SI da) m^3/s 'dir fakat pratikte ml/dak veya l/dak daha çok kullanılır. Örneğim kanın aorttaki debisi ortalama 5 l/ dak kadardır.

Viskozite Kavramı: Bir boru içinde sıvının akış hızı ile onu hareket ettiren basınç arasında doğrusal bir ilişki varsa sıvı Newtonian bir sıvıdır. Böyle bir sıvıya visköz sıvı da denir ve vizközlük sıvının iç sürtünme kuvvetleri ile ilgili bir özelliktir. Vizközlüğün ölçüsü vizközlük katsayısıdır ve genellikle η harfi ile gösterilir. Vizközitenin tersine **akışkanlık** denir. Bir akışkanın vizközite katsayısı ne kadar küçük ise akışkanlığı o kadar yüksektir.

Kan parçacıklar (hücreler) içerdiğinden tam olarak visköz bir sıvı değildir. Bu nedenle kanın görünürdeki visközitesinden bahsedilir ve örneğin suya göre değeri verilir.

Kompliyans ve Direnç Kavramları: Vizköz yani kan gibi iç sürtünmeli bir akışkanın yatay bir akış borusundaki akış debisinin (**D**) borunun uçları arasındaki basınç farkı (**P**) ile orantılı olduğu **Poiseuille** tarafından bir bağıntı ile ifade edilerek aşağıdaki bağıntı ile gösterilmiştir.

$$D = P / R$$

Akışkanın cinsine, niteliğine (vizkosite gibi) ve akış borularının özelliklerine (boy ve çap gibi) bağlı olan **R** parametresine akış direnci adı verilir.

Damar çeperleri esneklik katsayıları biribirinden farklı özel bir yapı olduğundan genişleyebilir ve şişebilir özelliktedirler. Bu özellikler damarlarda sert-rijit akış borularında gözlenmeyen türden olayların ortaya çıkmasına neden olur. Damarların genişleyebilmeleri birim basınç (**P**) başına hacimdeki bağıl değişim (**ΔV/V**) olarak verilir ve aşağıdaki bağıntı ile ifade edilir.

$$\beta = \Delta V/V\ P$$

Damar yataklarının genişleyebilmelerini açıklamak içim kompliyans kavramı kullanılır ve

$$C = \Delta V/\Delta P = \beta V$$

ile ifade edilir. Venlerin kompliyansları arterlerinkinden farklıdır ve venöz sistemin kompliyansı arteriyel sisteminkinden kat kat fazladır.

Laplace Yasası: Damar gibi silindirik ve genişleyebilir bir akış borusunun içi ile dışı arasındaki basınç farkına transmural basınç (P_t) denir. Bu farkı dengelemek için damar çeperlerinde ortayaçıkan gerilme (**T**) , laplace yasası ile verilir ve

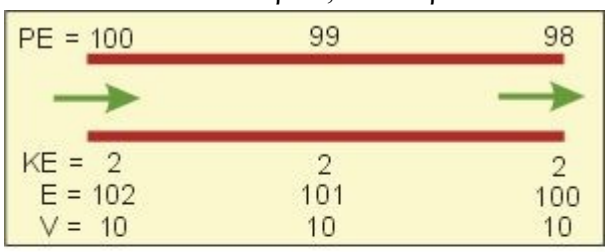
$$T = P_t.r$$

şeklinde ifade edilir.

Düzgün (Laminar) ve Girdaplı (Türbülan) Akış Biçimleri: Bir akış sırasında akış çizgilerinin hep biribirine paralel kaldığı akış hızının akış borusunun hiçbir yerinde zamanla değişmediği akış türü laminar veya düzgün akış olarak tanımlıdır. İç sürtünmeli bir akışkan yatağında akıyor iken bir engelle karşılaşıyorsa, çeperler pürüzlüise ve ya akış hızı kritik bir değerin üzerine çıkıyorsa akış girdaplı olur. Girdaplı akış sırasında Poiseuille yasası geçersizleşir ve akış direnci düzgün akışa göre daha büyüktür.

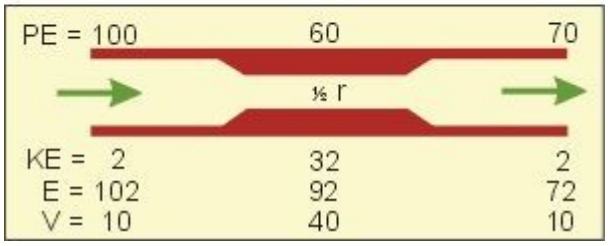
Bernoulli Principle

The Bernoulli principle, as applied to the circulatory system, is based upon the energetics associated with flowing blood (or any moving fluid or gas). The kinetic energy (KE) of flowing blood is proportionate to the velocity squared (derived from $KE = \frac{1}{2} \rho V^2$; where ρ = density and V = mean velocity). The total energy (E) of flowing blood is equal to KE plus potential energy (PE) (ignoring gravitational forces). The PE can be thought of as the pressure exerted against the wall of the blood vessel (i.e., lateral pressure).



$$\mathbf{E = KE + PE} \quad (\textit{where } KE \propto V^2)$$

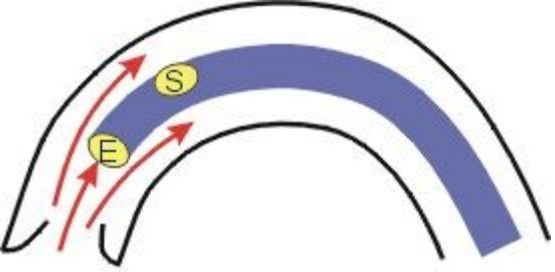
$$\textit{Therefore}, \ \mathbf{E \propto V^2 + PE}$$



This relationship shows that as the velocity of the flowing blood increases, there is a disproportionate increase in KE and total energy (E). Although we usually think of blood flowing through a vessel as being driven by a pressure gradient along the length of the vessel, it is actually the difference in the total energy of the flowing blood along the length of a vessel that determines the flow achieved at any given resistance. As blood flows through a vessel, there is a loss of total energy because of frictional (heat) energy loses. If we were to consider the energetics along the length of a vessel of constant radius, we would see that there is a gradual decline in total energy as the potential, or pressure energy falls. This is illustrated to the right (top panel) where a hypothetical length of blood vessel of constant radius shows a 2 mmHg decrease in potential and total energy between its two ends. The KE is constant along the length of the vessel because the velocity is the same at every point along the vessel.

The situation is very different for a blood vessel that has a stenosis, or narrowing of the lumen as shown to the right (bottom panel). The mid-section of the vessel has its radius decreased by 50%. This results in a 4-fold increase in velocity (from 10 to 40) in that section of the vessel because at constant flow, velocity is inversely related to radius squared ($V \propto 1/r^2$). This increase in velocity causes a 16-fold increase in KE because $KE \propto V^2$. If KE were the equivalent of 2 mmHg at the entrance of the vessel, it will now be 32 mmHg in the stenotic region instead of 2 mmHg. There will be a significant reduction in total energy in the stenotic region despite the increase in KE because there is a disproportionate loss of PE due to increased resistance (frictional forces). In the post-stenotic segment, the velocity will return to the pre-stenotic value (because radius and velocity are the same in the pre- and post-stenotic segments). Therefore, KE is the same in the post- and pre-stenotic segments. There will be, however, an additional loss of PE due to turbulence, thereby further decreasing total energy. It might seem paradoxical that the lateral pressure (PE) is lower in the stenotic segment than in the post-stenotic segment. Volume flow, however, stills goes from left to right in this illustration because it is the total energy that actually drives the flow along the vessel.

The above considerations illustrate an important principle. *Blood flowing at higher velocities has a higher ratio of kinetic energy to potential (pressure) energy.* High kinetic energies are found in the aortic arch because of the high ejection velocities achieved by the left ventricle



End-port (E) pressure = KE + PE
Side-port (S) pressure = PE

during systole. When stroke volume is augmented as during exercise, the moving blood has an even higher kinetic energy.

An interesting, yet practical application of the Bernoulli principle is found when blood pressure measurements are made from within the ascending aorta. As described above, during ventricular ejection, the velocity and hence kinetic energy of the flowing blood is very high. The instantaneous blood pressure that is measured within the aorta will be very different depending upon how the pressure is measured. As illustrated to the right, if a catheter has an end-port (E) sensor that is facing the flowing stream of blood, it will measure a pressure that is significantly higher than the pressure measured by a side-port (S) sensor on the same catheter. The reason for the discrepancy is that the end-port measures the total energy of the flowing blood. As the flow stream "hits" the end of the catheter, the kinetic energy (which is high) is converted to potential (or pressure) energy, and added to the potential energy to equal the total energy. The side-port will not be "hit" by the flowing stream so kinetic energy is not converted to potential energy. The side-port sensor, therefore, only measures the potential energy, which is the lateral pressure acting on the walls of the aorta. The difference between the two types of pressure measurements can range from a few mmHg to more than 20 mmHg depending upon the peak velocity of the flowing blood within the aorta.

Turbulent Flow

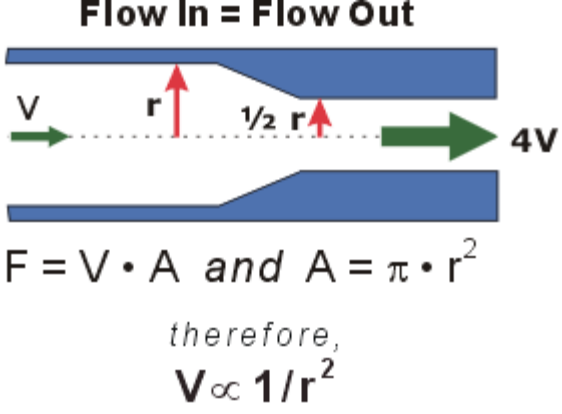
Turbulence occurs when smoothly flowing, laminar flow is disrupted. This occurs distal to stenotic (narrowed) heart valves or arterial vessels, at vessel branch points, and in the ascending aorta at high cardiac ejection velocities (e.g., during exercise).

The onset of turbulence under ideal conditions can be predicted by calculating the Reynolds number (Re):

$$\mathrm{Re} = \frac{(\bar{v} \cdot D \cdot \rho)}{\eta}$$

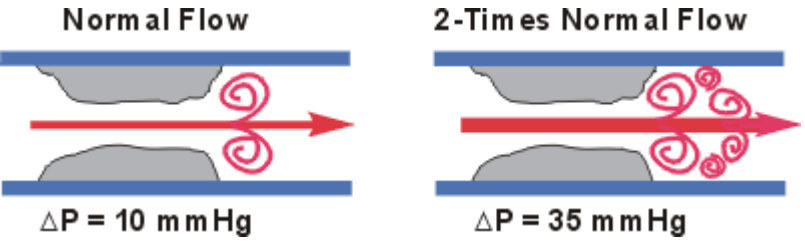
Where v = mean velocity, D = vessel diameter, ρ = blood density, and η = blood viscosity

There is a critical Reynolds number above which laminar flow is disrupted and turbulence occurs. Therefore, as blood flow velocity increases in a blood vessel or across a heart valve, there is not a gradual increase in turbulence as the Reynolds number increases. Instead, laminar flow will continue until a critical Reynolds number is reached, at which point, turbulence will develop. Under ideal conditions (e.g., long, straight, smooth blood vessels), the critical Re is relatively high. However, in branching vessels, or in vessels with atherosclerotic plaques protruding into the lumen, the critical Re is much lower so that there can be turbulence even at normal physiological flow velocities.



Volume flow (F) equals mean velocity (V) times vessel cross-sectional area (A), where A = π times radius squared (r^2). Therefore, at constant flow (flow in = flow out), $V \propto 1/r^2$.

It is important to note that as diameter decreases, there is a disproportionate increase in mean velocity because velocity $\propto 1/r^2$ (this relationship is based upon the relationship between flow, velocity, and cross-sectional area of a vessel, where flow = velocity x area, and area = $\pi \cdot r^2$ as shown to the right). For example, if an arterial stenosis reduces the vessel diameter by 50%, mean velocity will increase 4-fold. The net effect will be a 2-fold increase in Re, bringing the Re closer to its critical value for the development of turbulence. Besides increasing Re, increased velocity also increases the kinetic energy of the flowing blood, which can lead to a decrease in potential energy (Bernoulli effect) and result in vessel collapse and flutter under some conditions.



Turbulence generates sound waves (e.g., ejection murmurs, carotid bruits) that can be heard with a stethoscope. Because higher velocities enhance turbulence, audible sounds resulting from turbulence become louder whenever blood flow is increased across the valve or through the vessel where the turbulence is occurring. Elevated cardiac outputs, even across anatomically normal aortic valves, can cause physiological murmurs because of turbulence. This sometimes occurs in pregnant women who have elevated cardiac output and who may also have anemia, which decreases blood viscosity. Both factors increase the Reynolds number and increases the likelihood of turbulence.

Turbulence causes increased energy loss and a higher pressure drop than predicted by the Poiseuille relationship. For example, as illustrated to the right, if blood flow is increased 2-fold across a stenotic arterial segment, the pressure drop across the stenosis may increase by 3 or 4-fold. The Poiseulle relationship would simply predict a 2-fold increase in the pressure drop across the lesion because the pressure gradient is proportional to flow under laminar flow conditions.

Therefore, turbulence alters the relationship between flow and perfusion pressure such that the relationship is no longer linear as described by the Poiseuille relationship (see figure at right). Instead, a greater perfusion pressure is required to propel blood at a given flow rate. Alternatively, a given flow that is turbulent will result in a greater pressure drop across a resistance than predicted simply by the radius and length of the resistance element. This figure illustrates the relationship between pressure and flow across a stenotic lesion (e.g., stenotic valve or arterial segment) in which turbulence occurs.

Determinants of Resistance to Flow (Poiseuille's Equation)

There are three primary factors that determine the resistance to blood flow within a single vessel: diameter (or radius), length, and viscosity of the blood.

Vessel resistance (R) is directly proportional to the length (L) of the vessel and the viscosity (η) of the blood, and inversely proportional to the radius to the fourth power (r^4).

$$R \propto \frac{\eta \cdot L}{r^4}$$

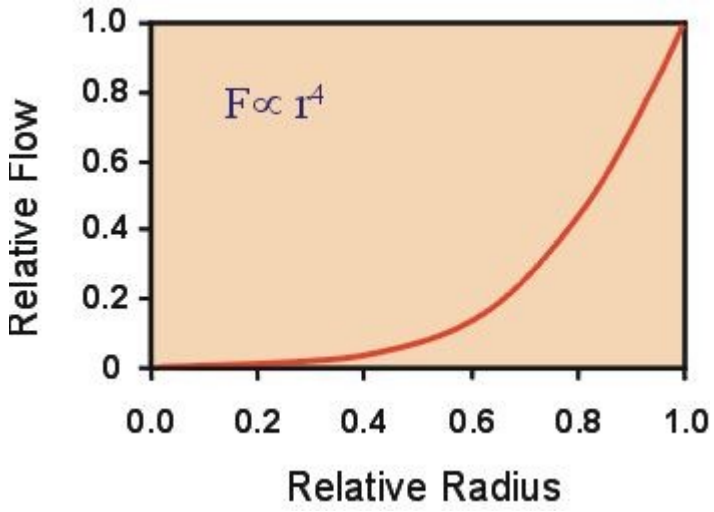
Therefore, a vessel having twice the length of another vessel (and each having the same radius) will have twice the resistance to flow. Similarly, if the viscosity of the blood increases 2-fold, the resistance to flow will increase 2-fold. In contrast, an increase in radius will reduce resistance. Furthermore, the change in radius will alter resistance to the fourth power of the change in radius. For example, a 2-fold increase in radius will decrease resistance by 16-fold! Therefore, vessel resistance is exquisitely sensitive to changes in radius (or diameter which is proportionate to radius).

Vessel length does not change appreciably in vivo and, therefore, can generally be considered as a constant. Blood viscosity normally does not change very much; however, it can be significantly altered by changes in hematocrit, temperature, and by low flow states.

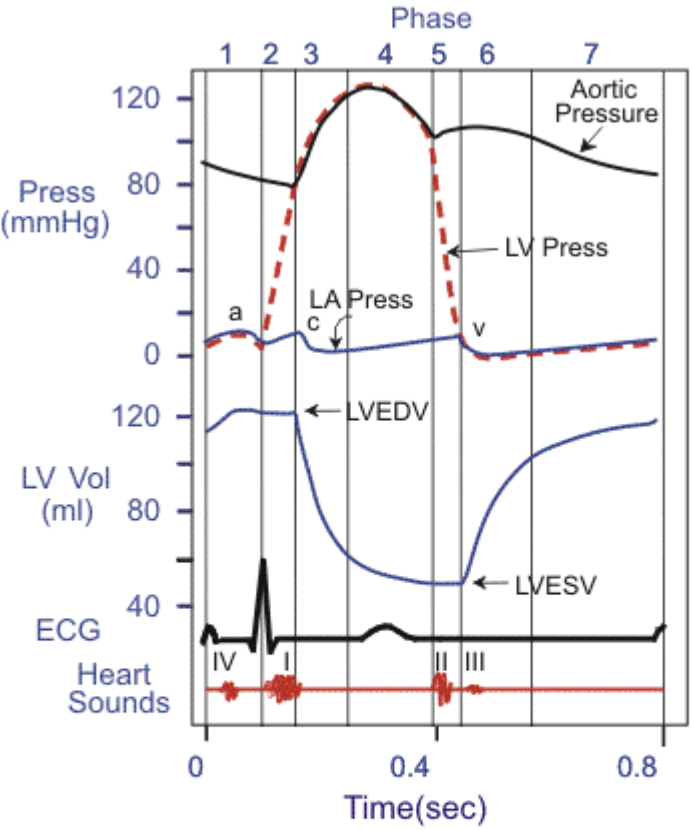
If the above expression for resistance is combined with the equation describing the relationship between flow, pressure and resistance ($F=\Delta P/R$), then

$$F \propto \frac{\Delta P \cdot r^4}{\eta \cdot L}$$

This relationship (**Poiseuille's equation**) was first described by the French physician Poiseuille (*ca.* 1820). It is a description of how flow is related to perfusion pressure, radius, length, and viscosity. In the body, however, flow does not conform quantitatively to this relationship because this relationship assumes long, straight tubes (blood vessels), a Newtonian fluid (e.g., water, not blood which is non-Newtonian), and steady, laminar flow conditions. Nevertheless, the relationship clearly shows the dominant influence of vessel radius on resistance and flow and therefore serves as an important concept to understand how physiological (e.g., vascular tone) and pathological (e.g., vascular stenosis) changes in vessel radius affect flow, and how changes in heart valve orifice size (e.g., in valvular stenosis) affect flow and pressure gradients across heart valves.



The relationship between flow and radius for a single vessel is shown in the figure to the right. In this analysis, laminar flow conditions are assumed, and pressure, viscosity, and vessel length are held constant. As vessel radius decreases, there is a dramatic fall in flow because flow is directly related to radius to the fourth power. For example, when radius is one-half normal (0.5 relative radius), flow is decreased by a factor of 16. The new flow, therefore, is only about 6% of the original flow. This illustrates how very small changes in vessel radius can have dramatic effects on flow.



Abbreviations:
LV Press, left ventricular pressure
a, a-wave; c, c-wave; v, v-wave
ECG, electrocardiogram
LVEDV, left ventricular end-diastolic volume
LVESV, left ventricular end-systolic volume

Although the above discussion is directed toward blood vessels, the factors that determine resistance across a heart valve are the same as described above except that length becomes insignificant because path of blood flow across a valve is extremely short compared to a blood vessel. Therefore, when resistance to flow is described for heart valves, the primary factors considered are radius and blood viscosity.

Cardiac Cycle

A single cycle of cardiac activity can be divided into two basic stages. The first stage is **diastole,** which represents ventricular filling and a brief period just prior to filling at which time the ventricles are relaxing. The second stage is **systole**, which represents the time of contraction and ejection of blood from the ventricles.

To analyze these two stages in more detail, it is convenient to divide the cardiac cycle into seven phases. The first phase begins with the p-wave in the electrocardiogram, which represents atrial depolarization. The last phase of the cardiac cycle ends with the appearance of the next p-wave. In order to understand the events of the cardiac cycle, the reader should first review basic cardiac anatomy.

The entire cardiac cycle, which contains information on aortic, left ventricular and left atrial pressures, along with ventricular volume, heart sounds and the electrocardiogram, is shown to the right. Detailed descriptions of each phase can be obtained by clicking on each of the seven phases listed below.

Phase 1 - Atrial Contraction

Phase 2 - Isovolumetric Contraction

Phase 3 - Rapid Ejection

Phase 4 - Reduced Ejection

Phase 5 - Isovolumetric Relaxation

Phase 6 - Rapid Filling

Phase 7 - Reduced Filling

Inotropy

Changes in stroke volume can be accomplished by changes in ventricular inotropy (contractility). Changes in inotropy are unique to cardiac muscle. Skeletal muscle, for example, cannot alter its intrinsic inotropic state. Changes in inotropy result in changes in force generation, which are independent of preload (i.e., sarcomere length). This is clearly

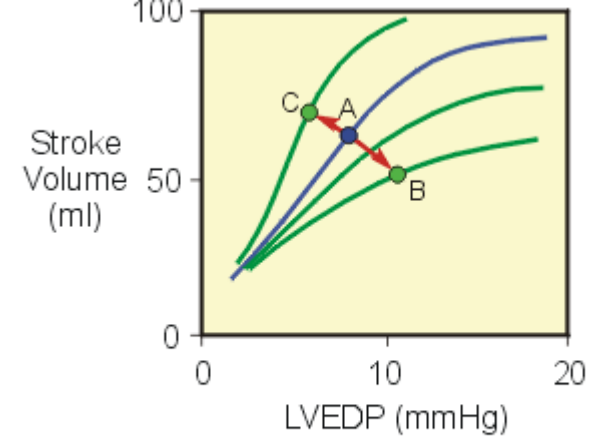


Figure 1. Effects of changes in inotropy on Frank-Starling curves. A shift from A to B occurs with decreased inotropy, and from A to C with increased inotropy.

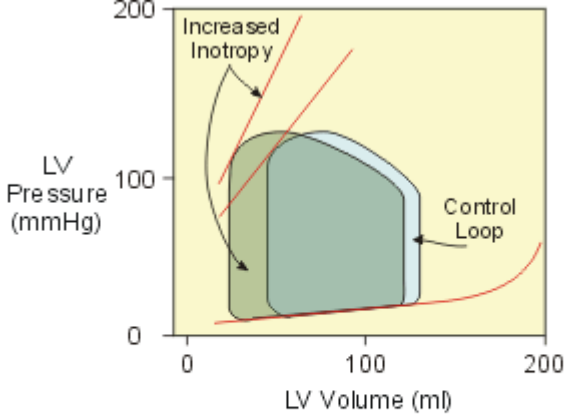


Figure 2. Effects of increasing inotropy on steady-state left ventricular pressure-volume loop. Heart rate and aortic pressure held constant.

demonstrated by use of length-tension diagrams in which an increase in inotropy results in an increase in active tension at a given preload. Furthermore, inotropy is displayed in the force-velocity relationship as a change in V_{max}; that is, a change in the maximal velocity of fiber shortening at zero afterload. The increased velocity of fiber shortening that occurs with increased inotropy increases the rate of ventricular pressure development. During the phase of isovolumetric contraction, an increase in inotropy is manifested as an increase in maximal dP/dt (i.e., rate of pressure change).

Changes in inotropy alter the rate of force and pressure development by the ventricle, and therefore change the rate of ejection (i.e., ejection velocity). For example, an increase in inotropy shifts the Frank-Starling curve up and to the left (point A to C in Figure 1). This causes a reduction in end-systolic volume and an increase in stroke volume as shown in the pressure-volume loops depicted in Figure 2. The increased stroke volume also causes a secondary reduction in ventricular end-diastolic volume and pressure because there is less end-systolic volume to be added to the incoming venous return. It should be noted that the active pressure curve that defines the limits of the end-systolic pressure-volume relationship (ESPVR) is shifted to the left and becomes steeper when inotropy is increased. The ESPVR is sometimes used as an index of ventricular inotropic state. It is analogous to the shift that occurs in the active tension curve in the length-tension relationship whenever there is a change in inotropy.

Changes in inotropy produce significant changes in ejection fraction (EF). Increasing inotropy leads to an increase in EF, while decreasing inotropy decreases EF. Therefore, EF is often used as a clinical index for evaluating the inotropic state of the heart. In heart failure, for example, there often is a decrease in inotropy that leads to a fall in stroke volume as well as an increase in preload, thereby decreasing EF. The increased preload, if it results in a left ventricular end-diastolic pressure greater than 20 mmHg, can lead to pulmonary congestion and edema. Treating a patient in heart failure with an inotropic drug (e.g., beta-adrenoceptor agonist or digoxin) will shift the depressed Frank-Starling curve up and to the left, thereby increasing stroke volume, decreasing preload, and increasing EF.

Changes in inotropic state are particularly important during exercise. Increases in inotropic state help to maintain stroke volume at high heart rates. Increased heart rate alone decreases stroke volume because of reduced time for diastolic filling, which decreases end-diastolic volume. When the inotropic state increases at the same time, end-systolic volume decreases so that stroke volume can be maintained.

Factors Regulating Inotropy

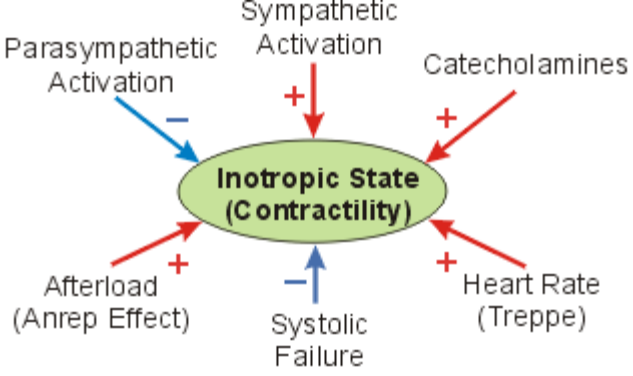


Figure 3. Factors regulating inotropy. (+) increased inotropy; (-) decreased inotropy.

The most important mechanism regulating inotropy is the autonomic nerves. Sympathetic nerves play a prominent role in ventricular and atrial inotropic regulation, while parasympathetic nerves (vagal efferents) have a significant negative inotropic effect in the atria but only a small effect in the ventricles. Under certain conditions, high levels of circulating epinephrine augment sympathetic adrenergic effects. In the human heart, an abrupt increase in afterload can cause a small increase in inotropy (Anrep effect) by a mechanism that is not fully understood. An increase in heart rate also stimulates inotropy (Bowditch effect; treppe; frequency-dependent inotropy). This latter phenomenon is probably due to an inability of the Na^+/K^+-ATPase to keep up with the sodium influx at higher heart rates, which leads to an accumulation of intracellular calcium via the sodium-calcium exchanger. Systolic failure that results from cardiomyopathy, ischemia, valve disease, arrhythmias, and other conditions is characterized by a loss of intrinsic inotropy.

In addition to these physiological mechanisms, a variety of inotropic drugs are used clinically to simulate the heart, particularly in acute and chronic heart failure. These drugs include digoxin (inhibits sarcolemmal Na^+/K^+-ATPase), beta-adrenoceptor agonists (e.g., dopamine, dobutamine, epinephrine, isoproterenol), and phosphodiesterase inhibitors (e.g., milrinone).

Mechanisms of Inotropy

Most of the signal transduction pathways that stimulate inotropy ultimately involve Ca^{++}, either by increasing Ca^{++} influx (via Ca^{++} channels) during the action potential (primarily during phase 2), by increasing the release of Ca^{++} by the sacroplasmic reticulum, or by sensitizing troponin-C (TN-C) to Ca^{++}.

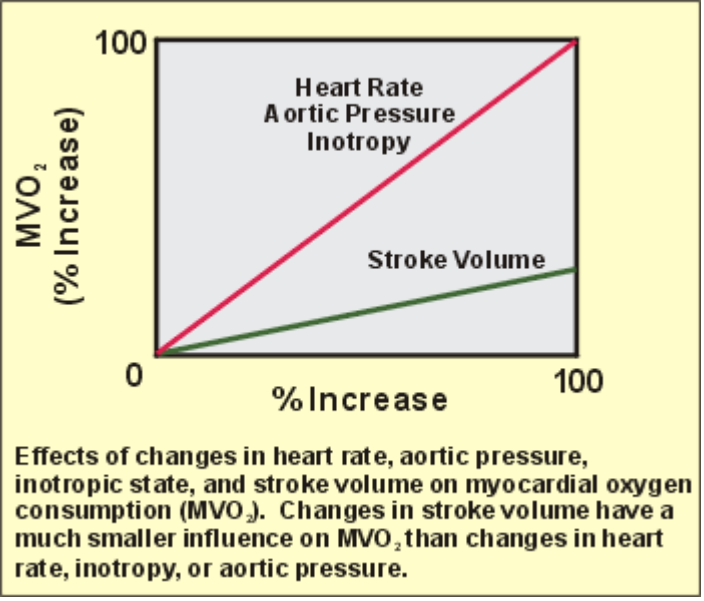
Determinants of myocardial oxygen consumption

Myocyte contraction is the primary factor determining myocardial oxygen consumption (MVO_2) above basal levels. Therefore, factors that enhance tension development, the rate of tension development, or the number of tension generating cycles per unit time will increase MVO_2. For example, doubling heart rate approximately doubles MVO_2 because ventricular myocytes are generating twice the number of tension cycles per minute. Increasing inotropy will also increase MVO_2 because the rate of tension development is increased as well as the magnitude of tension, both of which result in increased ATP hydrolysis and oxygen consumption. Increasing afterload, because it increases tension development, also increases MVO_2. Increasing preload (e.g., ventricular end-diastolic volume) will also increase MVO_2; however, the increase is much less than what might be expected because of the LaPlace relationship.

The LaPlace relationship says that wall tension (T) is proportional to the product of intraventricular pressure (P) and ventricular radius (r).

$$T \propto P \cdot r$$

(Law of LaPlace)



Effects of changes in heart rate, aortic pressure, inotropic state, and stroke volume on myocardial oxygen consumption (MVO_2). Changes in stroke volume have a much smaller influence on MVO_2 than changes in heart rate, inotropy, or aortic pressure.

Wall tension can be thought of as the tension generated by myocytes that results in a given intraventricular pressure at a particular ventricular radius. Therefore, when the ventricle needs to generate greater pressure, for example with increased afterload or inotropic stimulation, the wall tension is increased (i.e., increased myocyte tension development). This relationship also shows us that a dilated ventricle (as occurs in dilated cardiomyopathy) has to generate increased wall tension to produce the same intraventricular pressure.

We observe empirically that wall tension and MVO_2 are closely related. For this reason, changes in intraventricular pressure and ventricular radius affect MVO_2. As stated above, changes in ventricular preload volume do not affect MVO_2 to the same extent quantitatively as changes in afterload. This is because preload is usually expressed as the ventricular end-diastolic volume, not radius. If the ventricle is assumed to be a sphere, then the ventricular volume (V) is related to radius (r) by:

$$V = \frac{4}{3}\pi \cdot r^3$$

Therefore,

$$r \propto \sqrt[3]{V}$$

Substituting this relationship into the LaPlace relationship,

$$T \propto P \cdot \sqrt[3]{V}$$

This relationship indicates that a 100% increase in ventricular volume (V) will increase wall tension (T) by only 26%. In contrast, increasing intraventricular pressure (P) by 100% will increase wall tension (T) by 100%. For this reason, wall tension, and therefore MVO_2, is far less sensitive to changes in ventricular volume than pressure (see figure at right). In summary, increasing heart rate (HR), aortic pressure (AP), and inotropy (Ino) increase MVO_2 about 4-times more than an equivalent percent change in stroke volume (SV).

These finding have implications for the treatment of patients with coronary artery disease (CAD). For example, drugs that decrease afterload, heart rate, and inotropy are particularly effective in reducing MVO_2 and relieving anginal symptoms. CAD patients should avoid situations that lead to large increases in afterload such as lifting heavy weights. It is very important that hypertensive CAD patients are fully complying with their anti-hypertensive medications because hypertension dramatically increases MVO_2 due to increased afterload. CAD patients can also be encouraged to participate in exercise programs such as walking that utilize preload changes to augment cardiac output by the Frank-Starling mechanism. It is important to minimize adrenergic activation in CAD patients because sympathetic activation of the heart and vasculature increases heart rate, inotropy, and systemic vascular resistance, all of which lead to significant increases in oxygen demand by the heart.

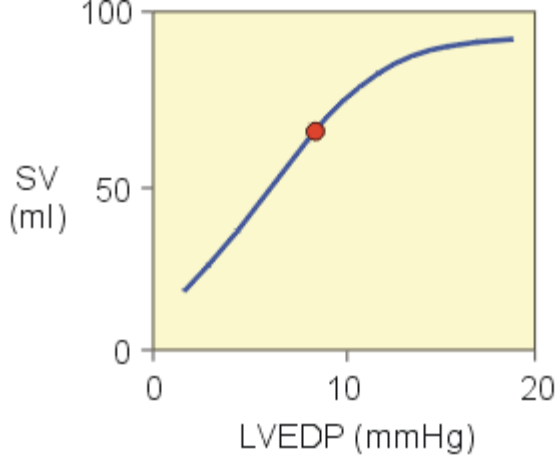


Figure 1. Frank-Starling mechanism. Increasing venous return to the left ventricle increases left ventricular end-diastolic pressure (LVEDP) and volume, thereby increasing ventricular preload. This results in an increase in stroke volume (SV). The "normal" operating point is at a LVEDP of ~8 mmHg and a SV of ~70 ml/beat.

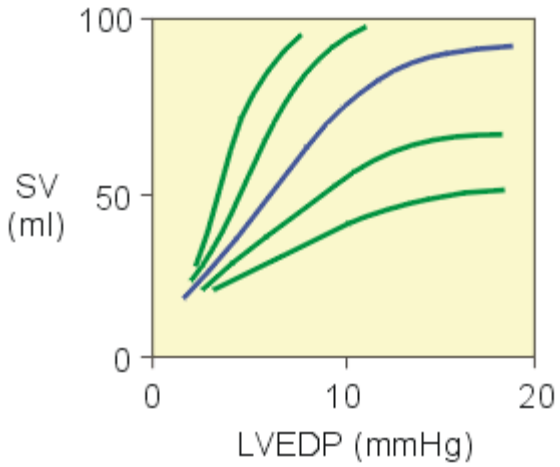


Figure 2. Family of Frank-Starling curves. Changes in afterload and inotropy shift the Frank-Starling curve up or down.

Frank-Starling Mechanism

The heart has the intrinsic capability of increasing its force of contraction and therefore stroke volume in response to an increase in venous return. This is called the **Frank-Starling mechanism** in honor of the scientific contributions of Otto Frank (late 19th century) and Ernest Starling (early 20th century). This phenomenon occurs in isolated hearts, and therefore is independent of neural and humoral influences. Increased venous return increases the ventricular filling (end-diastolic volume) and therefore preload, which is the initial stretching of the cardiac myocytes prior to contraction. Myocyte stretching increases the sarcomere length, which causes an increase in force generation. This mechanism enables the heart to eject the additional venous return, thereby increasing stroke volume (SV).

The mechanical basis for this mechanism is found in the length-tension and force-velocity relationships for cardiac myocytes. Briefly, increasing the sarcomere length increases troponin C calcium sensitivity, which increases the rate of cross-bridge attachment and detachment, and the amount of tension developed by the muscle fiber (see Excitation-Contraction Coupling). The effect of increased sarcomere length on the contractile proteins is termed **length-dependent activation**.

It is traditionally taught that the Frank-Starling mechanism does not result in a change in inotropy, although there is a change in force generation; however, because increases in preload are associated with altered calcium handling, a clear distinction cannot be made between length-dependent and length-independent changes in contractile function in terms of whether or not these are inotropic changes or non-inotropic changes.

There is no single Frank-Starling curve for the ventricle. There is actually a family of curves, each of which is defined by the afterload imposed upon the heart and the inotropic state of the heart. Figure 2 shows how a ventricle functions at different afterload and inotropic states. To summarize, changes in venous return will cause a ventricle to move along a single Frank-Starling curve that is defined by the existing conditions of afterload and inotropy.

Frank-Starling curves how changes in ventricular preload lead to changes in stroke volume. This graphical representation, however, does not show how changes in venous return affect end-diastolic and end-systolic volume. In order to do this, it is necessary to describe ventricular function in terms of pressure-volume diagrams.