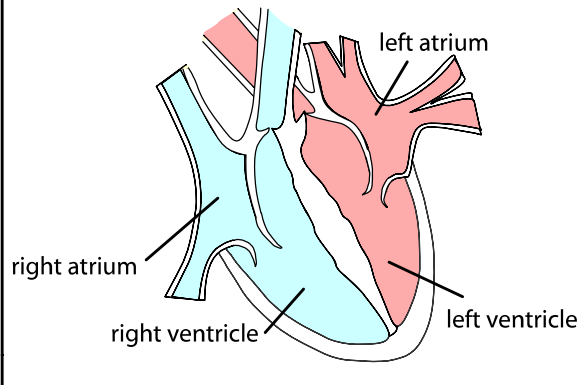


The Cardiac Cycle

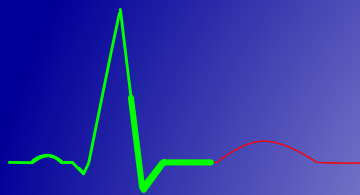
The Events of the Cardiac Cycle



The human heart is the circulatory system's pump, which forces blood through the blood vessels of the body. To pump blood, the muscle tissue of the heart contracts. The contraction begins in the upper two chambers of the heart, called the atria, and then proceeds to the lower two chambers, the ventricles. A complete contraction and relaxation of the heart is a single heartbeat, also called a cardiac cycle.

In the accompanying animation, we examine the events of the cardiac cycle, which can be divided into a phase in which the ventricles are contracted (systole) and a phase in which the ventricles are relaxed (diastole). We also correlate these phases of the cycle with the changing pressures in the ventricles and aorta and the changing blood volume in the ventricles.

120/80

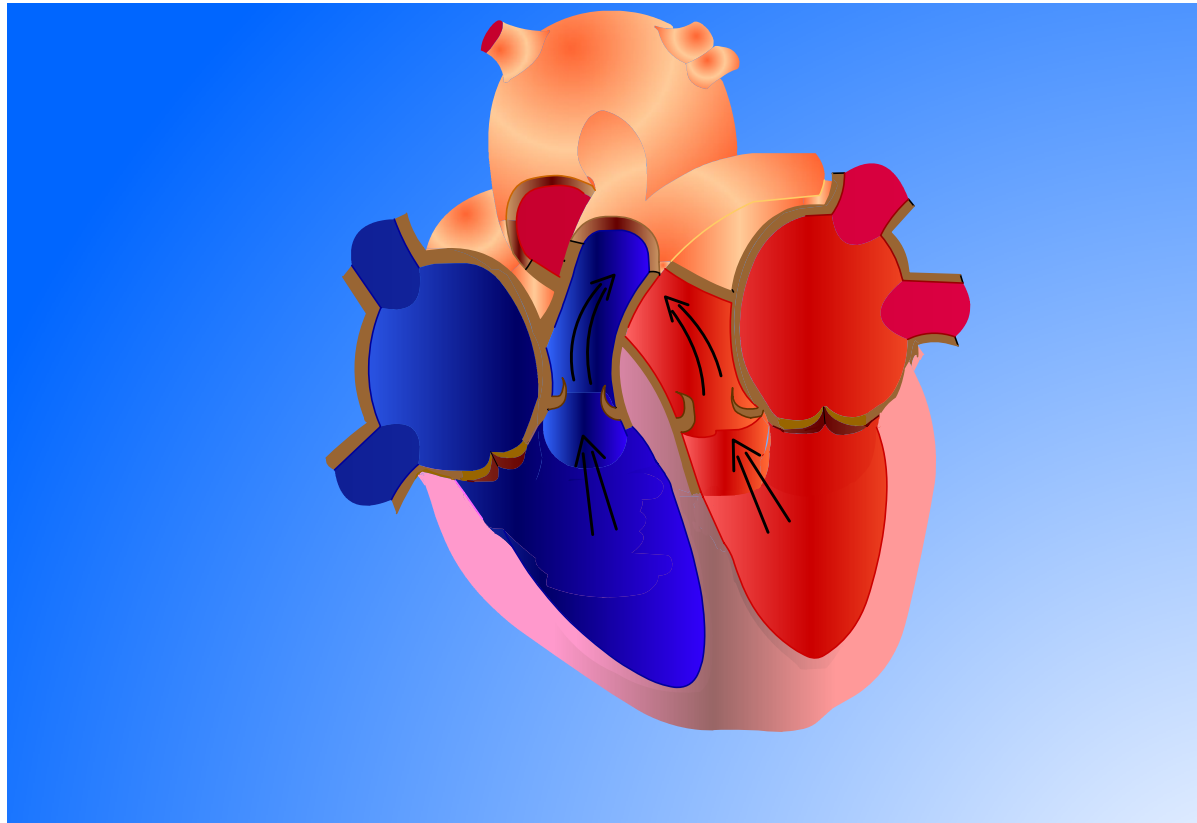
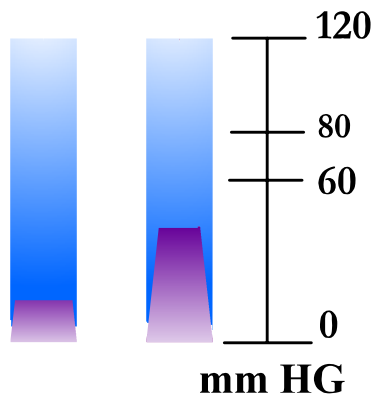


play stop step rew

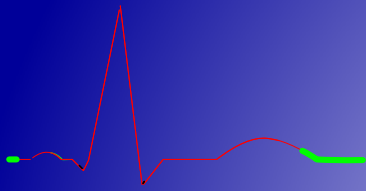
Ventricular Systole

Pressure

A V



120/80

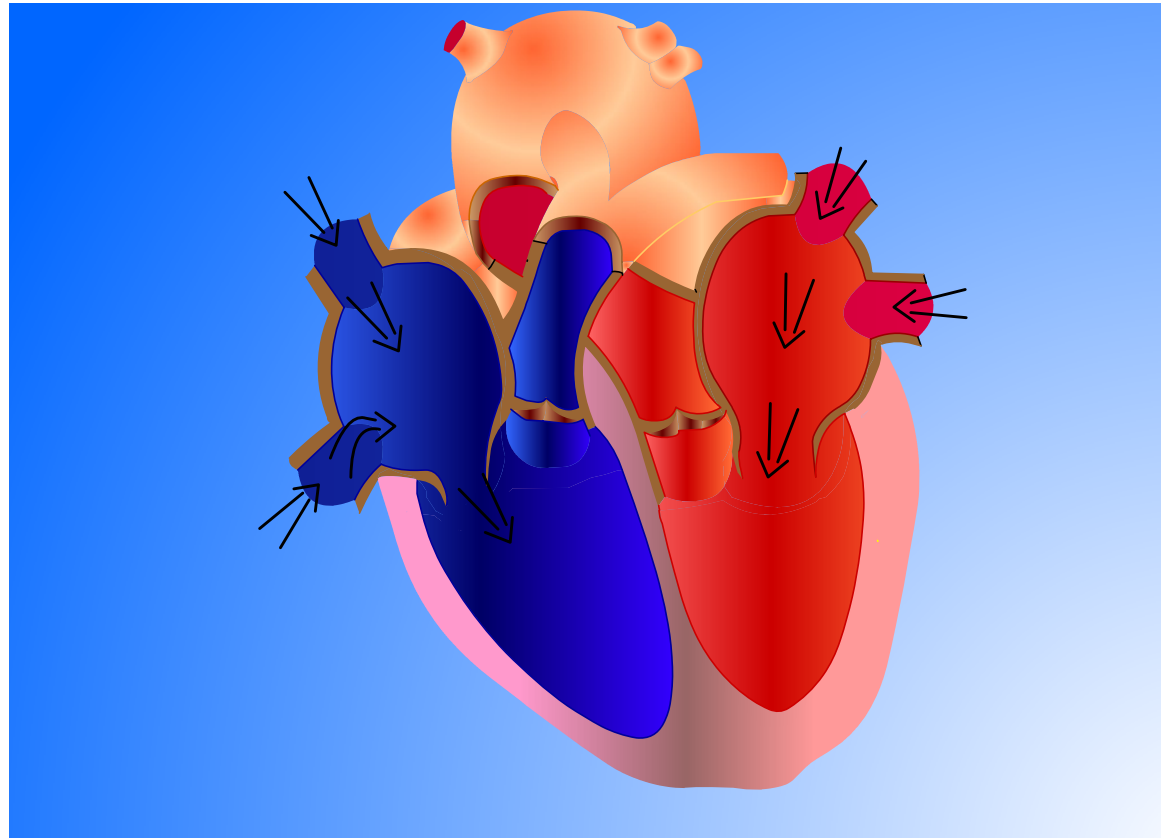
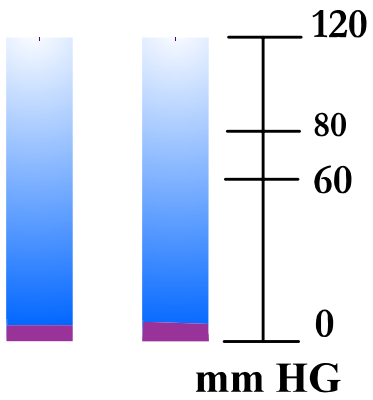


Passive Filling

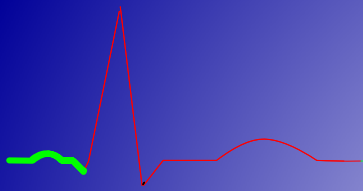
Ventricular Diastole

Pressure

A V



120/80



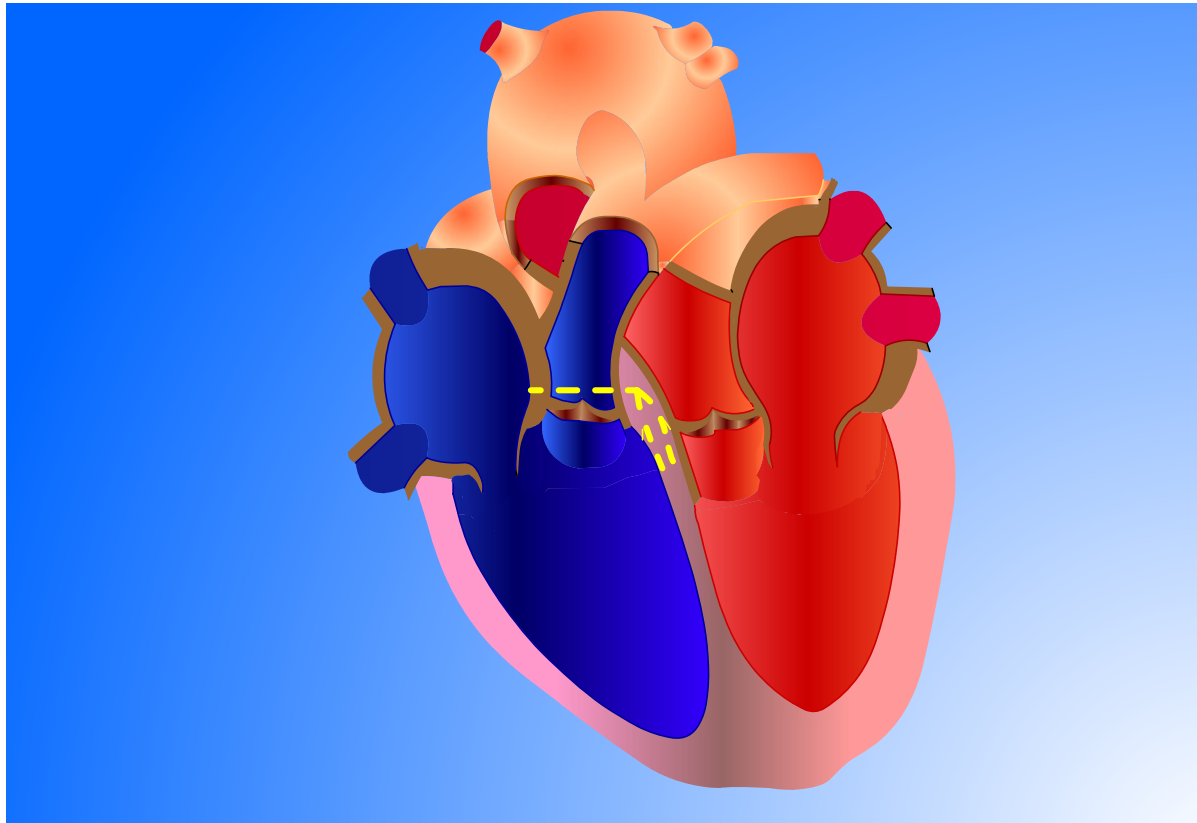
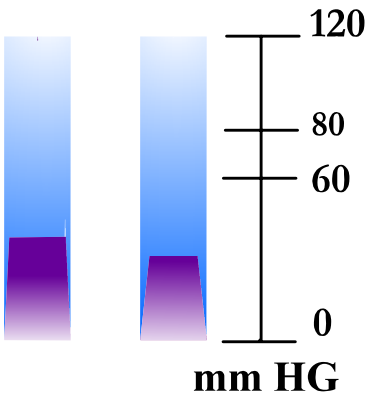
Atrial contraction

Ventricular Diastole

Pressure

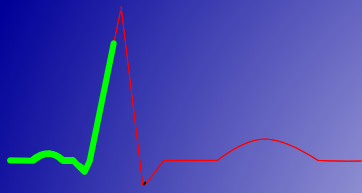
A

V



120/80

67 bpm



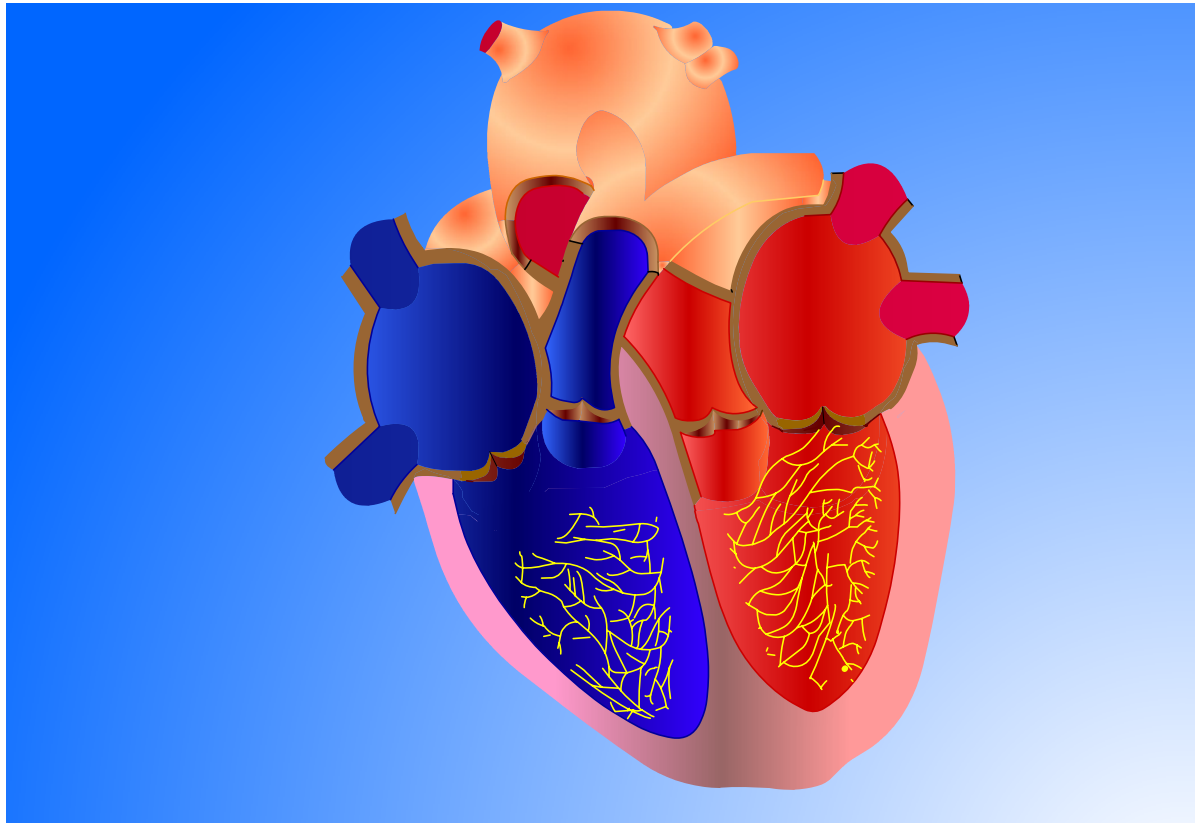
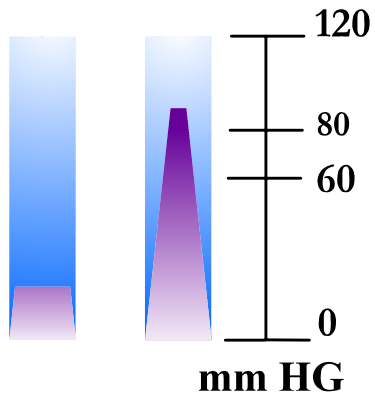
Isovolumetric ventricular contraction

Ventricular Systole

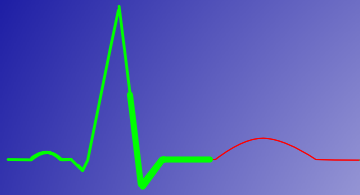
Pressure

A

V

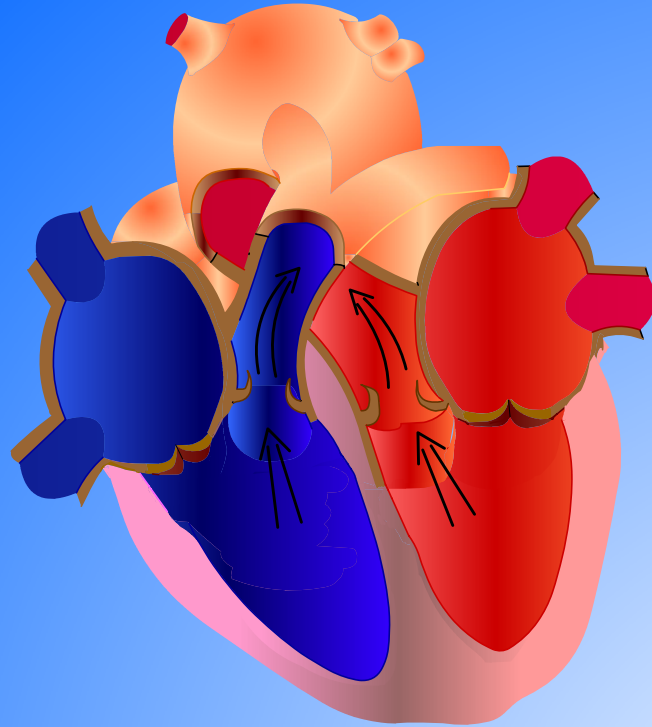
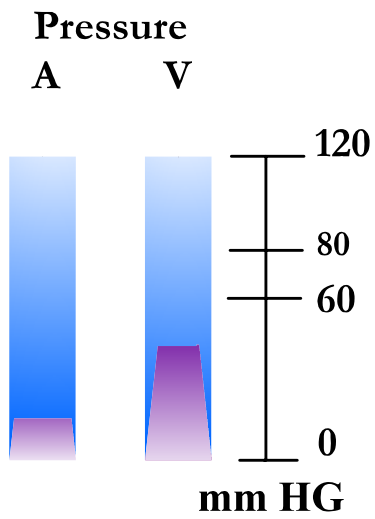


120/80



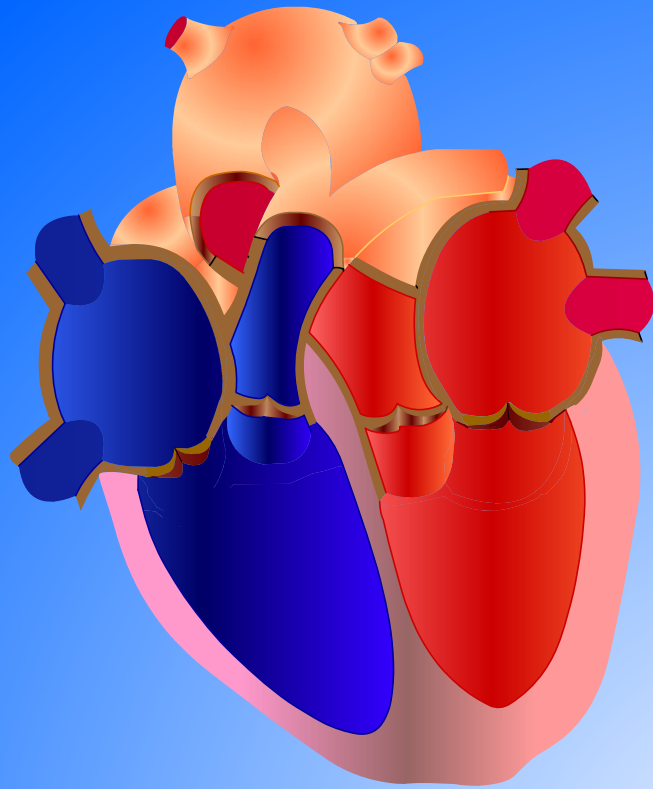
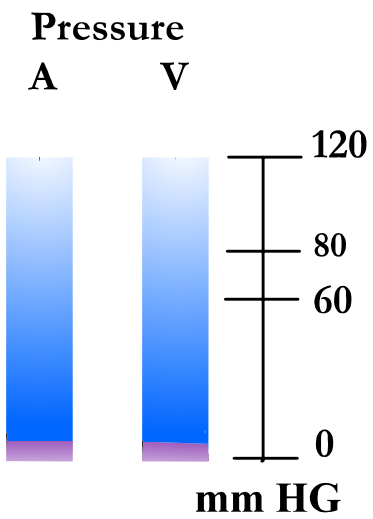
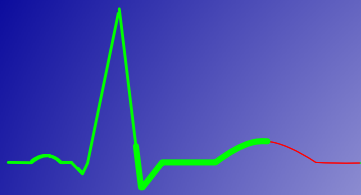
Ventricular ejection

Ventricular Systole



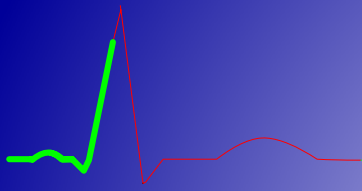
Isovolumetric ventricular relaxation

Ventricular Diastole



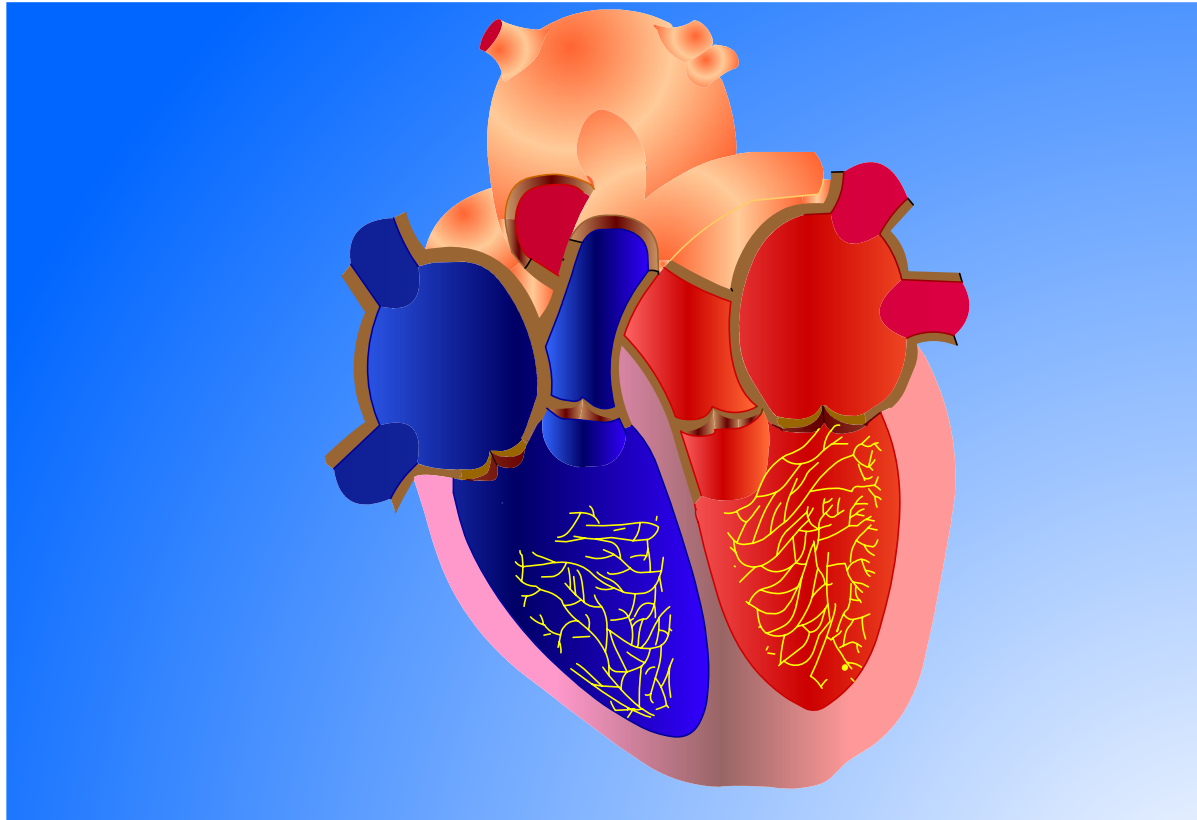
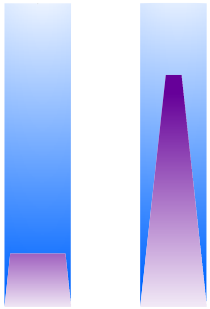
120/80

67 bpm

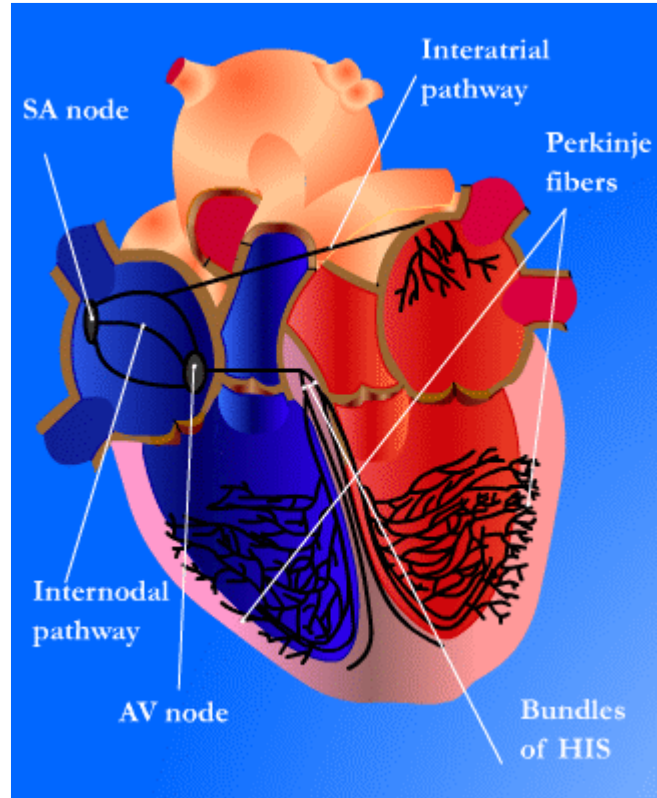


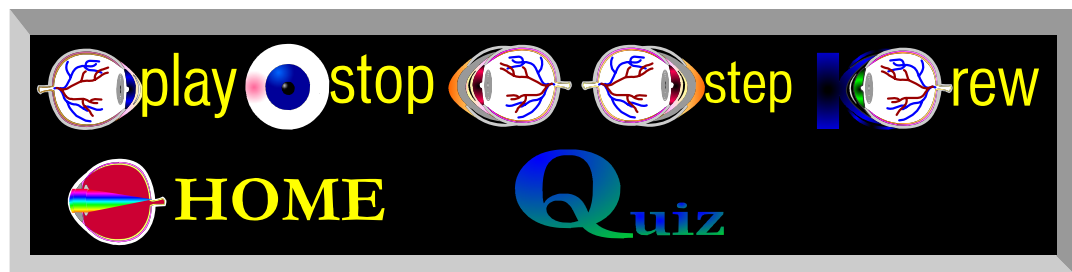
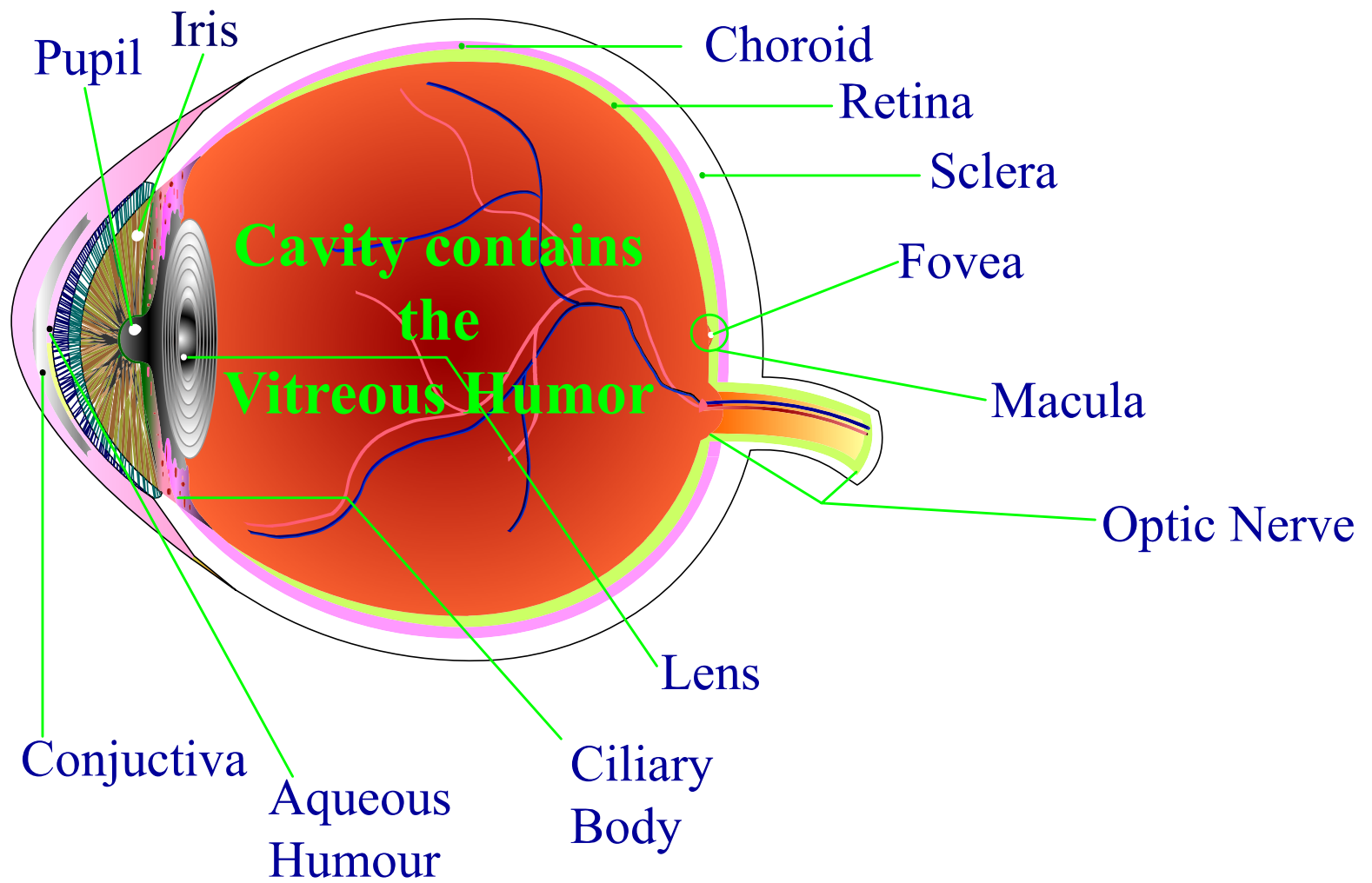
The Cardiac Cycle

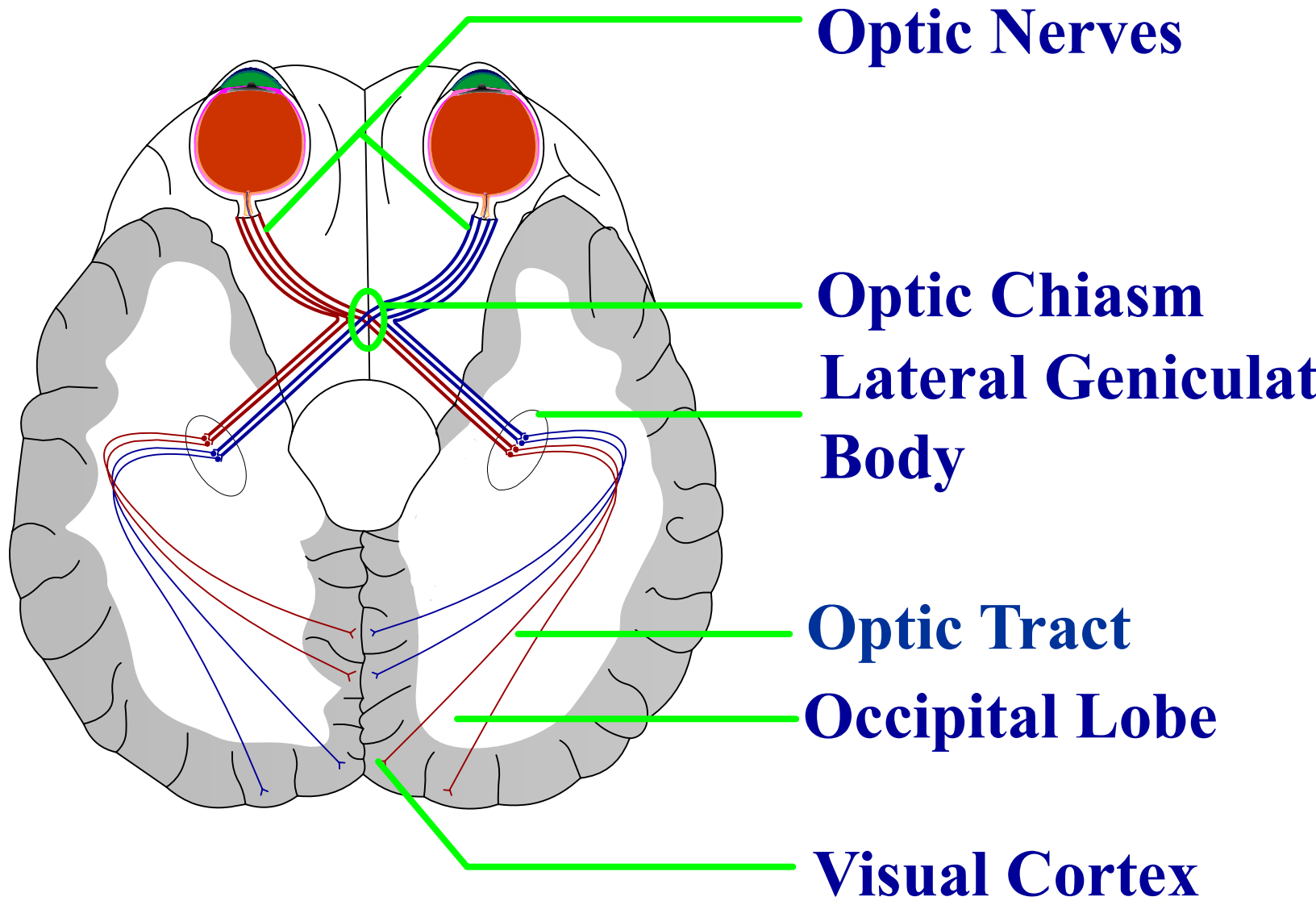
Pressure
A V

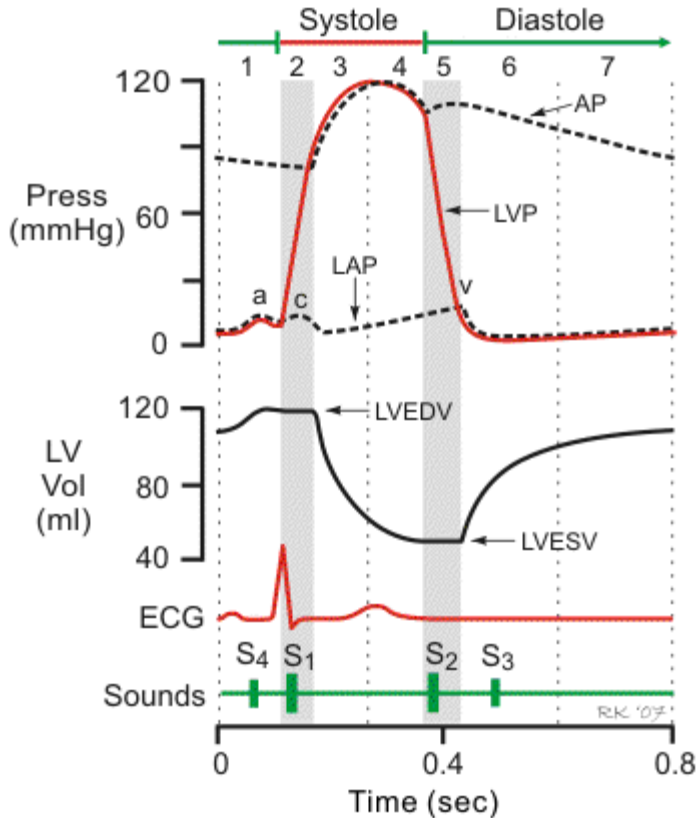


Conductive Diagram of Heart









Cardiovascular Physiology Concepts

The cardiac cycle diagram shown to the right depicts changes in aortic pressure (AP), left ventricular pressure (LVP), left atrial pressure (LAP), left ventricular volume (LV Vol), and heart sounds during a single cycle of cardiac contraction and relaxation. These changes are related in time to the electrocardiogram.

Aortic pressure is measured by inserting a pressure catheter into the aorta from a peripheral artery, and the left ventricular pressure is obtained by placing a pressure catheter inside the left ventricle and measuring changes in intraventricular pressure as the heart beats. Left atrial pressure is not usually measured directly, except in investigational procedures. Ventricular volume changes can be assessed in real time using echocardiography or radionuclide imaging, or by using a special volume conductance catheter placed within the ventricle.

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, the cardiac cycle is usually divided into seven phases. The first phase begins with the P wave of 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 diagram, which contains information on aortic, left ventricular and left atrial pressures, along with ventricular volume, [heart sounds](#) and the electrocardiogram, is shown above. 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

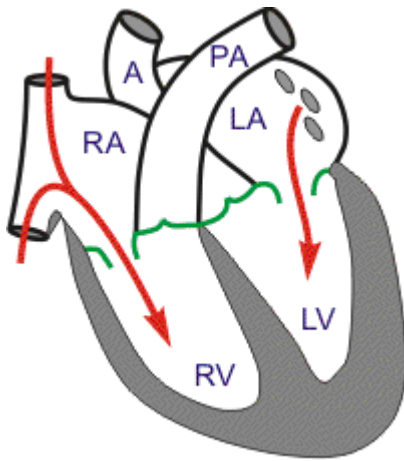
[Phase 5](#) - Isovolumetric Relaxation

[Phase 6](#) - Rapid Filling

[Phase 7](#) - Reduced Filling

Phase 1 - Atrial Contraction

A-V Valves Open; Semilunar Valves Closed

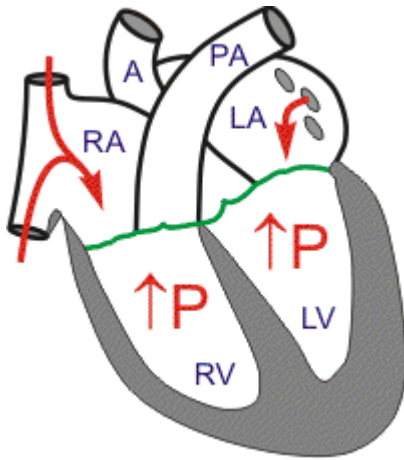


- This is the first phase of the cardiac cycle because it is initiated by the [p wave of the electrocardiogram \(ECG\)](#), which represents electrical depolarization of the atria. Atrial depolarization then causes contraction of the atrial musculature. As the atria contract, the pressure within the atrial chambers increases, which forces more blood flow across the open atrioventricular (AV) valves, leading to a rapid flow of blood into the ventricles. Blood does not flow back into the vena cava because of inertial effects of the venous return and because the wave of contraction through the atria moves toward the AV valve thereby having a "milking effect." However, atrial contraction does produce a small increase in venous pressure that can be noted as the "**a-wave**" of the left atrial pressure (LAP). Just following the peak of the a wave is the **x-descent**.
- Atrial contraction normally accounts for about 10% of left ventricular filling when a person is at rest because most of ventricular filling occurs prior to atrial contraction as blood passively flows from the pulmonary veins, into the left atrium, then into the left ventricle through the open mitral valve. At high heart rates, however, the atrial contraction may account for up to 40% of ventricular filling. This is sometimes referred to as the "atrial kick." The atrial contribution to ventricular filling varies inversely with duration of ventricular diastole and directly with atrial contractility.

- After atrial contraction is complete, the atrial pressure begins to fall causing a pressure gradient reversal across the AV valves. This causes the valves to float upward (pre-position) before closure. At this time, the ventricular volumes are maximal, which is termed the **end-diastolic volume** (EDV). The left ventricular EDV (LVEDV), which is typically about 120 ml, represents the ventricular [preload](#) and is associated with end-diastolic pressures of 8-12 mmHg and 3-6 mmHg in the left and right ventricles, respectively.
 - A [heart sound](#) is sometimes noted during atrial contraction (**fourth heart sound, S₄**). This sound is caused by vibration of the ventricular wall during atrial contraction. Generally, it is noted when the [ventricle compliance](#) is reduced ("stiff" ventricle) as occurs in [ventricular hypertrophy](#) and in many older individuals.
-

Phase 2 - Isovolumetric Contraction

All Valves Closed



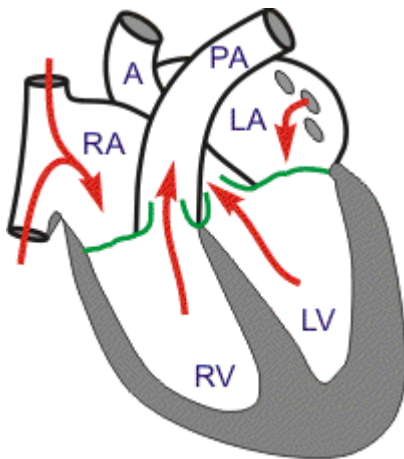
- This phase of the cardiac cycle begins with the appearance of the [QRS complex](#) of the ECG, which represents ventricular depolarization. This triggers [excitation-contraction coupling](#), myocyte contraction and a rapid increase in intraventricular pressure. Early in this phase, the rate of pressure development becomes maximal. This is referred to as **maximal dP/dt** .
- The AV valves close as intraventricular pressure exceeds atrial pressure. Ventricular contraction also triggers contraction of the papillary muscles with their attached chordae tendineae that prevent the AV valve leaflets from bulging back into the atria and becoming incompetent (i.e., "leaky"). Closure of the AV valves results in the **first heart sound (S_1)**. This sound is normally split (~0.04 sec) because mitral valve closure precedes tricuspid closure.
- During the time period between the closure of the AV valves and the opening of the aortic and pulmonic valves, ventricular pressure rises rapidly without a change in ventricular volume (i.e., no ejection occurs). Ventricular volume does not change because all valves are closed during this phase. Contraction, therefore, is said to be "isovolumic" or "isovolumetric." Individual myocyte contraction, however, is not necessarily isometric because individual myocyte are undergoing length changes. Individual fibers contract isotonically (i.e., concentric, shortening contraction), while

others contract isometrically (i.e., no change in length) or eccentrically (i.e., lengthening contraction). Therefore, ventricular chamber geometry changes considerably as the heart becomes more spheroid in shape; circumference increases and atrial base-to-apex length decreases.

- The rate of pressure increase in the ventricles is determined by the rate of contraction of the muscle fibers, which is determined by mechanisms governing [excitation-contraction coupling](#).
- The "**c-wave**" noted in the LAP may be due to bulging of mitral valve leaflets back into left atrium. Just after the peak of the c wave is the **x'-descent**.

Phase 3 - Rapid Ejection

Aortic and Pulmonic Valves Open; AV Valves Remain Closed



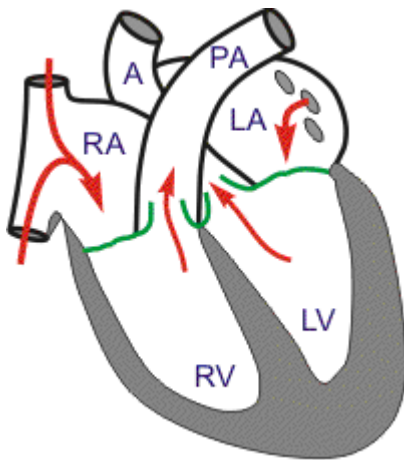
- This phase represents the initial and rapid ejection of blood into the aorta and pulmonary arteries from the left and right ventricles, respectively. Ejection begins when the intraventricular pressures exceed the pressures within the aorta and pulmonary artery, which causes the aortic and pulmonic valves to open. Blood is ejected because the total energy of the blood within the ventricle exceeds the [total energy of blood](#) within the aorta. In other words, there is an energy gradient to propel blood into the aorta and pulmonary artery from their respective ventricles. During this phase,

ventricular pressure normally exceeds outflow tract pressure by a few mmHg. This pressure gradient across the valve is ordinarily low because of the relatively large valve opening (i.e., low resistance). Maximal outflow velocity is reached early in the ejection phase, and maximal (systolic) aortic and pulmonary artery pressures are achieved.

- No heart sounds are ordinarily noted during ejection because the opening of healthy valves is silent. The presence of sounds during ejection (i.e., ejection [murmurs](#)) indicate [valve disease](#) or [intracardiac shunts](#).
- Left atrial pressure initially decreases as the atrial base is pulled downward, expanding the atrial chamber. Blood continues to flow into the atria from their respective venous inflow tracts and the atrial pressures begin to rise, and continue to rise until the AV valves open at the end of phase 5.

Phase 4 - Reduced Ejection

Aortic and Pulmonic Valves Open; AV Valves Remain Closed



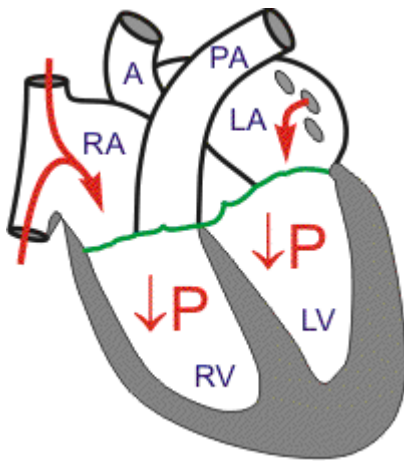
- Approximately 200 msec after the QRS and the beginning of ventricular contraction, [ventricular repolarization](#) occurs as shown by the [T-wave](#) of the electrocardiogram. Repolarization

leads to a decline in ventricular active tension and therefore the rate of ejection (ventricular emptying) falls. Ventricular pressure falls slightly below outflow tract pressure; however, outward flow still occurs due to kinetic (or inertial) energy of the blood.

- Left atrial and right atrial pressures gradually rise due to continued venous return from the lungs and from the systemic circulation, respectively.

Phase 5 - Isovolumetric Relaxation

All Valves Closed



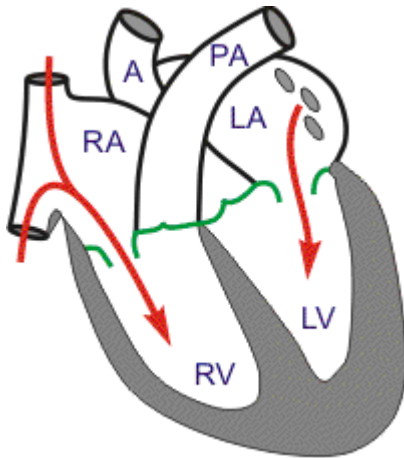
- When the intraventricular pressures fall sufficiently at the end of phase 4, the aortic and pulmonic valves abruptly close (aortic precedes pulmonic) causing the **second heart sound (S₂)** and the beginning of isovolumetric relaxation. Valve closure is associated with a small backflow of blood into the ventricles and a characteristic notch (**incisura** or **dicrotic notch**) in the aortic and pulmonary artery pressure tracings.

- After valve closure, the aortic and pulmonary artery pressures rise slightly (**dicrotic wave**) following by a slow decline in pressure.
- The rate of pressure decline in the ventricles is determined by the rate of relaxation of the muscle fibers, which is termed **lusitropy**. This relaxation is regulated largely by the sarcoplasmic reticulum that are responsible for rapidly re-sequestering calcium following contraction (see [excitation-contraction coupling](#)).
- Although ventricular pressures decrease during this phase, volumes remain constant because all valves are closed. The volume of blood that remains in a ventricle is called the **end-systolic volume** and is ~50 ml in the left ventricle. The difference between the end-diastolic volume and the end-systolic volume is ~70 ml and represents the **stroke volume**.
- Left atrial pressure (LAP) continues to rise because of venous return from the lungs. The peak LAP at the end of this phase is termed the **v-wave**.

Phase 6 - Rapid Filling

Cardiac Cycle - Rapid Filling (Phase 6)

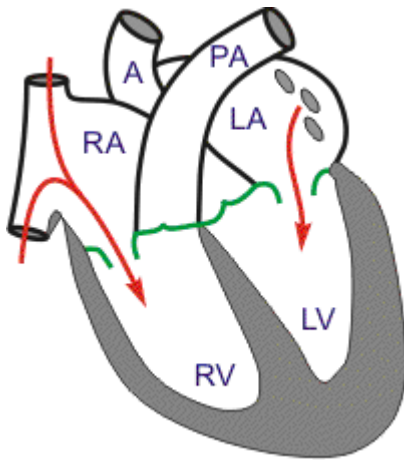
A-V Valves Open



- As the ventricles continue to relax at the end of phase 5, the intraventricular pressures will at some point fall below their respective atrial pressures. When this occurs, the AV valves rapidly open and ventricular filling begins. Despite the inflow of blood from the atria, intraventricular pressure continues to briefly fall because the ventricles are still undergoing relaxation. Once the ventricles are completely relaxed, their pressures will slowly rise as they fill with blood from the atria.
- The opening of the mitral valve causes a rapid fall in LAP. The peak of the LAP just before the valve opens is the **"v-wave."** This is followed by the **y-descent** of the LAP. A similar wave and descent are found in the right atrium and in the jugular vein.
- Ventricular filling is normally silent. When a **third heart sound (S₃)** is audible, it may represent tensing of chordae tendineae and AV ring during ventricular relaxation and filling. This heart sound is normal in children; but is often pathological in adults and caused by [ventricular dilation](#).

Phase 7 - Reduced Filling

A-V Valves Open



- As the ventricles continue to fill with blood and expand, they become less compliant and the intraventricular pressures rise. This reduces the pressure gradient across the AV valves so that the rate of filling falls.
 - In normal, resting hearts, the ventricle is about 90% filled by the end of this phase. In other words, about 90% of ventricular filling occurs before atrial contraction (phase 1).
 - Aortic pressure and pulmonary arterial pressures continue to fall during this period.
-

Arrhythmias

What is an arrhythmia?

The rhythm of the heart is normally generated and regulated by [pacemaker cells](#) within the sinoatrial ([SA](#)) [node](#), which is located within the wall of the right atrium. SA nodal pacemaker activity normally governs the rhythm of the atria and ventricles. Normal rhythm is very regular, with minimal cyclical fluctuation. Furthermore, atrial contraction is always followed by ventricular contraction in the normal heart. When this rhythm becomes irregular, too fast ([tachycardia](#)) or too slow ([bradycardia](#)), or the frequency of the atrial and ventricular beats are different, this is called an arrhythmia. The term "dysrhythmia" is sometimes used and has a similar meaning.

How common are arrhythmias?

About 14 million people in the USA have arrhythmias (5% of the population). The most common disorders are atrial fibrillation and flutter. The incidence is highly related to age and the presence of underlying heart disease; the incidence approaches 30% following open heart surgery.

What are the clinical symptoms?

Patients may describe an arrhythmia as a palpitation or fluttering sensation in the chest. For some types of arrhythmias, a skipped beat might be sensed because the subsequent beat produces a more forceful contraction and a thumping sensation in the chest. A "racing" heart is another description. Proper diagnosis of arrhythmias requires an [electrocardiogram](#), which is used to evaluate the electrical activity of the heart.

Depending on the severity of the arrhythmia, patients may experience dyspnea (shortness of breath), syncope (fainting), fatigue, heart failure symptoms, chest pain or cardiac arrest.

What causes arrhythmias?

A frequent cause of arrhythmia is coronary artery disease because this condition results in myocardial [ischemia](#) or [infarction](#). When cardiac cells lack oxygen, they become depolarized, which lead to [altered impulse formation](#) and/or [altered impulse conduction](#). The former concerns changes in rhythm that are caused by changes in the [automaticity](#) of pacemaker cells or by abnormal generation of action potentials at sites other than the [SA node](#) (termed [ectopic foci](#)). Altered impulse conduction is usually associated with complete or partial block of electrical conduction within the heart. Altered impulse conduction commonly results in [reentry](#), which can lead to [tachyarrhythmias](#). Changes in cardiac structure that accompany heart failure (e.g., dilated or hypertrophied cardiac chambers), can also precipitate arrhythmias. Finally, many different types of drugs (including antiarrhythmic drugs) as well as electrolyte disturbances (primarily K^+ and Ca^{++}) can precipitate arrhythmias.

What are the consequences of arrhythmias?

Arrhythmias can be either benign or more serious in nature depending on the [hemodynamic consequence of the arrhythmia](#) and the possibility of evolving into a lethal arrhythmia. Occasional [premature ventricular complexes](#) (PVCs), while annoying to a patient, are generally considered benign because they have little hemodynamic effect. Consequently, PVCs if not too frequent, are generally not treated. In contrast, [ventricular tachycardia](#) is a serious condition that can lead to heart failure, or worse, to [ventricular fibrillation](#) and death.

How are arrhythmias treated?

When arrhythmias require treatment, they are treated with drugs that suppress the arrhythmia. These drugs are called [antiarrhythmic drugs](#). There are many different types of antiarrhythmic drugs and many different mechanisms of action. Most of the drugs affect ion channels that are involved in the movement of sodium, calcium and potassium ions in and out of the cell. These drugs include mechanistic classes such as [sodium-channel blockers](#), [calcium-channel blockers](#) and [potassium-channel blockers](#). By altering the movement of these important ions, the electrical activity of the cardiac cells (both [pacemaker](#) and [non-pacemaker cells](#)) is altered, hopefully in a manner that suppresses arrhythmias. Other drugs affect autonomic influences on the the heart, which may be stimulating or aggravating arrhythmias. Among these drugs are [beta-blockers](#). More details on drug therapy and specific drugs can be obtained by [clicking here](#).

Cardiac Valve Disease

What are heart valves and what is their function?

[Valves](#) within the heart separate the right atrium and ventricle (tricuspid valve), the left atrium and ventricle (mitral valve), the right ventricle and the pulmonary artery (pulmonic valve), and the left ventricle and aorta (aortic valve) ([click here to see cardiac anatomy diagram](#)). The valves ensure that blood flows in a single pathway through the heart by opening and closing in a particular time sequence during the [cardiac cycle](#). Normal valves permit blood to flow in only one direction, for example, from the right atrium into the right ventricle. When heart valves become diseased or damaged, they may not fully open or close. This can seriously impair cardiac function by causing blood to leak back into cardiac chambers or by requiring heart chambers to contract more forcefully to move blood across a narrowed valve.

What causes valve defects?

A chronic disease process is responsible for defective valves in most older individuals. Sometimes, the disease results from a triggering event many years earlier, such as rheumatic fever. Bacterial infection, viral infection and inflammation of valves can trigger changes in valve structure and function. Normally, valve leaflets are very thin and flexible, but they can become thickened and rigid in response to a disease processes. When this occurs to a valve, it may not be able to fully open or to completely close. Valve disease found in younger individuals is usually due to a congenital defect in the embryologic development of the heart. Valve dysfunction can occur secondarily to other cardiac diseases, such as coronary artery disease, cardiac hypertrophy and cardiac dilation. If coronary artery disease progresses to the point where [papillary muscles](#) become hypoxic or infarcted, then the impaired contractile function of these muscles can lead to a leaky tricuspid or mitral valve. Cardiac [hypertrophy](#) or dilation, by altering cardiac chamber structure and dimensions, can lead to valve dysfunction. Finally, valve dysfunction can also occur if the [chordae tendineae](#) that connect the valve leaflet to the papillary muscle ruptures.

There are two general types of cardiac valve defects: stenosis and insufficiency. Some patients, however, may have a combination of stenosis and insufficiency.

Valvular [stenosis](#) results from a narrowing of the valve orifice that is usually caused by a thickening and increased rigidity of the valve leaflets, often accompanied by calcification. When this occurs, the valve does not open completely as blood flows across it, thereby resulting in a high resistance to flow and the development of a large pressure gradient across the valve when blood is flowing through the valve.

Valvular [insufficiency](#) results from the valve leaflets not completely sealing when the valve is closed so that regurgitation of blood occurs (backward flow of blood) into the proximal chamber.

What are the clinical symptoms of defective valves?

Valvular stenosis and insufficiency can have serious cardiac consequences, and produce the following clinical symptoms:

- Shortness of breath ([dyspnea](#))
 - Fatigue
 - Reduced exercise capacity
 - Light headedness or fainting (syncope)
 - [Heart failure](#)
 - Pulmonary hypertension
 - [Pulmonary/systemic edema](#)
 - [Chest pain \(angina\)](#)
 - [Arrhythmias](#)
 - Blood clots (thromboembolism) which can cause stroke

Coronary Artery Disease

What is the function of coronary arteries?

The [coronary arteries](#) supply blood flow to the heart, and when functioning normally, they ensure adequate oxygenation of the myocardium at all levels of cardiac activity. Constriction and dilation of the coronary arteries, governed primarily by [local regulatory mechanisms](#), regulate the amount of blood flow to the myocardium in a manner that matches the amount of [oxygen delivered](#) to the myocardium with the myocardial [demand for oxygen](#).

What is coronary artery disease?

Coronary artery disease (CAD) causes changes in both structure and function of the blood vessels. Atherosclerotic processes cause an abnormal deposition of lipids in the vessel wall, leukocyte infiltration and vascular inflammation, plaque formation and thickening of the vessel wall. These changes lead to a narrowing of the lumen (i.e., [stenosis](#)), which restricts blood flow. There are also subtle, yet functionally important changes that can occur before overt changes in structure are observed. Early in the disease process, the endothelial cells that line the coronary arteries become dysfunctional. Because the endothelium produces important substances such as [nitric oxide](#) and [prostacyclin](#) that are required for normal coronary function, endothelial dysfunction can lead to coronary [vasospasm](#), impaired relaxation, and formation of blood clots that can partially or completely occlude the vessel.

What are the physiological and clinical consequences of coronary artery disease?

When CAD restricts blood flow to the myocardium ([ischemia](#)) there is an imbalance between [oxygen supply](#) and [oxygen demand](#). When the oxygen supply is insufficient to meet the oxygen demand (reduced [oxygen supply/demand ratio](#)), the myocardium becomes [hypoxic](#). This is often associated with chest pain ([angina](#)) and other clinical symptoms. Severe ischemia can lead to [anoxia](#) and [infarction](#) of the tissue. Furthermore, acute or chronic ischemia caused by CAD can impair cardiac [mechanical](#) and [electrical](#) activities leading to [heart failure](#) and [arrhythmias](#).

How common is coronary artery disease?

About 13 million Americans (~7% of population) have coronary artery disease. About half of all deaths related to cardiovascular disease result from coronary artery disease. Coronary artery disease is the leading cause of death among American men and women, and represents about 20% of all deaths.

How is coronary artery disease treated?

As described above, CAD results in myocardial ischemia, which leads to chest pain ([angina](#)) and cardiac mechanical and electrical dysfunction. The goal in treating CAD is to restore normal coronary perfusion, or if that is not possible, then to reduce the oxygen demand by the heart (i.e., normalize the oxygen supply/demand ratio) so as to minimize myocardial hypoxia. In severe CAD in which one or more coronary arteries is very stenotic, some patients will have a stent implanted within the coronary artery to open up the lumen and restore blood flow. Other patients may undergo coronary artery bypass grafts in which the diseased segment is bypassed using an artery or vein harvested from elsewhere in their body (i.e., internal mammary artery). If the coronary is occluded by a blood clot, a thrombolytic drug may be administered to dissolve the clot. Anti-platelet drugs and anticoagulants are also given to patients with CAD. However, the vast majority of CAD patients are treated with [antianginal drugs](#) that reduce the myocardial oxygen demand by decreasing heart rate, contractility, afterload or preload (e.g., [beta-blockers](#), [calcium-channel blockers](#), [nitrodilators](#)), or they are treated with drugs that many prevent or reverse coronary vasospasm in patients with [variant angina](#). [Click here](#) for more information on drug treatment for CAD and angina.

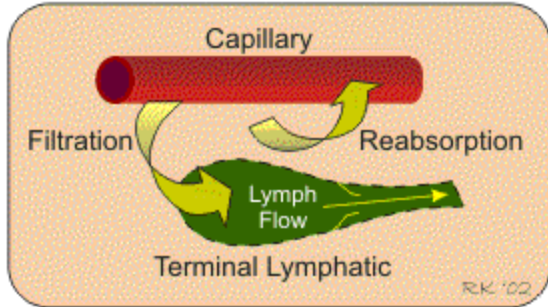
Tissue Edema and General Principles of Transcapillary Fluid Exchange

Edema refers to the swelling of tissues that result from excessive accumulation of fluid within the tissue. Edema can be highly localized as occurs in a small region of the skin subjected to a bee sting. Edema, however, can also comprise an entire limb, specific organs such as the lungs (e.g., [pulmonary edema](#)) or the whole body.

General principles

To understand how edema occurs, it is first necessary to explain the concept of tissue compartments. There are two primary fluid compartments in the body between which fluid is exchanged - the intravascular and extravascular compartments. The **intravascular compartment** contains fluid (i.e., blood) within the cardiac chambers and vascular system of the body. The **extravascular system** is everything outside of the intravascular compartment. Fluid and electrolytes readily move between these two compartments. The extravascular compartment is made up of many subcompartments such as the cellular, interstitial, and lymphatic subcompartments, and a specialized system containing cerebrospinal fluid.

The movement of fluid and accompanying solutes between compartments (mostly water, electrolytes, and smaller molecular weight solutes) is governed by [physical factors](#) such as [hydrostatic](#) and [oncotic](#) forces. These forces are normally balanced in such a manner the fluid volume remains relatively constant between the compartments. If the physical forces or barriers to fluid movement are altered, the volume of fluid may increase in one compartment and decrease in another. In some cases, total fluid volume increases in the body so that both intravascular and extravascular compartments increase in volume. This can occur, for example, when the kidneys fail to excrete sufficient amounts of sodium and water. When the fluid volume within the interstitial compartment increases, this compartment will increase in size leading to tissue swelling (i.e., **edema**). When excess fluid accumulates within the peritoneal space (space between the abdominal wall and organs), this is termed "**ascites**." Pulmonary congestion, which can occur in [heart failure](#) as the left atrial pressure increases and blood backs up in the pulmonary circuit, causes [pulmonary edema](#).



The interstitial volume (bounded area) depends on the rates of filtration, reabsorption, lymph flow, and the compliance of the interstitial compartment.

A model that helps us to understand what causes edema is shown to the right. **Filtration** is the movement of fluid out of the capillary and **reabsorption** is the movement of fluid back into the distal end of the capillary and small venules. In most capillary systems of the body, there is a small [net filtration](#) (typically about 1% of plasma) of fluid from the intravascular to the extravascular compartment. In other words, capillary fluid filtration exceeds reabsorption. This would cause fluid to accumulate within the interstitium over time if it were not for the [lymphatic system](#) that removes

excess fluid from the interstitium and returns it back to the intravascular compartment. Circumstances, however, can arise where net capillary filtration exceeds the capacity of the lymphatics to carry away the fluid (i.e., net filtration > lymph flow). When this occurs, the interstitium will swell with fluid, thereby become edematous.

Factors Precipitating Edema

- Increased [capillary hydrostatic pressure](#) (as occurs when venous pressures become elevated by gravitational forces, in heart failure or with venous obstruction)
- Decreased [plasma oncotic pressure](#) (as occurs with hypoproteinemia during malnutrition)
- Increased [capillary permeability](#) caused by proinflammatory mediators (e.g., histamine, bradykinin) or by damage to the structural integrity of capillaries so that they become more "leaky" (as occurs in tissue trauma, burns, and severe inflammation)
- Lymphatic obstruction (as occurs in filariasis or with tissue injury)

Prevention and Treatment of Edema

The treatment for edema involves altering one or more of the physical factors that regulate fluid movement. For example, in edema (pulmonary or systemic) secondary to [heart failure](#), [diuretic drugs](#) are given to reduce [blood volume](#) and [venous pressure](#). In heart failure patients, improving cardiac output by using [cardiostimulatory](#) or [vasodilators](#) drugs reduces venous and capillary pressures, thereby decreasing filtration and promoting reabsorption of fluid within tissues ([click here](#) to see why increasing cardiac output decreases venous pressure). If a patient suffers from ankle edema, that person will be instructed to keep their feet elevated whenever possible (to diminish the effects of [gravity](#) on capillary pressure), use tight fitting elastic hose (to increase [tissue hydrostatic pressure](#)), and possibly be prescribed a [diuretic](#) drug to enhance fluid removal by the kidneys.

Causes of Heart Failure

- Myocardial infarction
- Coronary artery disease
- Valve disease
- Idiopathic cardiomyopathy
- Viral or bacterial cardiomyopathy
- Myocarditis
- Pericarditis
- Arrhythmias
- Chronic hypertension
- Thyroid disease
- Pregnancy
- Septic shock

Heart Failure – Introduction

What is heart failure?

Heart failure is the inability of the heart to supply adequate blood flow and therefore oxygen delivery to peripheral tissues and organs. Under perfusion of organs leads to reduced exercise capacity, fatigue, and shortness of breath. It can also lead to organ dysfunction (e.g., renal failure) in some patients.

What is the incidence of heart failure and its prognosis?

It is estimated that there are more than 15 million new cases of heart failure each year worldwide. There are about 500,000 new cases of heart failure diagnosed each year in the USA, and ten times that number of Americans currently in heart failure. The numbers are rapidly increasing because of the aging population. Heart failure is the leading cause of hospitalization of patients over 65 years in age.

Despite many new advances in drug therapy and cardiac assist devices, the prognosis for chronic heart failure remains very poor. One year mortality figures are 50-60% for patients diagnosed with severe failure, 15-30% in mild to moderate failure, and about 10% in mild or asymptomatic failure.

What are the causes of chronic heart failure?

Heart failure can be caused by factors originating from within the heart (i.e., intrinsic disease or pathology) or from external factors that place excessive demands upon the heart. Intrinsic disease includes conditions such as dilated cardiomyopathy and hypertrophic cardiomyopathy. External factors that can lead to heart failure include long-term, uncontrolled hypertension, increased [stroke volume](#) (volume load; arterial-venous shunts), hormonal disorders such as hyperthyroidism, and pregnancy.

Acute heart failure develops rapidly and can be immediately life threatening because the heart does not have time to undergo compensatory adaptations. Acute failure (hours/days) may result from cardiopulmonary by-pass surgery, acute infection (sepsis), acute myocardial infarction, valve dysfunction, severe arrhythmias, etc. Acute heart failure can often be managed successfully by pharmacological or surgical interventions. Chronic heart failure is a long-term condition (months/years) that is associated with the heart undergoing adaptive responses (e.g., dilation, hypertrophy) to a precipitating cause. These adaptive responses, however, can be deleterious in the long-term and lead to a worsening condition.

The number one cause of heart failure is [coronary artery disease](#) (CAD). CAD reduces [coronary blood flow](#) and [oxygen delivery](#) to the myocardium. This leads to myocardial [hypoxia](#) and [impaired function](#). Another common cause of heart failure is [myocardial infarction](#), which is the final and often fatal culmination of CAD. Infarcted tissue does not contribute to the generation of mechanical activity so overall cardiac performance is diminished. Furthermore, non-infarcted regions must compensate for the loss of function and this extra burden can precipitate changes that lead to failure. [Valvular disease](#) and congenital defects place increased demands upon the heart that can precipitate failure. Cardiomyopathies, of known origin (e.g., bacterial or viral) or idiopathic (unknown origin), can lead to failure. Myocarditis can have a similar effect. [Arrhythmias](#) such as severe bradycardia or tachycardia can also precipitate failure.

Cardiac and Vascular Changes Accompanying Heart Failure

Cardiac

- Decreased stroke volume and cardiac output
- Increased end-diastolic pressure
- Ventricular dilation or hypertrophy
- Impaired filling (diastolic dysfunction)
- Reduced ejection fraction (systolic dysfunction)

Vascular

- Increased systemic vascular resistance
- Decreased arterial pressure
- Impaired organ perfusion
- Decreased venous compliance
- Increased venous pressure
- Increased blood volume

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Pathophysiology of Heart Failure

Cardiac dysfunction precipitates changes in vascular function, blood volume, and neurohumoral status. These changes serve as compensatory mechanisms to help maintain cardiac output (primarily by the [Frank-Starling mechanism](#)) and arterial blood pressure (by [systemic vasoconstriction](#)). However, these compensatory changes over months and years can worsen cardiac function. Therefore, some of the most effective treatments for chronic heart failure involve modulating non-cardiac factors such as arterial and venous pressures by administering [vasodilator](#) and [diuretic drugs](#).

Cardiac Function

Overall, the changes in cardiac function associated with heart failure result in a decrease in [cardiac output](#). This results from a decline in [stroke volume](#) that is due to systolic dysfunction, diastolic dysfunction, or a combination of the two. Briefly, [systolic dysfunction](#) results from a loss of intrinsic [inotropy](#) (contractility), most likely due to alterations in [signal transduction mechanisms](#) responsible for regulating inotropy. Systolic dysfunction can also result from the loss of viable, contracting muscle as occurs following acute [myocardial infarction](#). [Diastolic dysfunction](#) refers to the diastolic properties of

Compensatory Mechanisms During Heart Failure

Cardiac

- Frank-Starling mechanism
- Ventricular dilation or hypertrophy
- Tachycardia

Autonomic Nerves

- Increased sympathetic adrenergic activity
- Reduced vagal activity to heart

Hormones

- Renin-angiotensin-aldosterone system
- Vasopressin (antidiuretic hormone)
- Circulating catecholamines
- Natriuretic peptides

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the ventricle and occurs when the ventricle becomes less [compliant](#) (i.e., "stiffer"), which impairs ventricular filling. Both systolic and diastolic dysfunction result in a higher [ventricular end-diastolic pressure](#), which serves as a compensatory mechanism by utilizing the [Frank-Starling mechanism](#) to augment stroke volume. In some types of heart failure (e.g., dilated cardiomyopathy), the ventricle dilates as [preload](#) pressures increase in order to to recruit the Frank-Starling mechanism in an attempt to maintain normal stroke volumes.

Therapeutic interventions to improve cardiac function in heart failure include the use of [cardiostimulatory drugs](#) (e.g., [beta-agonists](#) and [digitalis](#)) that stimulate heart rate and contractility, and [vasodilator drugs](#) that reduce [ventricular afterload](#) and thereby enhance stroke volume.

Neurohumoral Status

Neurohumoral responses include activation of [sympathetic nerves](#) and the [renin-angiotensin system](#), and increased release of [antidiuretic hormone](#) (vasopressin) and [atrial natriuretic peptide](#). The net effect of these neurohumoral responses is to produce [arterial vasoconstriction](#) (to help maintain arterial pressure), venous constriction (to increase [venous pressure](#)), and increased [blood volume](#). In general, these neurohumoral responses can be viewed as compensatory mechanisms, but they can also

aggravate heart failure by increasing ventricular [afterload](#) (which depresses stroke volume) and increasing [preload](#) to the point where pulmonary or systemic congestion and [edema](#) occur. Therefore, it is important to understand the pathophysiology of heart failure because it serves as the rationale for drug therapy.

There is also evidence that other factors such as [nitric oxide](#) and [endothelin](#) (both of which are increased in heart failure) may play a role in the pathogenesis of heart failure.

Some drug treatments for heart failure involve attenuating the neurohumoral changes. For example, certain [beta-blockers](#) have been shown to provide significant long-term benefit, quite likely because they block the effects of excessive sympathetic activation on the heart. [Angiotensin-converting enzyme inhibitors](#), [angiotensin receptor blockers](#), and [aldosterone receptor antagonists](#) are commonly used to treat heart failure by inhibiting the actions of the renin-angiotensin-aldosterone system.

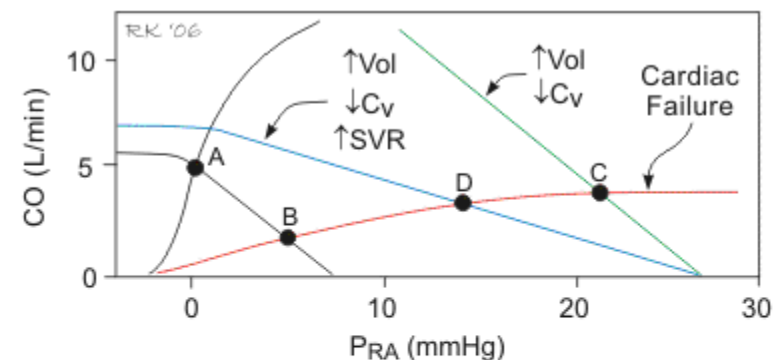
Systemic Vascular Function

In order to compensate for reduced cardiac output during heart failure, feedback mechanisms within the body try to maintain normal arterial pressure by constricting arterial resistance vessels through activation of the [sympathetic adrenergic nervous system](#), thereby increasing [systemic vascular resistance](#). Veins are also constricted to elevate [venous pressure](#). [Arterial baroreceptors](#) are important components of this feedback system. Humoral activation, particularly the [renin-angiotensin system](#) and [antidiuretic hormone](#) (vasopressin) also contribute to systemic vasoconstriction.

Heightened sympathetic activity, and increased circulating angiotensin II and increased vasopressin contribute to an increase in systemic vascular resistance. Drugs that block some of these mechanisms, such as [angiotensin-converting enzyme inhibitors](#), [angiotensin receptor blockers](#), improve ventricular stroke volume by reducing afterload on the ventricle. Arterial and venous [dilators](#) such as [hydralazine](#) and [sodium nitroprusside](#) are also used to reduce afterload on the ventricle.

Blood Volume

In heart failure, there is a compensatory increase in [blood volume](#) that serves to increase ventricular [preload](#) and thereby enhance [stroke volume](#) by the [Frank-Starling mechanism](#). Blood volume is augmented by a number of factors. Reduced renal perfusion results in decreased urine output and



retention of fluid. Furthermore, a combination of reduced renal perfusion and sympathetic activation of the kidneys stimulates the release of renin, thereby activating the [renin-angiotensin system](#). This, in turn, enhances [aldosterone](#) secretion. There is also an increase in circulating [arginine vasopressin](#) (antidiuretic hormone) that contributes to renal retention of water. The final outcome of humoral activation is an increase in renal reabsorption of sodium and water. The resultant increase in blood volume helps to maintain [cardiac output](#); however, the increased volume can be deleterious because it raises [venous pressures](#), which can lead to pulmonary and systemic [edema](#). When edema occurs in the lungs, this can result in [exertional dyspnea](#) (shortness of breath during exertion). Therefore, most patients in heart failure are treated with [diuretic drugs](#) to reduce blood volume and venous pressures in order to reduce edema.

Integration of Cardiac and Vascular Changes

As described above, both systolic and diastolic heart failure lead to changes in systemic vascular resistance, blood volume, and venous pressures. These changes can be examined graphically by using [cardiac and vascular function curves](#) as shown below. The decrease in cardiac performance causes a downward shift in the slope of the cardiac function curve. This alone would lead to an increase in right atrial or central venous pressure (point B) as well as a large decrease in cardiac output. The increase in blood volume and venoconstriction ([decreased venous compliance](#)) causes a parallel shift to the right of the systemic vascular function curve (point C). Because systemic vascular resistance also increases, the slope of the vascular function curve shifts downward (point D). These changes in vascular function, coupled with the downward shift in the cardiac function curve, result in a large increase in right atrial or central venous pressure, which helps to partially offset the large decline in cardiac output that would occur in the absence of the systemic vascular responses. Therefore, the systemic responses help to compensate for the loss of cardiac performance; however, this compensation is at the expense of a large increase in venous pressure that can lead to [edema](#) and at the expense of an increase in systemic vascular resistance that increases the [afterload](#) on the left ventricle, which can further depress its output.

Hypertension – Introduction

High blood pressure, termed "hypertension," is a condition that afflicts almost 1 billion people worldwide and is a leading cause of morbidity and mortality. More than 20% of Americans are hypertensive, and one-third of these Americans are not even aware they are hypertensive. Therefore, this disease is sometimes called the "silent killer." This disease is usually asymptomatic until the damaging effects of hypertension (such as stroke, myocardial infarction, renal dysfunction, visual problems, etc.) are observed.

Definition of hypertension. Hypertensive is defined as an abnormal elevation in [diastolic pressure](#) and/or [systolic pressure](#); [mean arterial pressure](#) is also elevated in hypertension, but it is not usually measured in people. In past years, the diastolic value was emphasized in assessing hypertension. However, elevations in systolic pressure ("systolic hypertension") are also associated with increased incidence of coronary and cerebrovascular disease (e.g., stroke). Therefore, we now recognize that both systolic and diastolic pressure values are important to note. According to the latest U.S. national guidelines ([JNC 7 Report](#))), the following represents different stages of hypertension:

Classification	Systolic (mmHg)	Diastolic (mmHg)
Normal	<120	<80
Prehypertension	120-139	80-89
Stage 1	140-159	90-99
Stage 2	>160	>100

Two classes of hypertension. In 90-95% of patients presenting with hypertension, the cause is unknown. This condition is called [primary \(or essential\) hypertension](#). The remaining 5-10% of

hypertensive patients have hypertension that results secondarily from renal disease, endocrine disorders, or other identifiable causes. This form of hypertension is called [secondary hypertension](#).

Hemodynamic basis of hypertension. Regardless of the origin of hypertension, the actual increase in arterial blood pressure is caused by either an increase in [systemic vascular resistance](#) (SVR) or an increase in [cardiac output](#) (CO). The former is determined by the [vascular tone](#) (i.e., state of constriction) of systemic resistance vessels, whereas the latter is determined by [heart rate](#) and [stroke volume](#). Therefore, in order to understand how arterial blood pressure can become elevated, it is necessary to understand the mechanisms that regulate both SVR and CO.

Treatment of hypertension. Most people with hypertension are treated with [antihypertensive medications](#). In most forms of hypertension, the hypertensive state is maintained by an elevation in [blood volume](#), which in turn increases cardiac output by the [Frank-Starling relationship](#). [Diuretic drugs](#), which enhance the removal of sodium and water by the kidneys and thereby decrease blood volume, are very effective in the treatment of hypertension. Hypertension is also commonly treated with drugs that decrease cardiac output. These [cardioinhibitory drugs](#) either block beta-adrenoceptors on the heart (i.e., [beta-blockers](#)) or L-type calcium channels (i.e., [calcium-channel blockers](#)), which decreases cardiac output by decreasing [heart rate](#) and [contractility \(inotropy\)](#). [Vasodilator drugs](#), which decrease systemic vascular resistance, are also used to treat hypertension. Included in these drugs are alpha-adrenoceptor antagonists ([alpha-blockers](#)), [direct-acting vasodilators](#), [angiotensin-converting enzyme inhibitors](#) and [angiotensin receptor blockers](#). A complete list of drugs used to treat hypertension can be found by [clicking here](#).

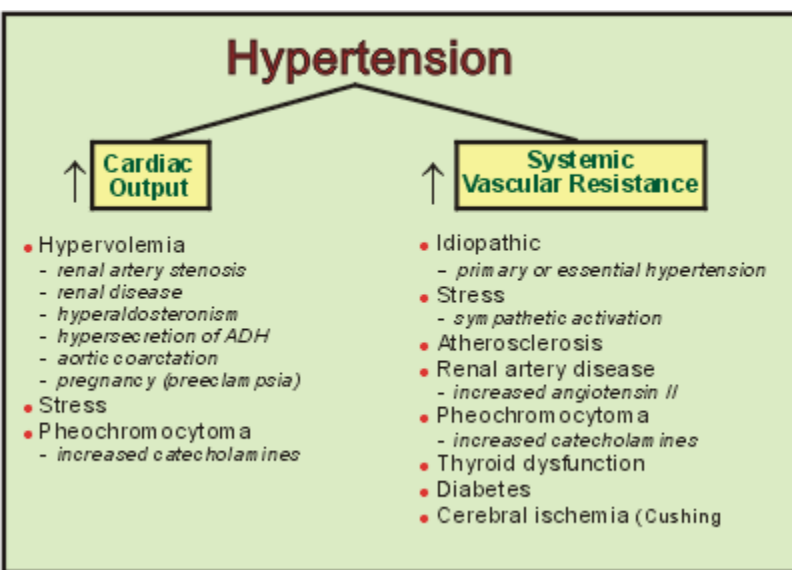
Primary (Essential) Hypertension

There are two broad categories of hypertension - primary (or essential) and secondary hypertension. Approximately 90-95% of patients diagnosed with hypertension have primary hypertension. Unlike [secondary hypertension](#), there is no known cause of primary hypertension. Therefore, the diagnosis of primary hypertension is made after excluding known causes that comprise what is called secondary hypertension.

Despite many years of active research, there is no unifying hypothesis to account for the pathogenesis of primary hypertension. There is a natural progression of this disease that suggests early elevations in [blood volume](#) and [cardiac output](#) might initiate subsequent changes in the systemic vasculature (increased [resistance](#)). This has suggested to some researchers that a basic underlying defect in many hypertensive patients is an inability of the kidneys to adequately handle sodium. Increased sodium retention could then account for the increase in blood volume. In chronic, long-standing hypertension, blood volume and cardiac output are often normal, therefore the hypertension is sustained by an elevation in systemic vascular resistance rather than by an increase in cardiac output. This increased resistance is caused by a thickening of the walls of resistance vessels and by a reduction in lumen diameters. There is also evidence for increased [vascular tone](#). This could be mediated by enhanced [sympathetic activity](#) or by increased circulating levels of [angiotensin II](#). In recent years, considerable evidence has suggested that changes in vascular [endothelial function](#) may cause the increase in vascular tone. For example, in hypertensive patients, the vascular endothelium produces less [nitric oxide](#) and the vascular smooth muscle is less sensitive to the actions of this powerful vasodilator. There is also an increase in [endothelin](#) production, which can enhance vasoconstrictor tone. There is compelling evidence that hyperinsulinemia and hyperglycemia in type 2 diabetes (non-insulin dependent diabetes) causes endothelial dysfunction by enhanced oxygen free radical mediated damage and decreased nitric oxide bioavailability.

Many mechanisms may operate to initiate and sustain hypertension. Treatment of patients with primary hypertension is in reality a pharmacologic intervention to modify factors (e.g., angiotensin II, sympathetic activity, calcium entry into cells) in a way that leads to a reduction in arterial pressure. However, these treatments do not target the cause(s) of the underlying disease. Nevertheless, treatment of hypertension with [antihypertensive drugs](#) is vitally important because hypertension increases the risk for coronary artery disease, stroke, renal disease and other disorders. The three broad classes of drugs used to treat primary hypertension are [diuretics](#) (to reduce blood volume), [vasodilators](#) (to decrease systemic vascular resistance), and [cardioinhibitory drugs](#) (to decrease cardiac output).

Secondary Hypertension



Secondary hypertension accounts for approximately 5-10% of all cases of hypertension, with the remaining being primary hypertension. Secondary hypertension has an identifiable cause whereas primary hypertension has no known cause (i.e., idiopathic).

There are many known conditions that can cause secondary hypertension. Regardless of the cause, arterial pressure becomes elevated either due to an increase in cardiac output, an increase in systemic vascular resistance, or both. When cardiac output is elevated, it is generally due to either increased [neurohumoral activation](#) of the heart or increased [blood volume](#).

Patients with [secondary hypertension](#) are best treated by controlling or removing the underlying disease or pathology, although they may still require [antihypertensive drugs](#).

Some causes for secondary hypertension are listed below:

- [Renal artery stenosis](#)
- [Chronic renal disease](#)
- [Primary hyperaldosteronism](#)
- [Stress](#)
- [Sleep apnea](#)
- [Hyper- or hypothyroidism](#)
- [Pheochromocytoma](#)
- [Preeclampsia](#)
- [Aortic coarctation](#)

Renal artery stenosis (renovascular disease)

Renal artery disease can cause narrowing of the vessel lumen ([stenosis](#)). The reduced lumen diameter increases the pressure drop along the length of the diseased artery, which reduces the pressure at the afferent arteriole in the kidney. Reduced arteriolar pressure and reduced renal perfusion stimulate [renin](#) release by the kidney. This increases circulating [angiotensin II](#) (AII) and [aldosterone](#). These hormones increase blood volume by enhancing renal reabsorption of sodium and water. Increased AII causes systemic vasoconstriction and enhances sympathetic activity. Chronic elevation of AII promotes cardiac and vascular hypertrophy. The net effect of these renal mechanisms is an increase in [blood volume](#) that augments cardiac output by the [Frank-Starling mechanism](#). Therefore, hypertension caused by renal artery stenosis results from both an increase in systemic vascular resistance and an increase in cardiac output.

Chronic renal disease

Any number of pathologic processes (e.g., diabetic nephropathy, glomerulonephritis) can damage nephrons in the kidney. When this occurs, the kidney cannot excrete normal amounts of sodium which leads to sodium and water retention, increased [blood volume](#), and increased cardiac output by the [Frank-Starling mechanism](#). Renal disease may also result in increased release of [renin](#) leading to a renin-dependent form of hypertension. The elevation in arterial pressure secondary to renal disease can be viewed as an attempt by the kidney to increase renal perfusion and restore glomerular filtration.

Primary hyperaldosteronism

Increased secretion of aldosterone generally results from adrenal adenoma or adrenal hyperplasia. Increased circulating [aldosterone](#) causes renal retention of sodium and water, so [blood volume](#) and arterial pressure increase. Plasma [renin](#) levels are generally decreased as the body attempts to suppress the renin-angiotensin system; there is also hypokalemia associated with the high levels of aldosterone.

Stress

Emotional stress leads to activation of the [sympathetic nervous system](#), which causes increased release of norepinephrine from sympathetic nerves in the heart and blood vessels, leading to increased cardiac

output and increased systemic vascular resistance. Furthermore, the adrenal medulla secretes more [catecholamines](#) (epinephrine and norepinephrine). Activation of the sympathetic nervous system increases circulating [angiotensin II](#), [aldosterone](#), and [vasopressin](#), which can increase systemic vascular resistance. Prolonged elevation of angiotensin II and catecholamines can lead to cardiac and vascular hypertrophy, both of which can contribute to a sustained increase in blood pressure.

Sleep Apnea

Sleep apnea is a disorder in which people repeatedly stop breathing for short periods of time (10-30 seconds) during their sleep. This condition is often associated with obesity, although it can have other causes such as airway obstruction or disorders of the central nervous system. These individuals have a higher incidence of hypertension. The mechanism of hypertension may be related to sympathetic activation and hormonal changes associated with repeated periods of apnea-induced hypoxia and hypercapnea, and from stress associated with the loss of sleep.

Hyper- or hypothyroidism

Excessive thyroid hormone induces systemic vasoconstriction, an increase in blood volume, and increased cardiac activity, all of which can lead to hypertension. It is less clear why some patients with hypothyroidism develop hypertension, but it may be related to decreased tissue metabolism reducing the release of [vasodilator metabolites](#), thereby producing vasoconstriction and increased systemic vascular resistance.

Pheochromocytoma

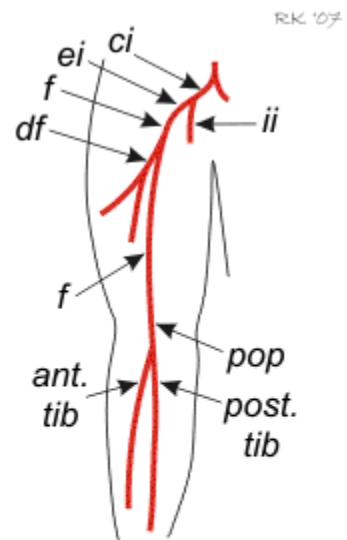
Catecholamine secreting tumors in the adrenal medulla can lead to very high levels of circulating [catecholamines](#) (both epinephrine and norepinephrine). This leads to [alpha-adrenoceptor](#) mediated systemic vasoconstriction and [beta-adrenoceptor](#) mediated cardiac stimulation, both of which contribute to significant elevations in arterial pressure.. Despite the elevation in arterial pressure, tachycardia occurs because of the direct effects of the catecholamines on the heart and vasculature. Excessive beta-adrenoceptor stimulation in the heart often leads to [arrhythmias](#). The pheochromocytoma is diagnosed by measuring plasma or urine catecholamine levels and their metabolites (vanillylmandelic acid and metanephrine).

Preeclampsia

This is a condition that sometimes develops during the third trimester of pregnancy that causes hypertension due to increased [blood volume](#) and tachycardia. The former increases cardiac output by the [Frank-Starling mechanism](#).

Aortic coarctation

Coarctation, or narrowing of the aorta (typically just distal to the left subclavian artery), is a congenital defect that obstructs aortic outflow leading to elevated pressures proximal to the coarctation (i.e., elevated arterial pressures in the head and arms). Distal pressures, however, are not necessarily reduced as would be expected from the hemodynamics associated with a [stenosis](#). The reason for this is that reduced systemic blood flow, and in particular reduced renal blood flow, leads to an increase in the release of renin and an activation of the [renin-angiotensin-aldosterone system](#). This in turn elevates blood volume and arterial pressure. Although the aortic arch and carotid sinus [baroreceptors](#) are exposed to higher than normal pressures, the baroreceptor reflex is blunted due to structural changes in the walls of vessels where the baroreceptors are located. Also, baroreceptors become desensitized to chronic elevation in pressure and become "reset" to the higher pressure.



ci = common iliac artery
ei = external iliac artery
ii = internal iliac artery
f = femoral artery
df = deep femoral artery
pop = popliteal artery
ant. tib = anterior tibial artery
post. tib = posterior tibial artery

Peripheral Arterial Occlusive Disease

Peripheral arterial occlusive disease (PAOD) results either from atherosclerotic or inflammatory processes causing lumen narrowing (stenosis), or from thrombus formation (usually associated with underlying atherosclerotic disease). When these conditions arise, there is an increase in [vessel resistance](#) that can lead to a reduction in distal perfusion pressure and blood flow. The following discussion assumes chronic atherosclerotic conditions in the human lower limb that result in stenotic lesions. The hemodynamics and underlying mechanisms of PAOD in the human limb are very similar to what is found in [coronary artery disease](#).

A common site for PAOD is in the leg (see figure at right). The circulation to the leg is derived from the femoral artery that is a continuation of the external iliac artery. A major branch from the femoral artery is the deep femoral artery. Distal to the deep femoral branch, the femoral artery (sometimes referred to as the superficial femoral artery at this point) continues down the leg and becomes the popliteal artery just above the knee. Two major arteries at the termination of the popliteal artery are the anterior and posterior tibial arteries, which supply blood flow to the lower leg and foot.

The process of atherosclerosis causes intimal thickening and plaque formation, which decrease the effective radius of the afflicted arterial segment. Although atherosclerosis is generally a diffuse process affecting all of the arteries to some degree, some arterial segments in the limb often undergo greater stenosis than others. Therefore, it is common to find stenotic lesions associated with specific arteries such as the external iliac or femoral artery.

Based on [Poiseuille's equation](#), a decrease in vessel radius will increase the resistance to the fourth power of the change in radius. Therefore, a 50% reduction in radius (one-half radius) will cause the resistance to increase by a factor of 16. [Hydrodynamically](#), this would cause flow to decrease by a factor of 16 assuming the pressure gradient is constant, [laminar flow](#) conditions prevail, and that the resistance of this segment represents the total resistance to flow (i.e., the segment is not one of multiple [in-series](#) segments). However, because the major arteries of the limb circulation are both [in-series and in-parallel](#), a stenotic lesion generally has to have its radius decreased by more than 60% to result in a significant hemodynamic effect (i.e., [critical stenosis](#)). Furthermore, for any given reduction

in radius, the longitudinal [pressure drop](#) along the length of the lesion will be significantly enhanced by the presence of [turbulence](#).

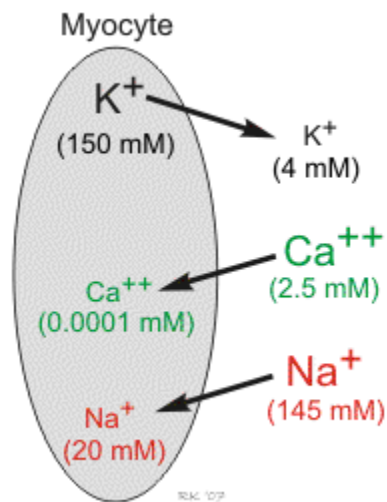
PAOD can lead to limb [ischemia](#). In mild to moderate PAOD, the increased resistance to flow will lead to decreased flow capacity during limb exercise (i.e., decreased [active hyperemia](#)). This can result in ischemic pain during exercise that is termed [intermittent claudication](#). The pain is caused by tissue hypoxia that results from the high [oxygen demand](#) that is not met by an adequate increase in [oxygen delivery](#) (i.e., increased blood flow). In other words, there is a reduction in the [oxygen supply/demand ratio](#). Metabolites formed under anaerobic conditions in the muscle can stimulate pain receptors in the muscle. Also associated with the relative ischemia during exercise is muscle weakness and fatigue.

Stenotic arterial lesions may or may not alter resting blood flow. Atherosclerosis is a disease process that occurs over years. The circulation distal to a stenotic lesion will often undergo [collateralization](#) which reduces resistance and thereby maintains normal resting blood flow despite a reduced perfusion pressure. Furthermore, even acute reductions in perfusion pressure lead to a fall in distal vascular resistance and normalization of blood flow by the mechanism of [autoregulation](#).

[CLICK HERE](#) to learn more about the hemodynamics associated with single and multiple stenotic lesions in the limb

Cardiac Electrophysiology Tutorial

Membrane Potentials



If a voltmeter is attached to the two terminals of a battery, a voltage difference will be measured across the two terminals. Likewise, if a voltmeter is used to measure voltage across the cell membrane (inside versus outside) of a cardiomyocyte, it will be found that the inside of the cell has a negative voltage (measured in millivolts; mV) with respect to the outside of the cell (which is referenced as 0 mV). Under resting conditions, this is called the **resting membrane potential**. With appropriate stimulation of the cell, this negative voltage inside the cell (negative membrane potential) may transiently become positive owing to the generation of an **action potential**. Membrane potentials result from a separation of positive and negative charges (ions) across the membrane, similar to the plates within a battery that separate positive and negative charges.

Membrane potentials in cells are determined primarily by three factors: 1) the concentration of ions on the inside and outside of the cell; 2) the permeability of the cell membrane to those ions (i.e., [ion conductance](#)) through specific [ion channels](#); and 3) by the activity of electrogenic pumps (e.g., [Na⁺/K⁺-ATPase](#) and [Ca⁺⁺ transport pumps](#)) that maintain the ion concentrations across the membrane.

Cardiac cells, like all living cells, have different concentrations of ions across the cell membrane, the most important of which are Na⁺, K⁺, Cl⁻, and Ca⁺⁺ (see figure to right). There are also negatively charged proteins within the cell to which the cell membrane is impermeable. In a cardiac cell, the concentration of K⁺ is high inside the cell and low outside. Therefore, there is a chemical gradient for K⁺ to diffuse out of the cell. The opposite situation is found for Na⁺ and Ca⁺⁺ where their chemical gradients (high outside, low inside concentrations) favor an inward diffusion.

Potassium ion. To understand how a membrane potential is generated, first consider a hypothetical cell in which K⁺ is the only ion across the membrane other than the large negatively charged proteins inside of the cell. Because the cell has [potassium channels](#) through which K⁺ can move in and out of the cell, K⁺ diffuses down its chemical gradient (out of the cell) because its concentration is much higher inside the cell than outside. As K⁺ (a positively charged ion) diffuses out of the cell, it leaves behind negatively charged proteins. This leads to a separation of charges across the membrane and therefore a potential difference across the membrane. Experimentally it is possible to prevent the K⁺ from diffusing out of the cell. This can be achieved by applying a negative charge to the inside of the cell that prevents the positively charged K⁺ from leaving the cell. The negative charge across the membrane that would be necessary to oppose the movement of K⁺ down its concentration gradient is termed the **equilibrium potential for K⁺** (E_K; **Nernst potential**). The Nernst potential for K⁺ can be calculated as follows:

$$E_K = -61 \log [K^+]_i / [K^+]_o = -96 \text{ mV}$$

(where [K⁺]_i = 150 mM and [K⁺]_o = 4 mM)

The E_K represents the electrical potential necessary to keep K⁺ from diffusing out of the cell, down its chemical gradient. If the outside K⁺ concentration were increased from 4 to 40 mM, then the chemical gradient driving K⁺ out of the cell would be reduced, and therefore the membrane potential required to maintain electrochemical equilibrium (E_K) would be less negative according to the Nernst relationship. In this example, the E_K becomes -35 mV when the outside K⁺ concentration is 40 mM. In other words, when

K^+ is elevated 10-fold outside of the cell, the chemical gradient driving K^+ out of the cell is reduced and therefore a less negative voltage is required to keep K^+ from diffusing out of the cell.

The resting potential for a ventricular myocyte is about -90 mV, which is near the equilibrium potential for K^+ when extracellular K^+ concentration is 4 mM. Since the equilibrium potential for K^+ is -96 mV and the resting membrane potential is -90 mV, there is a net driving force (difference between membrane potential and equilibrium potential) of 6 mV acting on the K^+ . The membrane potential is more positive than the equilibrium potential, therefore the net driving force is outward due to K^+ having a positive charge. Because the resting cell has a finite permeability to K^+ and the presence of a small net outward driving force acting upon K^+ , there is a slow outward leak of K^+ from the cell. If K^+ continued to leak out of the cell, its chemical gradient would be lost over time; however, a [Na⁺/K⁺-ATPase pump](#) brings the K^+ back into the cell and thereby maintains the K^+ chemical gradient.

Sodium and calcium ions. Because the Na^+ concentration is higher outside the cell, this ion diffuses down its chemical gradient into the cell. Experimentally, this inward diffusion of Na^+ can be prevented by applying a positive charge to the inside of the cell. When this positive charge counterbalances the chemical diffusion force driving Na^+ into the cell, there will be no net movement of Na^+ into the cell, and Na^+ will therefore be in electrochemical equilibrium. The membrane potential required to produce this electrochemical equilibrium is called the **equilibrium potential for Na⁺** (E_{Na}) and is calculated by:

$$E_{Na} = -61 \log [Na^+]_i / [Na^+]_o = +52 \text{ mV}$$

(where $[Na^+]_i = 20 \text{ mM}$ and $[Na^+]_o = 145 \text{ mM}$)

The positive E_{Na} means that in order to balance the inward directed chemical gradient for Na^+ , the cell interior needs to be +52 mV to prevent Na^+ from diffusing into the cell. At a resting membrane potential of -90 mV, there is not only a large chemical driving force, but also a large electrical driving force acting upon external Na^+ to cause it to diffuse into the cell. The difference between the membrane potential and the equilibrium potential (-142 mV) represents the net electrochemical force driving Na^+ into the cell at resting membrane potential. At rest, however, the permeability of the membrane to Na^+ is very low so that only a small amount Na^+ leaks into the cell. During an [action potential](#), the cell membrane becomes more permeable to Na^+ , which increases sodium entry into the cell through [sodium channels](#). At the peak of the action potential in a cardiac cell (e.g., ventricular myocyte), the membrane potential is approximately +20 mV. Therefore, while the resting potential is far removed from the E_{Na} , the peak of the

action potential approaches E_{Na} . Because a small amount of Na^+ enters the cell at rest, and a relatively large amount of Na^+ enters during action potentials, a [Na⁺/K⁺-ATPase pump](#) is required to transport Na^+ out of the cell (in exchange for K^+) in order to maintain the chemical gradient for Na^+ .

Similar to Na^+ , there is a large Ca^{++} concentration difference across the cell membrane. Therefore, Ca^{++} diffuses into the cell through [calcium channels](#). Applying the Nernst equation to the calcium concentrations given in the figure results in an equilibrium potential of +134 mV. This value also includes that the fact that Ca^{++} is a divalent instead of a monovalent cation. Because the equilibrium potential is much more positive than the resting membrane potential, there is a net electrochemical force trying to drive Ca^{++} into the cell, which occurs when the calcium channels are open.

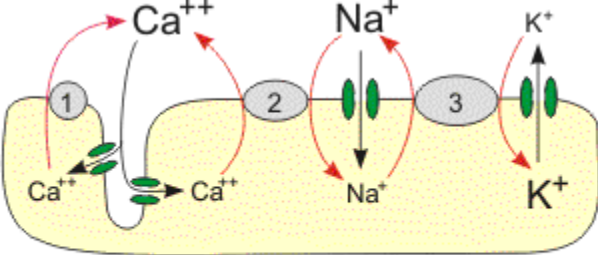
The above discussion shows how changes in the concentration of individual ions across the membrane can alter the membrane potential. However, to fully understand how multiple ions affect the membrane potential, and ultimately how the membrane potential changes during action potentials, it is necessary to learn how changes in membrane ion permeability, that is, changes in [ion conductance](#), affect the membrane potential. Furthermore, electrogenic ion pumps such as the [Na⁺/K⁺-ATPase pump](#) contribute to the membrane potential as they transport ions across the membrane to maintain the ion concentrations across the membrane.

Normal and abnormal cardiac rhythm

Na^+/K^+ -ATPase

Under resting conditions, Na^+ slowly leaks into the cells and K^+ leaks out of the cell because of [electrochemical driving forces](#). Whenever an action potential is generated, additional Na^+ enters the cell and K^+ leaves the cell. While the number of ions moving across the sarcolemmal membrane in a single action potential is very small relative to the total number of ions, after many action potentials are generated, there would occur a significant change in the extracellular and intracellular concentration of these ions. To maintain the concentration gradients for Na^+ and K^+ , it is necessary to transport Na^+ out of the cell and K^+ back into the cell. There is located on the sarcolemma an energy dependent (ATP-dependent) pump system (**Na^+/K^+ -ATPase**) that performs this function. This pump is essential for the maintenance of Na^+ and K^+ concentrations across the membrane. If this pump stops working (as occurs under anoxic conditions when ATP is lost), or if the activity of the pump is inhibited (as occurs with cardiac glycosides such as [digitalis](#)), Na^+ accumulates within the cell and intracellular K^+ falls. This causes depolarization of the resting membrane potential. Furthermore, it is important to note that this pump is electrogenic in nature because it extrudes 3 Na^+ for every 2 K^+ entering the cell. By pumping more positive charges out of the cell than into the cell, the pump activity creates a negative potential within the cell. This potential may be up to -10 mV. Inhibition of this pump, therefore, causes depolarization resulting not only from changes in Na^+ and K^+ concentration gradients, but also from the loss of an electrogenic component of the membrane potential. Small increases in external K^+ can stimulate the pump activity and thereby cause hyperpolarization, which is the opposite of what would be predicted by the [Nernst equation](#) for a small increase in external K^+ .

Because Ca^{++} enters the cell during action potentials, it is necessary to maintain its concentrations gradients. This is accomplished by [calcium pumps and exchangers](#) on the membrane.



- 1 = ATP-dependent Ca⁺⁺ pump
- 2 = Na⁺/Ca⁺⁺ exchanger (3:1)
- 3 = Na⁺/K⁺-ATPase pump (3:2)

Calcium Exchange

Intracellular calcium concentrations in both cardiac and vascular smooth muscle cells range from 10^{-7} to 10^{-5} M. Extracellular concentration of calcium is about 2×10^{-3} M (2 mM). Therefore, there is a chemical gradient for

calcium to diffuse into the cell. Because cells have a negative [resting membrane potential](#) (about -90 mV in a cardiac myocyte), there is also an electrical force driving calcium into the cell. However, except during [action potentials](#) when the cell membrane permeability to calcium increases, there is little leakage of calcium into the cell. The calcium that enters the cell during action potentials (e.g., during depolarization of [pacemaker](#) and [non-pacemaker](#) cardiac cells) must be removed from the cell otherwise an accumulation of calcium would lead to cellular dysfunction.

Calcium is removed from cells by two basic mechanisms. The first mechanism involves an **ATP-dependent Ca⁺⁺ pump** that actively removes calcium from the cell (see figure at right). The second mechanism is the **sodium-calcium exchanger**. The exact mechanism by which this exchanger works is unclear. It is known that calcium and sodium can move in either direction across the sarcolemma. Furthermore, three sodium ions are exchanged for each calcium, therefore an electrogenic potential is generated by this exchanger. The direction of movement of these ions (either inward or outward) depends upon the membrane potential and the chemical gradient for the ions. When the membrane potential is negative (e.g., in resting cells), the exchanger transports Ca⁺⁺ out as Na⁺ enters the cell. When the cell is depolarized and has a positive membrane potential, the exchanger works in the opposite direction (i.e., Na⁺ leaves and Ca⁺⁺ enters the cell).

We also know that an increase in intracellular sodium concentration leads to an increase in intracellular calcium concentration through this exchange. This has important physiological implications. One example of this occurring is when the activity of the [Na⁺/K⁺-ATPase pump](#) is decreased. This energy requiring, ATP-dependent pump transports sodium out of the cell and potassium into the cell. When the activity of this pump is reduced, for example, by cellular [hypoxia](#) (which causes ATP levels to fall) or by chemical inhibitors of this pump such as [digitalis](#), then intracellular Na⁺ concentrations increase. One way to envision how this affects Ca⁺⁺ exchange is that the increased intracellular Na⁺ reduces the concentration gradient of Na⁺ across the sarcolemma, which reduces the inward movement of Na⁺ down its concentration gradient via the exchanger. This, in turn, reduces the outward movement and exchange of Ca⁺⁺, which leads to an accumulation of intracellular calcium. This is the mechanism by

which digitalis increases cardiac [inotropy](#). Under hypoxic conditions, the enhanced calcium concentrations cannot increase inotropy because of the lack of ATP; however, the increased intracellular calcium (termed calcium overload) can damage mitochondria and alter cellular function.

Ionic Conductances

Ions move across the cell membrane through specific [ion channels](#). When these channels open, the permeability and electrical conductance to their respective ion increases, which leads to a change in the membrane potential.

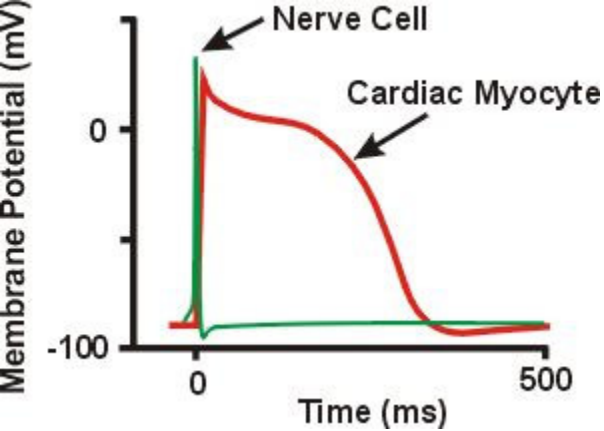
The [membrane potential](#) in a resting cell is near the [equilibrium potential for K⁺](#). That occurs because the membrane is relatively more permeable in the resting state to K⁺ than to the other ionic species such as Na⁺ (or Ca⁺⁺). Therefore, the membrane potential reflects not only the concentration gradients of individual ions (i.e., the equilibrium potentials), but also the relative permeability of the membrane to those ions. If the membrane has a very high permeability to one ion over all the others, then that ion will have a greater influence on determining the membrane potential. One way to express this relationship is as follows:

$$E_m = g'_K E_K + g'_{Na} E_{Na} + g'_{Ca} E_{Ca} + g'_{Cl} E_{Cl}$$

The membrane potential (E_m) depends on the sum of the individual equilibrium potentials times the relative membrane conductance of each ionic species. The relative conductance (g'_x) of a given ionic species is the conductance for that single ion divided by the total conductance for all of the ionic species (i.e., $g'_x = g_x/g_{Total}$).

If the equilibrium potential values for a typical myocyte are incorporated into the equation describing E_m , then

$$E_m = g'_K (-96 \text{ mV}) + g'_{Na} (+52 \text{ mV}) + g'_{Ca} (+134 \text{ mV}) + g'_{Cl} (-90 \text{ mV})$$



In a cardiac cell, the individual ion concentration gradients change very little, even when Na^+ and Ca^{++} enter the cell, and K^+ leaves the cell during [action potentials](#). Therefore, changes in E_m are primarily due to changes in ionic conductances and the associated changes in ion currents. For example, in a resting cell, g_K is very high relative to all the other ionic conductances so the E_m is near the E_K . At the peak of an action potential, g_{Na} is very high relative to the other ions, therefore the E_m approaches E_{Na} . In the heart, the most important ions determining the membrane potential are Na^+ , K^+ and Ca^{++} .

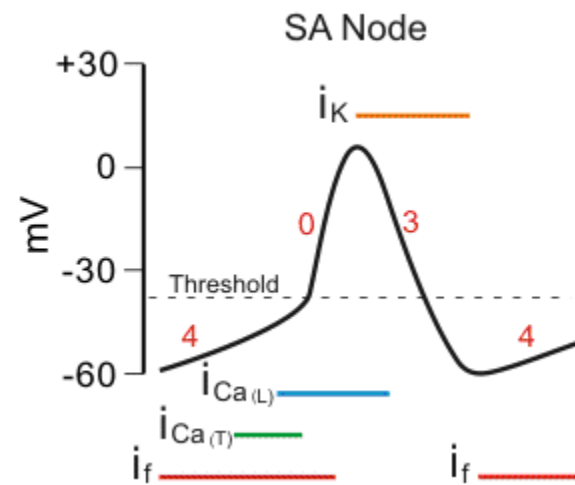
Ion conductances are altered by [antiarrhythmic drugs](#) that block specific ion channels. [Sodium-channel blockers](#) such as quinidine inactivate fast-sodium channels and thereby reduce the conductance of sodium ions into the cell. [Calcium-channel blockers](#) such as verapamil and diltiazem decrease calcium conductance into the cell. [Potassium-channel blockers](#) decrease potassium conductance.

Action Potentials

Many cells in the body have the ability to undergo a transient [depolarization and repolarization](#) that is either triggered by external mechanisms (e.g., motor nerve stimulation of skeletal muscle or cell-to-cell depolarization in the heart) or by intracellular, spontaneous mechanisms (e.g., cardiac pacemaker cells).

There are two general types of cardiac action potentials. [Non-pacemaker action potentials](#), also called "fast response" action potentials because of their rapid depolarization, are found throughout the heart except for the pacemaker cells. The [pacemaker cells](#) generate spontaneous action potentials that are also termed "slow response" action potentials because of their slower rate of depolarization. These are found in the [sinoatrial and atrioventricular nodes](#) of the heart.

Both types of action potentials in the heart differ considerably from action potentials found in neural and skeletal muscle cells. One major difference is in the duration of the action potentials. In a typical nerve, the action potential duration is about 1 ms. In skeletal muscle cells, the action potential duration is approximately 2-5 ms. In contrast, the duration of cardiac action potentials range from 200



to 400 ms. Another difference between cardiac and nerve and muscle action potentials is the role of calcium ions in depolarization. In nerve and muscle cells, the depolarization phase of the action potential is caused by an opening of sodium channels. This also occurs in non-pacemaker cardiac cells. However, in cardiac [pacemaker cells](#), calcium ions are involved in the initial depolarization phase of the action potential. In [non-pacemaker cells](#), calcium influx prolongs the duration of the action potential and produces a characteristic [plateau phase](#).

Sinoatrial Node Action Potentials

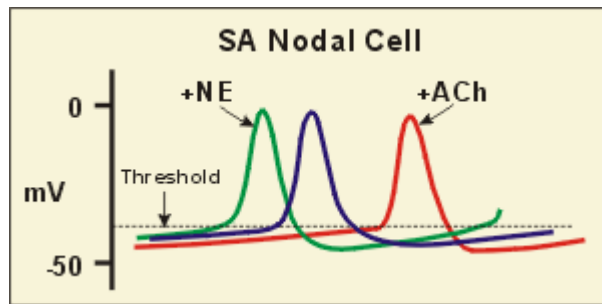
Cells within the sinoatrial (SA) node are the primary pacemaker site within the heart. These cells are characterized as having no true [resting potential](#), but instead generate regular, spontaneous action potentials. Unlike [non-pacemaker action potentials](#) in the heart, and most other cells that elicit action potentials (e.g., nerve cells, muscle cells), the depolarizing current is carried primarily by relatively slow, inward Ca^{++} currents instead of by [fast \$\text{Na}^+\$](#) currents. There are, in fact, no fast Na^+ channels and currents operating in SA nodal cells. This results in a slower action potentials in terms of how rapid they depolarize. Therefore, these pacemaker action potentials are sometimes referred to as "slow response" action potentials.

SA nodal action potentials are divided into three phases. **Phase 4** is the spontaneous depolarization (pacemaker potential) that triggers the action potential once the membrane potential reaches threshold between -40 and -30 mV). **Phase 0** is the depolarization phase of the action potential. This is followed by **phase 3** repolarization. Once the cell is completely repolarized at about -60 mV, the cycle is spontaneously repeated.

The changes in membrane potential during the different phases are brought about by changes in the movement of ions (principally Ca^{++} and K^+ , and to a lesser extent Na^+) across the membrane through [ion channels](#) that open and close at different times during the action potential. When a channel is opened, there is increased [electrical conductance](#) (g) of specific ions through that ion channel. Closure of ion

channels causes ion conductance to decrease. As ions flow through open channels, they generate electrical currents (i or I) that change the membrane potential.

Regulation of Pacemaker Activity



The SA node displays intrinsic automaticity ([spontaneous pacemaker activity](#)) at a rate of 100-110 action potentials ("beats") per minute. This intrinsic rhythm is primarily influenced by [autonomic nerves](#), with vagal influences being dominant over sympathetic influences at rest. This "**vagal tone**" reduces the resting heart rate down to 60-80 beats/min. The SA node is predominantly innervated by efferent branches of the right vagus nerves, although some innervation from the left vagus is often observed. Experimental denervation of the right vagus to the heart leads to an abrupt increase in SA nodal firing rate if the resting heart rate is below 100 beats/min. A similar response is noted when a drug such as [atropine](#) is administered. This drug blocks vagal transmission at the SA node by antagonizing the [muscarinic receptors](#) that bind to acetylcholine, which is the neurotransmitter released by the vagus nerve.

Parasympathetic (vagal) activation, which releases acetylcholine (ACh) onto the SA node, decreases pacemaker rate by increasing gK^+ and decreasing slow inward gCa^{++} and gNa^+ ; the pacemaker current (I_f) is suppressed. These ionic conductance changes decrease the slope of [phase 4](#) of the action potential, thereby increasing the time required to reach threshold. Vagal activity also hyperpolarizes the pacemaker cell during Phase 4, which results in a longer time to reach threshold voltage.

The rate of SA nodal firing can be altered by:

1. changes in autonomic nerve activity (sympathetic and vagal)

To increase heart rate, the autonomic nervous system increases sympathetic outflow to the SA node, with concurrent inhibition of vagal tone. Inhibition of vagal tone is necessary for the sympathetic nerves to increase heart rate because vagal influences inhibit the action of sympathetic nerve activity. Sympathetic activation, which releases [norepinephrine](#) (NE), increases pacemaker rate by decreasing gK^+ and increasing slow inward gCa^{++} and gNa^+ ; the pacemaker current (I_f) is enhanced. These changes increase the slope of phase 4 so that the pacemaker potential more rapidly reaches the threshold for action potential generation.

2. circulating hormones

Pacemaker activity is also altered by hormones. For example, hyperthyroidism induces [tachycardia](#) and hypothyroidism induces [bradycardia](#). Circulating [epinephrine](#) causes tachycardia by a mechanism similar to [norepinephrine](#) released by sympathetic nerves.

3. serum ion concentrations

Changes in the serum concentration of ions, particularly potassium, can cause changes in SA nodal firing rate. Hyperkalemia induces bradycardia or can even stop SA nodal firing. Hypokalemia increases the rate of phase 4 depolarization and causes tachycardia. It apparently does this by [decreasing \$gK\$](#) during phase 4.

4. cellular hypoxia

Cellular [hypoxia](#) (usually due to [ischemia](#)) depolarizes the membrane potential causing bradycardia; severe hypoxia completely stops pacemaker activity.

5. drugs

Various drugs used as antiarrhythmics also affect SA nodal rhythm. [Calcium-channel blockers](#), for example, cause bradycardia by inhibiting the [slow inward \$\text{Ca}^{++}\$ currents](#) during phase 4 and phase 0. Drugs affecting autonomic control or [autonomic receptors](#) (e.g., [beta-blockers](#), [muscarinic antagonists](#)) directly or indirectly alter pacemaker activity. [Digitalis](#) causes bradycardia by increasing parasympathetic (vagal) activity on the SA node; however, at toxic concentrations, digitalis increases [automaticity](#) and therefore can cause tachyarrhythmias. This toxic effect is related to the inhibitory effects of digitalis on the membrane [\$\text{Na}^+/\text{K}^+\$ -ATPase](#), which leads to cellular depolarization, increased intracellular calcium, and changes in ion conductances.

Pacemaker activity is influenced dramatically by age. The maximal heart rate that can be achieved in an individual is estimated by

$$\text{Maximal Heart Rate} \cong 220 \text{ beats/min} - \text{age in years}$$

Therefore a 20-year-old person will have a maximal heart rate of about 200 beats/min, and this will decrease to about 170 beats/min when the person is 50 years of age. This maximal heart rate is genetically determined and cannot be modified by exercise training or by external factors.

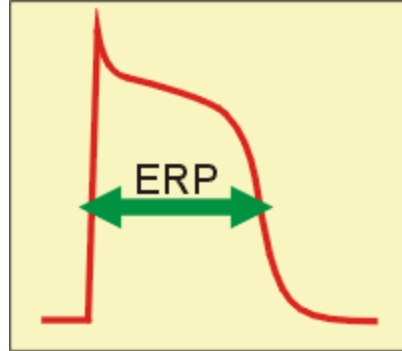
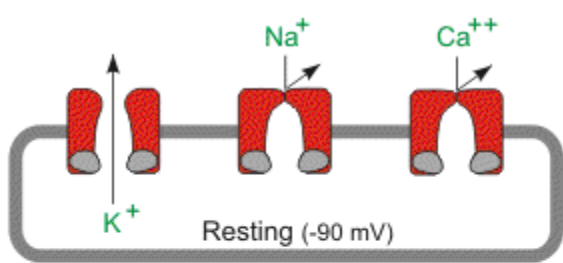
Non-Pacemaker Action Potentials

Atrial myocytes, ventricular myocytes and Purkinje cells are examples of non-pacemaker action potentials in the heart. Because these action potentials undergo very rapid depolarization, they are sometimes referred to as "fast response" action potentials.

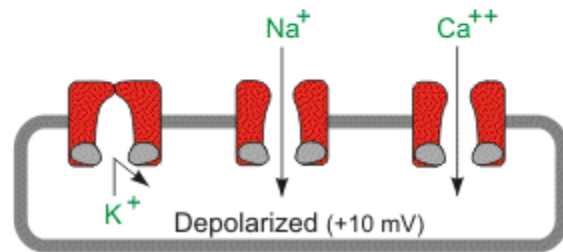
Unlike [pacemaker cells](#) found in nodal tissue within the heart, non-pacemaker cells have a true resting membrane potential (**phase 4**) that remains near the [equilibrium potential](#) for K^+ (E_K). The resting membrane potential is very negative during phase 4 (about -90 mV) because [potassium channels](#) are open (K^+ conductance [g_{K^+}] and K^+ currents [I_K] are high). As shown in the figure, phase 4 is associated with K^+ currents, in which positive potassium ions are leaving the cell and thereby making the membrane potential more negative inside. At the same time, [fast sodium channels](#) and [\(L-type\) slow calcium channels](#) are closed.

When these cells are rapidly depolarized to a **threshold voltage** of about -70 mV (e.g., by an action potential in an adjacent cell), there is a rapid depolarization (**phase 0**) that is caused by a transient increase in fast Na^+ -channel conductance (g_{Na^+}) through fast [sodium channels](#). This increases the inward directed, depolarizing Na^+ currents (I_{Na}) that are responsible for the generation of these "fast-response" action potentials (see above figure). At the same time sodium channels open, g_{K^+} and outward directed K^+ currents fall as [potassium channels](#) close. These two conductance changes move the membrane potential away from E_K (which is negative) and closer toward the equilibrium potential for sodium (E_{Na}), which is positive.

Phase 1 represents an initial repolarization that is caused by the opening of a special type of transient outward K^+ channel (K_{to}), which causes a short-lived, hyperpolarizing outward K^+ current (I_{Kto}). However, because of the large increase in slow inward $g_{Ca^{++}}$ occurring at the same time and the transient nature of I_{Kto} , the repolarization is delayed and there is a plateau phase in the action potential (**phase 2**). This inward calcium movement is through long-lasting [\(L-type\) calcium channels](#) that open up when the membrane potential depolarizes to about -40 mV. This plateau phase prolongs the action potential



duration and distinguishes cardiac action potentials from the much shorter action potentials found in nerves and skeletal muscle.



Repolarization (**phase 3**) occurs when gK^+ (and therefore I_K) increases, along with the inactivation of Ca^{++} channels (decreased gCa^{++}).

Therefore, the action potential in non-pacemaker cells is primarily determined by relative changes in fast Na^+ , slow Ca^{++} and K^+ conductances and currents. As described under the discussion on [membrane potentials](#) and summarized in the following relationship and in the figure to the right, the membrane potential (E_m) is determined by the relative conductances of the major ions distributed across the cell membrane. When $g'K^+$ is high and $g'Na^+$ and $g'Ca^{++}$ are low (phases 3 and 4), the membrane potential will be more negative. When $g'K^+$ is low and $g'Na^+$ and/or $g'Ca^{++}$ are high, the membrane potential will be more positive (phases 0, 1 and 2).

$$E_m = g'K^+ (-96 \text{ mV}) + g'Na^+ (+50 \text{ mV}) + g'Ca^{++} (+134 \text{ mV})$$

These fast-response action potentials in non-nodal tissue are altered by [antiarrhythmic drugs](#) that block specific ion channels. [Sodium-channel blockers](#) such as quinidine inactivate fast-sodium channels and reduce the rate of depolarization (decrease the slope of phase 0). [Calcium-channel blockers](#) such as verapamil and diltiazem affect the plateau phase (phase 2) of the action potential. [Potassium-channel blockers](#) delay repolarization (phase 3) by blocking the potassium channels that are responsible for this phase.

Effective Refractory Period

Once an action potential is initiated, there is a period of time comprising phases 0, 1, 2, and part of phase 3 that a new action potential cannot be initiated. This is termed the **effective refractory period** (ERP) or the **absolute refractory period** (ARP) of the cell. During the ERP, stimulation of the cell by an adjacent cell undergoing depolarization does not produce new, propagated action potentials. The ERP acts as a protective mechanism in the heart by preventing multiple, compounded action potentials from occurring (i.e., it limits the frequency of depolarization and therefore heart rate). This is important because at very

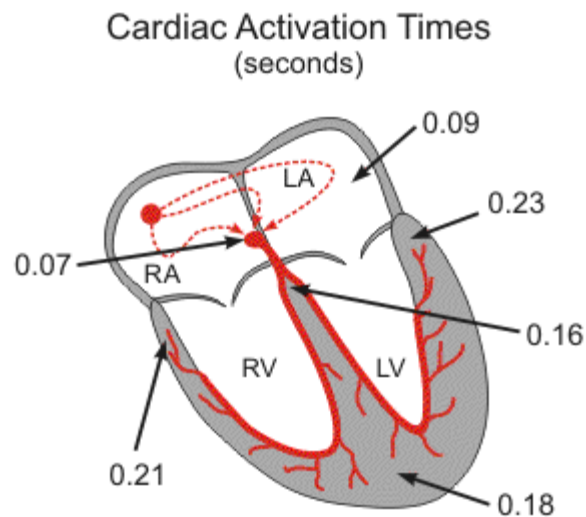
high heart rates, the heart would be unable to adequately fill with blood and therefore ventricular ejection would be reduced.

Many [antiarrhythmic drugs](#) alter the ERP, thereby altering cellular excitability. For example, [drugs that block potassium channels](#) (e.g., amiodarone, a [Class III antiarrhythmic](#)) delays phase 3 repolarization and increases the ERP. Drugs that increase the ERP can be particularly effective in abolishing [reentry currents](#) that lead to tachyarrhythmias.

Transformation of non-pacemaker into pacemaker cells

It is important to note that non-pacemaker action potentials can change into pacemaker cells under certain conditions. For example, if a cell becomes hypoxic, the membrane depolarizes, which closes fast Na^+ channels. At a membrane potential of about -50 mV, all the fast Na^+ channels are inactivated. When this occurs, action potentials can still be elicited; however, the inward current are carried by Ca^{++} (slow inward channels) exclusively. These action potentials resemble those found in [pacemaker cells](#) located in the [SA node](#), and can sometimes display spontaneous depolarization and automaticity. This mechanism may serve as the electrophysiological mechanism behind certain types of [ectopic beats](#) and arrhythmias, particularly in [ischemic heart disease](#) and following [myocardial infarction](#).

Normal Impulse Conduction

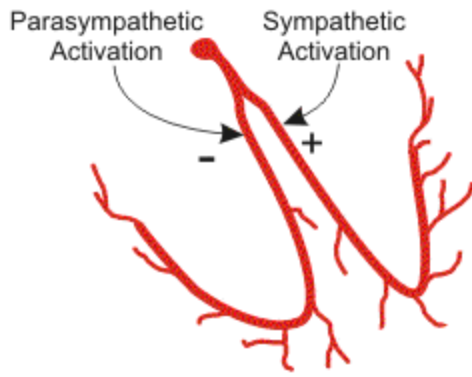


Sequence of Cardiac Electrical Activation

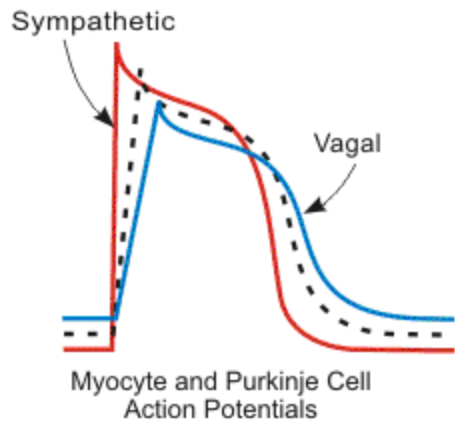
The [action potentials](#) generated by the [SA node](#) spread throughout the atria primarily by cell-to-cell conduction. There is some functional evidence for the existence of specialized conducting pathways within the atria (termed internodal tracts), although this is controversial. The conduction velocity of action potentials in the atrial muscle is about 0.5 m/sec. As the wave of action potentials depolarizes the atrial muscle, the cardiomyocytes contract by a process termed [excitation-contraction coupling](#).

Normally, the only pathway available for action potentials to enter the ventricles is through a specialized region of cells (**atrioventricular node**, or AV node) located in the inferior-posterior region of the

interatrial septum. The AV node is a highly specialized conducting tissue (cardiac, not neural in origin) that slows the impulse conduction considerably (to about 0.05 m/sec) thereby allowing sufficient time for complete atrial depolarization and contraction (systole) prior to ventricular depolarization and contraction.



The impulses then enter the base of the ventricle at the **Bundle of His** and then follow the **left and right bundle branches** along the interventricular septum. These specialized fibers conduct the impulses at a very rapid velocity (about 2 m/sec). The bundle branches then divide into an extensive system of **Purkinje fibers** that conduct the impulses at high velocity (about 4 m/sec) throughout the ventricles. This results in [depolarization of ventricular myocytes](#) and ventricular contraction.

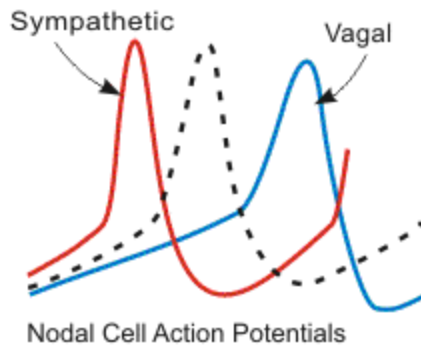


The conduction system within the heart is very important because it permits a rapid and organized depolarization of ventricular myocytes that is necessary for the efficient generation of pressure during systole. The time (in seconds) to activate the different regions of the heart are shown in the figure to the right. Atrial activation is complete within about 0.09 sec (90 msec) following SA nodal firing. After a delay at the AV node, the septum becomes activated (0.16 sec). All the ventricular mass is activated by about 0.23 sec.

Regulation of Conduction

The conduction of electrical impulses throughout the heart, and particularly in the specialized conduction system, is strongly influenced by [autonomic nerve activity](#). Sympathetic activation increases conduction velocity in nodal and non-nodal tissues by increasing the slope of phase 0 of the action potentials. This leads to more rapid depolarization of adjacent cells. This positive dromotropic effect of sympathetic activation results from norepinephrine binding to [beta-adrenoceptors](#), which increases intracellular [cAMP](#). Therefore, drugs that block beta-adrenoceptors ([beta-blockers](#)) decrease conduction velocity and can produce [AV block](#).

Parasympathetic (vagal) activation decreases conduction velocity (negative dromotropy) in nodal and non-nodal tissues by decreasing the slope of phase 0 of the action potentials. This leads to slower depolarization of adjacent cells. Acetylcholine,



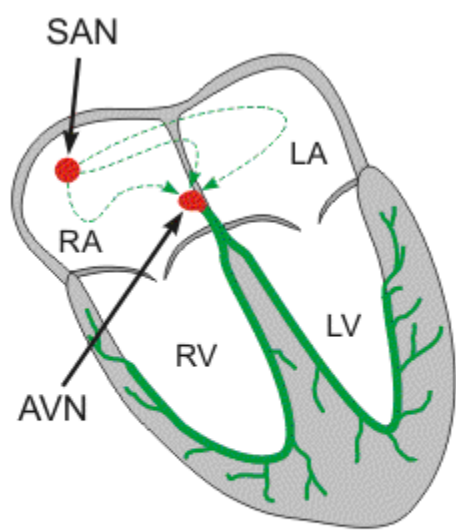
released by the vagus nerve, binds to cardiac [muscarinic receptors](#), which decreases intracellular [cAMP](#). Excessive vagal activation can produce [AV block](#). Drugs such as [digitalis](#), which increase vagal activity to the heart, are used to reduce AV nodal conduction in patients that have atrial flutter or fibrillation. These atrial arrhythmias lead to excessive ventricular rate (tachycardia) that can be suppressed by partially blocking impulses being conducted through the AV node.

Because conduction velocity depends on the rate of tissue depolarization, which is related to the slope of [phase 0 of the action potential](#), conditions (or drugs) that alter phase 0 will affect conduction velocity. For example, conduction can be altered by changes in membrane potential, which can occur during myocardial [ischemia and hypoxia](#). Cellular hypoxia leads to membrane depolarization, inhibition of [fast Na⁺ channels](#), a decrease in the slope of [phase 0](#), and a decrease in action potential amplitude in non-nodal cardiac muscle. These membrane changes result in a decrease in speed by which action potentials are conducted within the heart. [Antiarrhythmic drugs](#) such as [quinidine](#) (a [Class IA antiarrhythmic](#)) that block sodium channels and cause a decrease in conduction velocity in non-nodal tissue.

Phase 0 action potentials at the AV node is not dependent on fast sodium channels, but instead are generated by the entry of calcium into the cell through slow-inward, L-type calcium channels. Blocking these channels with a [calcium-channel blocker](#) such as verapamil or diltiazem reduces the conduction velocity of impulses through the AV node and can produce [AV block](#).

Conduction Defects

If the conduction system becomes damaged or dysfunctional, as can occur during [ischemic conditions](#) or myocardial infarction, electrical conduction becomes impaired. This can have a number of consequences. First, activation of the heart will be delayed, and in some cases, the sequence of activation will be altered. This can seriously impair ventricular pressure development. Second, damage to the conducting system can precipitate tachyarrhythmias by [reentry](#) mechanisms. [Click here](#) to learn more about altered impulse conduction.



Normal Heart Rhythm

The rhythm of the heart is normally determined by a pacemaker site called the **sinoatrial (SA) node** located in the posterior wall of the right atrium near the superior vena cava. The SA node consists of specialized cells that undergo [spontaneous generation of action potentials](#) at a rate of 100-110 action potentials ("beats") per minute. This intrinsic rhythm is strongly influenced by [autonomic nerves](#), with the vagus nerve being dominant over sympathetic influences at rest. This "vagal tone" brings the resting heart rate down to 60-80 beats/minute. The normal range for sinus rhythm is 60-100 beats/minute. Sinus rates below this range are termed [sinus bradycardia](#) and sinus rates above this range are termed [sinus tachycardia](#).

The sinus rhythm normally controls both atrial and ventricular rhythm. Action potentials generated by the SA node spread throughout the atria, depolarizing this tissue and causing atrial contraction. The impulse then travels into the ventricles via the atrioventricular node ([AV node](#)). Specialized [conduction pathways](#) (bundle branches and Purkinje fibers) within the ventricle rapidly conduct the wave of depolarization throughout the ventricles to elicit ventricular contraction. Therefore, normal cardiac rhythm is controlled by the pacemaker activity of the SA node.

Abnormal cardiac rhythms can occur if

1. the SA node fails to function normally (e.g., [sinus bradycardia or tachycardia](#))
2. impulses are not conducted from the atria to the ventricles through the AV node (termed [AV block](#))
3. abnormal conduction pathways are followed (e.g., [accessory pathways](#) between atria and ventricles)
4. other pacemaker sites within the atria or ventricles (e.g., [ectopic pacemakers](#)) trigger depolarization

Abnormal Rhythms – Definitions

General Terms:

- **Normal sinus rhythm** - heart rhythm controlled by sinus node at a rate of 60-100 beats/min; each P wave followed by QRS and each QRS preceded by a P wave.
- **Bradycardia** - a heart rate that is lower than normal.
- **Tachycardia** - a heart rate that is higher than normal.
- **Paroxysmal** - an arrhythmia that suddenly begins and ends.

Specific Arrhythmias:

- **Sinus bradycardia** - low sinus rate <60 beats/min.
- **Sinus tachycardia** - high sinus rate of 100-180 beats/min as occurs during exercise or other conditions that lead to increased SA nodal firing rate.
- **Sick sinus syndrome** - a disturbance of SA nodal function that results in a markedly variable rhythm (cycles of bradycardia and tachycardia).
- **Atrial tachycardia** - a series of 3 or more consecutive atrial premature beats occurring at a frequency >100/min; usually due to abnormal focus within the atria and paroxysmal in nature, therefore appearance of P wave is altered in different ECG leads. This type of rhythm includes paroxysmal atrial tachycardia (PAT).
- **Atrial flutter** - sinus rate of 250-350 beats/min.
- **Atrial fibrillation** - uncoordinated atrial depolarizations.
- **Junctional escape rhythm** - SA node suppression can result in AV node-generated rhythm of 40-60 beats/min (not preceded by P wave).
- **AV nodal blocks** - a conduction block within the AV node (or occasionally in the bundle of His) that impairs impulse conduction from the atria to the ventricles.

First-degree AV nodal block - the conduction velocity is slowed so that the P-R interval is increased to greater than 0.2 seconds. Can be caused by enhanced vagal tone, digitalis, beta-blockers, calcium channel blockers, or ischemic damage.



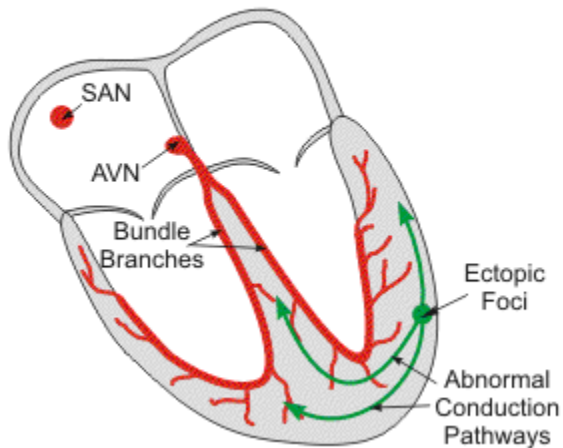
Second-degree AV nodal block - the conduction velocity is slowed to the point where some impulses from the atria cannot pass through the AV node. This can result in P waves that are not followed by QRS complexes. For example, 1 or 2 P waves may occur alone before one is followed by a QRS. When the QRS follows the P wave, the P-R interval is increased. In this type of block, the ventricular rhythm will be less than the sinus rhythm.



Third-degree AV nodal block - conduction through the AV node is completely blocked so that no impulses are able to be transmitted from the atria to the ventricles. QRS complexes will still occur (escape rhythm), but they will originate from within the AV node, bundle of His, or other ventricular regions. Therefore, QRS complexes will not be preceded by P waves. Furthermore, there will be complete asynchrony between the P wave and QRS complexes. Atrial rhythm may be completely normal, but ventricular rhythm will be greatly reduced depending upon the location of the site generating the ventricular impulse. Ventricular rate typically range from 30 to 40 beats/min.



- **Supraventricular tachycardia (SVT)** - usually caused by reentry currents within the atria or between ventricles and atria producing high heart rates of 140-250; the QRS complex is usually normal width, unless there are also intraventricular conduction blocks (e.g., bundle branch block).
- **Ventricular premature beats (VPBs)** - caused by ectopic ventricular foci; characterized by widened QRS; often referred to as a premature ventricular complex, or PVC.
- **Ventricular tachycardia (VT)** - high ventricular rate caused by aberrant ventricular automaticity (ventricular foci) or by intraventricular reentry; can be sustained or non-sustained (paroxysmal); usually characterized by widened QRS (>0.14 sec); rates of 100 to 280 beats/min; life-threatening.
- **Ventricular flutter** - very rapid ventricular depolarizations >250/min; sine wave appearance; leads to fibrillation.



- **Ventricular fibrillation** - uncoordinated ventricular depolarizations; leads to death if not quickly converted to a normal rhythm or at least a rhythm compatible with life.
-

Ectopic Foci

Ectopic foci are abnormal pacemaker sites within the heart (outside of the [SA node](#)) that display [automaticity](#). Their pacemaker activity, however, is normally suppressed ([overdrive suppression](#)) by the higher rate of the SA node. They can occur within the atria or ventricles.

Ectopic foci can cause additional beats (observed as [premature beats](#)) or take over the normal pacemaker activity of the SA node. These ectopic pacemakers can lead to either [tachycardia](#) or [bradycardia](#) depending upon their location and surrounding electrical conditions. For example, an ectopic foci in the ventricle when coupled with a [reentry pathway](#) can precipitate ventricular tachycardia. In [third degree AV nodal block](#), a ventricular rhythm still occurs because of the expression of normally latent ectopic pacemaker sites within the ventricle. These ectopic ventricular pacemakers generally produce a rhythm (30-40 beats/minutes); this rate is much slower than that generally produced by the SA node (60-100 beats/min).

When an ectopic foci drives the rhythm of the heart, the spread of depolarization generally does not follow the normal, fast [conducting pathways](#) within the heart. Because of this, the depolarization wave takes longer to spread throughout the myocardium. This typically causes a shape change in [QRS complex](#) and prolongs its duration (>0.10 sec) because more time is required for the entire ventricle to become depolarized.

Hemodynamic Consequences of Arrhythmias

[Bradycardia](#), whether of atrial or ventricular origin, decreases [cardiac output](#) and thereby decreases arterial pressure. The reduced pressure can result in syncope (i.e., fainting) and other symptoms related to hypotension.

[Tachycardia](#) of atrial or ventricular origin reduces stroke volume and cardiac output particularly when the ventricular rate is greater than 160 beats/min. The stroke volume becomes reduced because of decreased [ventricular filling time](#) and decreased ventricular filling ([preload](#)) at high rates of contraction. Furthermore, if the tachyarrhythmia is associated with abnormal ventricular conduction, the synchrony and therefore effectiveness of ventricular contraction will be impaired leading to reduced ejection. Another consequence of tachycardia is increased [myocardial oxygen demand](#). This can cause [angina \(chest pain\)](#), particularly in patients having underlying coronary artery disease. Finally, chronic states of tachycardia can lead to [systolic heart failure](#). In fact, a commonly used animal model for studying dilated cardiomyopathy is to induce ventricular failure by rapidly pacing the ventricular for a few weeks.

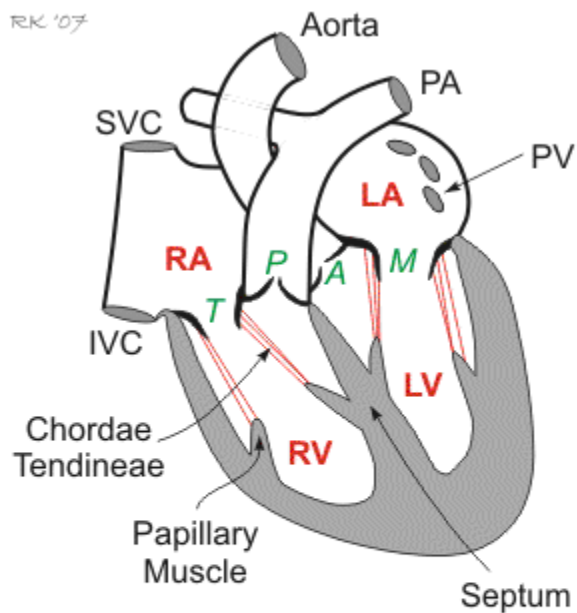
[Atrial fibrillation](#) abolishes the contribution of atrial contraction to ventricular filling. Normally, under low, resting heart rates, atrial contractions account for about 10% of ventricular filling. However, during exercise when heart rate is elevated and ventricular filling time is reduced, atrial contraction can contribute up to 40% of ventricular filling. Therefore, atrial fibrillation generally has relatively minor hemodynamic consequence at rest, but can significantly limit normal increases in ventricular stroke volume and cardiac output during exercise. This may cause shortness of breath (exertional dyspnea) and impaired perfusion of active muscles, which will limit exercise capacity. Furthermore, in some cardiac pathologies such as [ventricular hypertrophy](#) in which [ventricular compliance](#) is reduced, atrial contraction contributes significantly to ventricular filling even at rest. Therefore, in these patients, atrial fibrillation can significantly effect resting cardiac output. Of major concern with atrial fibrillation is the increased risk of thrombus formation within the atria and the release of these thrombi into the pulmonary or systemic circulation, which can lead to pulmonary embolism or stroke. For this reason, patients with atrial fibrillation are commonly placed on anticoagulants such as coumadin. Atrial fibrillation also produces ventricular tachycardia because more impulses pass through the [AV node](#). This is often treated with drugs (e.g., [digoxin](#), [calcium-channel blockers](#), [beta-blockers](#)) to reduce conduction velocity through the AV node, and thereby reduce ventricular rate.

[Ventricular fibrillation](#) causes cardiac output to go to zero, and therefore leads to death unless it is quickly converted to a rhythm compatible with sustaining life.

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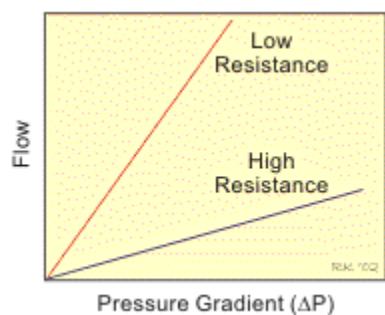
Cardiac Anatomy

The detailed anatomy of the heart can be found in anatomy textbooks. The following presents only a brief description of cardiac anatomy so that the physiology of the cardiac cycle can be understood.

Venous blood enters the **right atrium** (RA) of the heart through the **superior vena cava** (SVC) and **inferior vena cava** (IVC). The right atrium has a relatively thin muscular wall and easily expands with blood as it fills (i.e., it is highly [compliant](#)). Because of its high compliance, the RA pressure is normally very low (0-3 mmHg). It also undergoes spontaneous contractions (see [cardiac cycle](#)) to aid in the filling of the **right ventricle** (RV). Blood passes from the RA to the RV through the **tricuspid valve**. The free wall of the **right ventricle** is

not as thick as the left ventricle, and anatomically it wraps itself around part of the larger, and thicker, left ventricle. The RV wall, however, is thicker and more muscular than the RA, so that when it contracts, it can develop considerably more pressure (~25 mmHg) than the RA. As the RV contracts and generates pressure, blood leaves the RV, flows across an open semilunar **pulmonic valve**, and enters the pulmonary artery that distributes the output of the right ventricle to the lungs where exchange of oxygen and carbon dioxide occur. The pulmonic valve, like all healthy heart valves, permits blood to flow in only one direction. Blood returns to the heart from the lungs through four **pulmonary veins** that enter the **left atrium** (LA). This chamber is similar to the RA in that it is very distensible, although the blood pressure within the LA is several mmHg higher than the RA (6-10 mmHg in the LA compared to 0-3 mmHg in the RA). Blood flows from the LA, across the **mitral valve**, and into the **left ventricle** (LV). The LV wall is very thick so that it can generate high pressures when it contracts (normally ~120 mmHg at rest). When the LV contracts, blood is expelled through the semilunar **aortic valve** and into the **aorta**, which then distributes blood to the arterial system.

The tricuspid and mitral valves (also called atrioventricular, or AV valves) have fibrous strands (**chordae tendineae**) on their leaflets that attach to **papillary muscles** located on the respective ventricular walls.



The papillary muscles contract during ventricular contraction and generate tension on the valve leaflets via the chordae tendineae to prevent the AV valves from bulging back into the atria and becoming incompetent. The semilunar valves (pulmonic and aortic) do not have analogous attachments.

Pressure Gradients

In order for blood to flow through a vessel or across a heart valve, there must be a force propelling the blood. This force is the difference in blood pressure (i.e., pressure gradient) across the vessel length or across the valve ($P_1 - P_2$ in the figure to the right). At any given pressure gradient (ΔP), the actual flow rate is determined by the resistance (R) to that flow. The factors determining the resistance are described by the [Poiseuille relationship](#). The most important factor, quantitatively and functionally, is the radius of the vessel, or in the case of a heart valve, the orifice area of the opened valve. Resistance is inversely related to the fourth power of the radius (r^4) of a blood vessel. For heart valves, it is not possible to use orifice radius because the opening is not circular. Therefore, in actual practice, the area of the valve orifice is used to compute resistance instead of radius, where area (A) is proportional to the square of the radius (r^2), based upon the equation $A = \pi r^2$. For a heart valve, therefore, the resistance to flow is inversely proportional to A^2 .

The pressure gradient can be viewed as the force driving flow (F), where $F = \Delta P / R$. This relationship is based upon Ohm's Law from physics in which current equals the voltage difference divided by the resistance ($I = \Delta V / R$). Flow is decreased, for example, if there is a decrease in ΔP or an increase in R as shown in the figure below. In this example, ΔP is an independent variable while flow is the dependent variable.

The pressure gradient can also be viewed as the pressure drop (i.e., energy loss) that results from a given flow and resistance (i.e., ΔP is the dependent variable), where $\Delta P = F \cdot R$. In other words, ΔP is increased by either an increase in flow or resistance. For example, under [laminar flow](#) conditions, doubling the flow across a heart valve or along a length of blood vessel doubles the pressure drop across the valve or along the length of vessel.

A normal valve, like a normal large artery, has a very small resistance to flow, and therefore the pressure gradient across the valve is very small. In contrast, in vascular or valvular [stenosis](#) the pressure gradient is increased because of the increased resistance to flow (e.g., by decreased vessel radius or valve cross-sectional area). Furthermore, as flow increases across the stenotic lesion (e.g., when cardiac output increases during exercise), the pressure gradient (ΔP) increases. Other factors such as [turbulence](#) can further enhance the pressure gradient for any given flow.

Heart Sounds

When a stethoscope is placed over different regions of the heart, there are four basic heart sounds that can be heard (listening to heart sounds is called cardiac auscultation). The sound waves responsible for heart sounds (including abnormal sounds such as [murmurs](#)) are generated by vibrations induced by valve closure, abnormal valve opening, vibrations in the ventricular chambers, tensing of the chordae tendineae, and by turbulent or abnormal blood flow across valves or between cardiac chambers (see [heart anatomy](#)).

The most fundamental heart sounds are the first and second sounds, usually abbreviated as S_1 and S_2 . S_1 is caused by closure of the mitral and tricuspid valves at the beginning of [isovolumetric ventricular contraction](#). S_1 is normally slightly split (~ 0.04 sec) because mitral valve closure precedes tricuspid valve closure; however, this very short time interval cannot normally be heard with a stethoscope so only a single sound is perceived. S_2 is caused by closure of the aortic and pulmonic valves at the beginning of [isovolumetric ventricular relaxation](#). S_2 is physiologically split because aortic valve closure normally precedes pulmonic valve closure. This splitting is not of fixed duration. S_2 splitting changes

depending on respiration, body posture and certain pathological conditions.

The third heart sound (S_3), when audible, occurs early in [ventricular filling](#), and may represent tensing of the chordae tendineae and the atrioventricular ring, which is the connective tissue supporting the AV valve leaflets. This sound is normal in children, but when heard in adults it is often associated with ventricular dilation as occurs in systolic ventricular failure.

The fourth heart sound (S_4), when audible, is caused by vibration of the ventricular wall during [atrial contraction](#). This sound is usually associated with a stiffened ventricle (low [ventricular compliance](#)), and therefore is heard in patients with ventricular [hypertrophy](#), myocardial ischemia, or in older adults.

Heart Sound	Occurs during:	Associated with:
S1	Isovolumetric contraction	Closure of mitral and tricuspid valves
S2	Isovolumetric relaxation	Closure of aortic and pulmonic valves
S3	Early ventricular filling	Normal in children; in adults, associated with ventricular dilation (e.g. ventricular systolic failure)
S4	Atrial contraction	Associated with stiff, low compliant ventricle (e.g., ventricular hypertrophy)

In addition to these four basic heart sounds, other sounds such as murmurs can be heard. To learn more about these, [click here](#).

An excellent resource for listening to the heart sounds can be found at:
<http://www.cardiosource.com/heartsounds/index.asp#>

Murmurs

Murmurs are abnormal heart sounds that are heard using a stethoscope. The sounds most commonly originate from the abnormal movement of blood across valves and between cardiac chambers. When this occurs, [turbulence](#) results, which produces vibrations in the chambers of the heart or outflow vessels (aorta or pulmonary artery) that are detected as audible, low frequency sounds. Murmurs are distinct from the normal [heart sounds](#) that represent the closure of semilunar and atrioventricular valves during the [cardiac cycle](#).

Murmurs can be divided into two general classifications related to origin: those caused by [valve defects](#) and those caused by [interchamber defects](#) that permit an abnormal flow of blood between cardiac chambers. In order to understand the pathophysiology of murmurs, it is first necessary to understand the physical factors governing the flow of blood (i.e., [hemodynamics](#)), the basic anatomy of the heart, and the sequence of events that occurs as the heart contracts and relaxes (i.e., [cardiac cycle](#)).

Murmurs can also be separated into [systolic and diastolic murmurs](#). The former occurs during ventricular contraction ([systole](#)) and the latter occur during ventricular filling ([diastole](#)).

Systolic and Diastolic Murmurs

Systolic murmurs occurs between S_1 and S_2 (first and second [heart sounds](#)), and therefore are associated with mechanical systolic and ventricular ejection. Mid-systolic murmurs typically have a crescendo-decrescendo character, that is, they start softly and become loudest near mid-systole, followed by a decrease in sound amplitude as shown in the figure. This type of murmur is caused by either [aortic or pulmonic valve stenosis](#). A second type of systolic murmur is holosystolic (sometimes

called pansystolic) because the amplitude is high throughout systole as shown in the figure. This type of murmur is caused by [mitral or tricuspid regurgitation](#), or by a [ventricular septal defect](#).

Diastolic murmurs occur after S₂ and are therefore associated with ventricular relaxation and filling. They may be caused by [aortic or pulmonic valve regurgitation](#), or by [mitral or tricuspid valve stenosis](#). They can occur early (e.g., aortic regurgitation), mid-diastolic, or late diastolic (e.g., mitral stenosis).

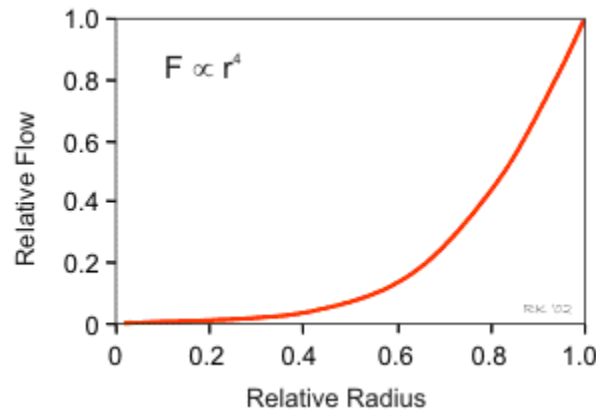
Determinants of Resistance to Flow (Poiseuille's Equation)

There are three primary factors that determine the resistance to blood flow within a single vessel: vessel diameter (or radius), vessel length, and viscosity of the blood. Of these three factors, the most important quantitatively and physiologically is vessel diameter. The reason for this is that vessel diameter changes because of contraction and relaxation of the vascular smooth muscle in the wall of the blood vessel. Furthermore, as described below, very small changes in vessel diameter lead to large changes in resistance. Vessel length does not change significantly and blood viscosity normally stays within a small range (except when hematocrit changes).

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). Because changes in diameter and radius are directly proportional to each other ($D = 2r$; therefore $D \propto r$), diameter can be substituted for radius in the following expression.

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

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 alters resistance to the fourth power of the change in radius. For example, a 2-fold



increase in radius decreases resistance by 16-fold! Therefore, vessel resistance is exquisitely sensitive to changes in radius.

The relationship between flow and vessel radius to the fourth power (assuming constant ΔP , L , η and laminar flow conditions) is illustrated in the figure to the right. This figure shows how very small decreases in radius dramatically reduces flow.

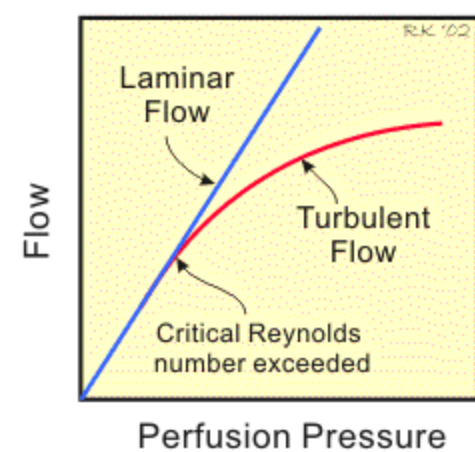
Vessel length does not change appreciably in vivo and, therefore, can generally be considered as a constant. [Blood viscosity](#) normally does not change very much; however, it can be significantly altered by changes in hematocrit, temperature, and by low flow states.

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 19th century French physician Poiseuille. It is a description of how flow is related to perfusion pressure, radius, length, and viscosity. The full equation contains a constant of integration and pi, which are not included in the above proportionality.

In the body, however, flow does not conform exactly 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 pressure and flow, and how changes in heart valve orifice size (e.g., in [valvular stenosis](#)) affect flow and pressure gradients across heart valves.

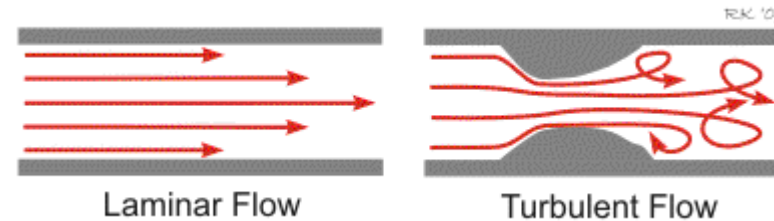


Although the above discussion is directed toward blood vessels, the factors that determine resistance across a heart valve are the same as described above except that length becomes insignificant because path of blood flow across a valve is extremely short compared to a blood vessel. Therefore, when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

Turbulent Flow

Generally in the body, blood flow is [laminar](#). However, under conditions of high flow, particularly in the ascending aorta, laminar flow can be disrupted and become turbulent. When this occurs, blood does not flow linearly and smoothly in adjacent layers, but instead the flow can be described as being chaotic. Turbulent flow also

occurs in large arteries at branch points, in diseased and [narrowed \(stenotic\) arteries](#) (see figure below), and across [stenotic heart valves](#).



Turbulence increases the energy required to drive blood flow because turbulence increases the loss of energy in the form of friction, which generates heat. When plotting a pressure-flow relationship (see figure to right), turbulence increases the [perfusion pressure](#) required to drive a given flow. Alternatively, at a given perfusion pressure, turbulence leads to a decrease in flow.

Turbulence does not begin to occur until the velocity of flow becomes high enough that the flow lamina break apart. Therefore, as blood flow velocity increases in a blood vessel or across a heart valve, there is not a gradual increase in turbulence. Instead, turbulence occurs when a critical **Reynolds number** (Re) is exceeded. Reynolds number is a way to predict under ideal conditions when turbulence will occur. The equation for Reynolds number is:

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

Where \bar{v} = mean velocity, D = vessel diameter, ρ = blood density, and η = [blood viscosity](#)

As can be seen in this equation, Re increases as velocity increases and decreases as [viscosity](#) increases. Therefore, high velocities and low blood viscosity (as occurs with anemia due to reduced hematocrit) are more likely to cause turbulence. An increase in diameter without a change in velocity also increases Re and the likelihood of turbulence; however, the velocity in vessels ordinarily decreases disproportionately as diameter increases. The reason for this is that flow (F) equals the product of mean velocity (V) times cross-sectional area (A), and area is proportionate to radius squared; therefore, the velocity at constant flow is inversely related to radius (or diameter) squared. For example, if radius (or diameter) is doubled, the velocity decreases to one-fourth its normal value, and Re decreases by one-half.

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.

Turbulence generates sound waves (e.g., ejection [murmurs](#), carotid bruits) that can be heard with a stethoscope. Because higher velocities enhance turbulence, murmurs intensify as flow increases. 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 increase the likelihood of turbulence.

Ventricular Pressure-Volume Loop Changes in Valve Disease

Cardiac valve disease significantly alters ventricular pressure and volume relationships during the [cardiac cycle](#). A convenient way to analyze cardiac pressure and volume changes is by using ventricular [pressure-volume loops](#). The links below will illustrate the pressure-volume changes that occur with the following valve defects:

Mitral Stenosis

The following describes changes that occur in the left ventricular [pressure-volume loop](#) when there is [mitral stenosis](#). Mitral stenosis (red pressure-volume loop in figure) impairs left ventricular filling so that there is a decrease in end-diastolic volume ([preload](#)). This leads to a decrease in stroke volume by the [Frank-Starling mechanism](#) and a fall in cardiac output and aortic pressure. This reduction in [afterload](#) (particularly aortic diastolic pressure) enables the end-systolic volume to decrease slightly, but not enough to overcome the decline in end-diastolic volume. Therefore, because end-diastolic volume decreases more than end-systolic volume decreases, the stroke volume (shown as the width of the loop) decreases.

The changes described above and shown in the figure do not include cardiac and systemic compensatory mechanisms (e.g., systemic vasoconstriction, increased blood volume, and increased heart rate and inotropy) that attempt to maintain cardiac output and arterial pressure.

Aortic Stenosis

The following describes changes that occur in the left ventricular [pressure-volume loop](#) when there is [aortic stenosis](#). In aortic stenosis (red loop in figure), left ventricular emptying is impaired because of high outflow resistance caused by a reduction in the valve orifice area when it opens. This high outflow resistance causes a large pressure gradient to occur across the aortic valve during ejection, such that the peak systolic pressure within the ventricle is greatly increased. This leads to an increase in ventricular [afterload](#), a decrease in stroke volume, and an increase in end-systolic volume. Stroke volume (width of pressure-volume loop) decreases because the velocity of fiber shortening is decreased by the increased afterload (see [force-velocity relationship](#)). Because end-systolic volume is elevated, the excess residual volume added to the incoming venous return causes the end-diastolic volume to increase. This increases preload and activates the [Frank-Starling mechanism](#) to increase the force of contraction to help the ventricle overcome, in part, the increased outflow resistance. In mild aortic stenosis, this can be adequate to maintain normal stroke volume, but in moderate stenosis (as shown in the figure) or severe stenosis, the stroke volume may fall considerably because the end-systolic volume increases substantially more than the end-diastolic volume increases. The fall in stroke

volume can lead to a reduction in arterial pressure. Stroke volume falls even further if the ventricle begins to exhibit [systolic and diastolic dysfunction](#). Compensatory increases in end-diastolic volume will be limited by ventricular hypertrophy that occurs due to the chronic increase in afterload. This hypertrophy can lead to large increases in end-diastolic pressure.

The changes described above and shown in the figure do not include cardiac and systemic compensatory mechanisms (e.g., systemic vasoconstriction, increased blood volume, and increased heart rate and inotropy) that attempt to maintain cardiac output and arterial pressure, nor do they include the ventricular [hypertrophy](#) (remodeling) that decreases ventricular compliance.

Mitral Regurgitation

The following describes changes that occur in the left ventricular [pressure-volume loop](#) when there is [mitral regurgitation](#). In mitral valve regurgitation (red pressure-volume loop in figure), as the left ventricle contracts, blood is not only ejected into the aorta but also back up into the left atrium. This causes left atrial volume and pressure to increase during ventricular systole. Note in the pressure-volume loop that there is no true [isovolumetric contraction](#) phase because blood begins to flow across the mitral valve and back into the atrium before the aortic valve opens as soon as ventricular pressure exceeds left atrial pressure. Because of mitral regurgitation, the [afterload](#) on the ventricle is reduced (total outflow resistance is reduced) so that end-systolic volume can be smaller than normal; however, end-systolic volume can increase if the heart also goes into [systolic failure](#). There is no true [isovolumetric relaxation](#) because when the aortic valve closes and the ventricle begins to relax, the mitral valve is not completely closed so blood flows back into the left atrium (therefore further decreasing ventricular volume) as long as intraventricular pressure is greater than left atrial pressure. During ventricular diastolic filling, the elevated pressure within the left atrium is transmitted to the left ventricle during filling so that left ventricular end-diastolic volume (and pressure) increases. This would cause [wall stress](#) (afterload) to increase if it were not for the reduced outflow resistance because of mitral regurgitation that tends to decrease afterload during ejection because of reduced pressure development by the ventricle. The net effect of these changes is that the width of the pressure-volume loop is increased (i.e., ventricular stroke volume is increased); however, ejection into the aorta (forward flow) is reduced. The increased ventricular "stroke volume" (measured as the end-diastolic minus the end-systolic volume) in this case includes the volume of blood ejected into the aorta as well as the volume ejected back into the left atrium. These changes just described do not include cardiac and systemic compensatory mechanisms (e.g., systemic vasoconstriction, increased blood

volume, and increased heart rate and inotropy) that attempt to maintain cardiac output and arterial pressure, nor do they include the ventricular dilation (remodeling) that increases ventricular compliance.

Aortic Regurgitation

The following describes changes that occur in the left ventricular [pressure-volume loop](#) when there is [aortic regurgitation](#). In aortic valve regurgitation (red loop in figure), the aortic valve does not close completely at the end of systolic ejection. As the ventricle relaxes during diastole, blood flows from the aorta back into the ventricle so the ventricle immediately begins to fill from the aorta. Therefore, there is no true phase of [isovolumetric relaxation](#) because as the ventricle relaxes, even before the mitral valve opens, blood is entering the ventricle from the aorta thereby increasing ventricular volume. Once the mitral valve opens, filling occurs from the left atrium; however, blood continues to flow from the aorta into the ventricle throughout diastole because aortic pressure is higher than ventricular pressure during diastole. This greatly enhances ventricular filling so that end-diastolic volume is increased as shown in the pressure-volume loop. When the ventricle begins to contract and develop pressure, blood is still entering the ventricle from the aorta because aortic pressure is higher than ventricular pressure; therefore, there is no true isovolumetric contraction because volume continues to increase. Once the ventricular pressure exceeds the aortic diastolic pressure, the ventricle then begins to eject blood into the aorta. The increased end-diastolic volume (increased preload) activates the [Frank-Starling mechanism](#) to increase the force of contraction, ventricular peak (systolic) pressure, and stroke volume (as shown by the increased width of the pressure-volume loop). As long as the ventricle is not in failure, end-systolic volume may only be increased a small amount (as shown in figure) due to the increased afterload ([ventricular wall stress](#)). If the ventricle goes into [systolic failure](#), then end-systolic volume will increase by a large amount and the peak systolic pressure and stroke volume (net forward flow into aorta) will fall. These changes just described do not include cardiac and systemic compensatory mechanisms (e.g., systemic vasoconstriction, increased blood volume, and increased heart rate and inotropy) that attempt to maintain cardiac output and arterial pressure, nor do they include the ventricular dilation (remodeling) that increases ventricular compliance.

Shortness of breath during exercise (exertional dyspnea) produces a sensation of not being able to "get enough air" and a feeling of being "out of breath." A number of factors can cause exertional dyspnea, but they are usually related to insufficient tissue oxygenation by the blood. This usually results from impaired oxygen exchange by the lungs and can be caused by [pulmonary edema](#) or by insufficient blood being pumped by the heart to the lungs and peripheral organs during exertion (i.e., reduced tissue perfusion). Therefore, a very common cause of exertional dyspnea is [heart failure](#), which results in both impaired perfusion (reduced cardiac output) and, in some types of failure, elevations in [pulmonary capillary pressure](#) leading to pulmonary edema.

Exertional Dyspnea

Shortness of breath during exercise (exertional dyspnea) produces a sensation of not being able to "get enough air" and a feeling of being "out of breath." A number of factors can cause exertional dyspnea, but they are usually related to insufficient tissue oxygenation by the blood. This usually results from impaired oxygen exchange by the lungs and can be caused by [pulmonary edema](#) or by insufficient blood being pumped by the heart to the lungs and peripheral organs during exertion (i.e., reduced tissue perfusion). Therefore, a very common cause of exertional dyspnea is [heart failure](#), which results in both impaired perfusion (reduced cardiac output) and, in some types of failure, elevations in [pulmonary capillary pressure](#) leading to pulmonary edema.

Coronary Anatomy and Blood Flow

The major vessels of the coronary circulation are the left main coronary that divides into **left anterior descending** and **circumflex** branches, and the right main coronary artery. The **left and right coronary arteries** originate at the base of the aorta from openings called the **coronary ostia** located behind the aortic valve leaflets.

The left and right coronary arteries and their branches lie on the surface of the heart, and therefore are sometimes referred to as the **epicardial coronary vessels**. These vessels distribute blood flow to different regions of the heart muscle. When the vessels are not diseased, they have a low [vascular resistance](#) relative to their more distal and smaller branches that comprise the [microvascular network](#). As in all vascular beds, it is the small arteries and arterioles in the microcirculation that are the primary sites of vascular resistance, and therefore the primary site for regulation of blood flow. The arterioles branch into numerous capillaries that lie adjacent to the cardiac myocytes. A high capillary-to-cardiomyocyte ratio and short diffusion distances ensure adequate oxygen delivery to the myocytes and removal of metabolic waste products from the cells (e.g., CO₂ and H⁺). Capillary blood flow enters venules that join together to form cardiac veins that drain into the **coronary sinus** located on the posterior side of the heart, which

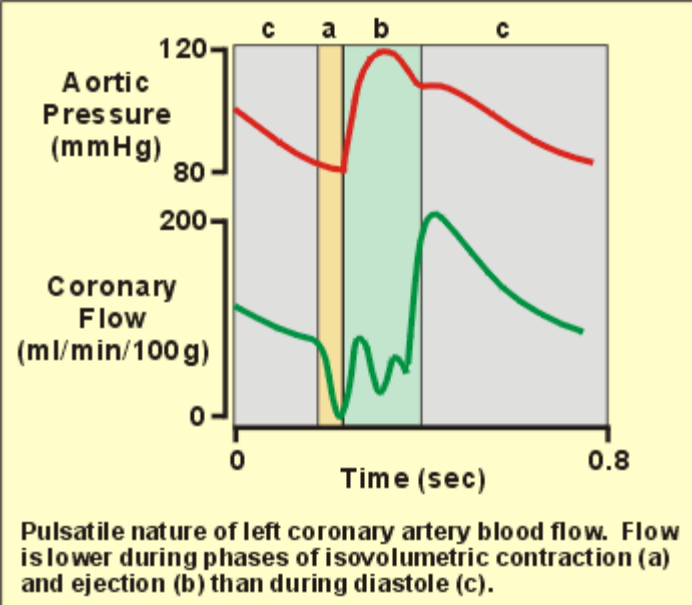
drains into the right atrium. There are also **anterior cardiac veins** and **thesbesian veins** drain directly into the cardiac chambers.

Although there is considerable heterogeneity among people, the following table indicates the regions of the heart that are generally supplied by the different coronary arteries. This anatomic distribution is important because these cardiac regions are assessed by [12-lead ECGs](#) to help localize ischemic or infarcted regions, which can be loosely correlated with specific coronary vessels; however, because of vessel heterogeneity, actual vessel involvement in ischemic conditions needs to be verified by coronary angiograms or other imaging techniques.

Anatomic Region of Heart	Coronary Artery (most likely associated)
Inferior	Right coronary
Anteroseptal	Left anterior descending
Anteroapical	Left anterior descending (distal)
Anterolateral	Circumflex
Posterior	Right coronary artery

The following summarizes important features of coronary blood flow:

- Flow is tightly coupled to oxygen demand. This is necessary because the heart has a very high basal [oxygen consumption](#) (8-10 ml O₂/min/100g) and the highest [A-VO₂ difference](#) of a major organ (10-13 ml/100 ml). In non-diseased coronary vessels, whenever cardiac activity and oxygen consumption increases, there is an increase in coronary blood flow ([active hyperemia](#)) that is nearly proportionate to the increase in oxygen consumption.
- Good [autoregulation](#) between 60 and 200 mmHg perfusion pressure helps to maintain normal coronary blood flow whenever coronary perfusion pressure changes due to changes in aortic pressure.
- [Adenosine](#) is an important mediator of active hyperemia and autoregulation. It serves as a metabolic coupler between oxygen consumption and coronary blood flow. [Nitric oxide](#) is also an important regulator of coronary blood flow.



- Activation of sympathetic nerves innervating the coronary vasculature causes only transient vasoconstriction mediated by [\$\alpha_1\$ -adrenoceptors](#). This brief (and small) vasoconstrictor response is followed by vasodilation caused by enhanced production of [vasodilator metabolites](#) ([active hyperemia](#)) due to increased mechanical and metabolic activity of the heart resulting from [\$\beta_1\$ -adrenoceptor](#) activation of the myocardium. Therefore, sympathetic activation to the heart results in coronary vasodilation and increased coronary flow due to increased metabolic activity (increased heart rate, contractility) despite direct vasoconstrictor effects of sympathetic activation on the coronaries. This is termed "functional sympatholysis."

- [Parasympathetic stimulation of the heart](#) (i.e., vagal nerve activation) elicits modest coronary vasodilation (due to the direct effects of released acetylcholine on the coronaries). However, if parasympathetic activation of the heart results in a significant decrease in [myocardial oxygen demand](#) due to a reduction in heart rate, then intrinsic [metabolic mechanisms](#) will increase coronary vascular resistance by constricting the vessels.
- Progressive ischemic coronary artery disease results in the growth of new vessels (termed angiogenesis) and [collateralization](#) within the myocardium. Collateralization increases myocardial blood supply by increasing the number of parallel vessels, thereby reducing vascular resistance within the myocardium.
- Extravascular compression (shown to the right) during systole markedly affects coronary flow; therefore, most of the coronary flow occurs during diastole. Because of extravascular compression, the endocardium is more susceptible to [ischemia](#) especially at lower perfusion pressures. Furthermore, with tachycardia there is relatively less time available for coronary flow during diastole to occur – this is particularly significant in patients with coronary artery disease where [coronary flow reserve](#) (maximal flow capacity) is reduced.

In the presence of [coronary artery disease](#), coronary blood flow may be reduced. This will increase [oxygen extraction](#) from the coronary blood and decrease the venous oxygen content. This leads to tissue [hypoxia](#) and [angina](#). If the lack of blood flow is due to a fixed [stenotic lesion](#) in the coronary artery (because of atherosclerosis), blood flow can be improved within that vessel by 1) placing a stent within the vessel to expand the lumen, 2) using an intracoronary angioplasty balloon to stretch the vessel open, or 3) bypassing the diseased vessel with a vascular graft. If the insufficient blood flow is caused by a blood clot (thrombosis), a thrombolytic drug that dissolves clots may be administered. Anti-platelet drugs and aspirin are commonly used to prevent the reoccurrence of clots. If the

reduced flow is due to coronary [vasospasm](#), then coronary vasodilators can be given (e.g., [nitrodilators](#), [calcium-channel blockers](#)) to reverse and prevent vasospasm.

Vascular tone

Vascular tone refers to the degree of constriction experienced by a blood vessel relative to its maximally dilated state. All [arterial and venous vessels](#) under basal conditions exhibit some degree of [smooth muscle contraction](#) that determines the diameter, and hence tone, of the vessel.

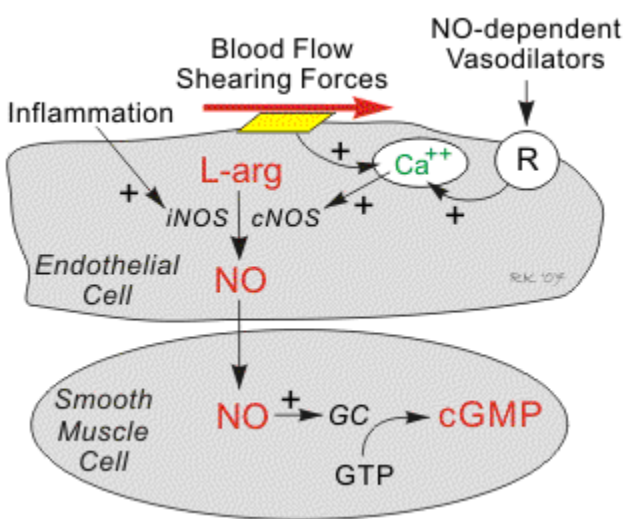
Basal vascular tone differs among organs. Those organs having a large vasodilatory capacity (e.g., myocardium, skeletal muscle, skin, splanchnic circulation) have high vascular tone, whereas organs having relatively low vasodilatory capacity (e.g., cerebral and renal circulations) have low vascular tone.

Vascular tone is determined by many different competing vasoconstrictor and vasodilator influences acting on the blood vessel. These influences can be separated into [extrinsic factors](#) that originate from outside of the organ or tissue in which the blood vessel is located, and [intrinsic factors](#) that originate from the vessel itself or the surrounding tissue. The primary function of extrinsic factors is to regulate arterial blood pressure by altering [systemic vascular resistance](#), whereas intrinsic mechanisms are important for [local blood flow regulation](#) within an organ. Vascular tone at any given time is determined by the balance of competing vasoconstrictor and vasodilator influences.

In general, extrinsic factors ([neurohumoral](#)) such as [sympathetic nerves](#) and circulating [angiotensin II](#) increase vascular tone (i.e., cause vasoconstriction); however, some circulating factors (e.g., [atrial natriuretic peptide](#)) decrease vascular tone.

Intrinsic factors include:

- [Myogenic](#) mechanisms (originating from vascular smooth muscle), which increase tone.
- [Endothelial factors](#) such as [nitric oxide](#) and [endothelin](#) can either decrease or increase tone, respectively.
- Local hormones/chemical substances (e.g., [arachidonic acid metabolites](#), [histamine and bradykinin](#)) can either increase or decrease tone.



- [Metabolic by-products or hypoxia](#), which generally decrease tone.

The mechanisms by which the above influences either constrict or relax blood vessels involve a variety of [signal transduction mechanisms](#) that ultimately influence the interaction between [actin and myosin](#) in the smooth muscle.

Nitric Oxide

Nitric oxide (NO) is produced by many cells in the body; however, its production by vascular endothelium is particularly important in the regulation of blood flow. Because of its importance in vascular function, abnormal production of NO, as occurs in different disease states, can adversely affect blood flow and other vascular functions.

NO Biosynthesis

NO is produced from the amino acid **L-arginine** by the enzymatic action of nitric oxide synthase (NOS). There are two endothelial forms of NOS: constitutive NOS (**cNOS**; type III) and inducible NOS (**iNOS**; type II). Co-factors for NOS include oxygen, NADPH, tetrahydrobiopterin and flavin adenine nucleotides. In addition to endothelial NOS, there is a neural NOS (**nNOS**; type I) that serves as a transmitter in the brain and in different nerves of the peripheral nervous system, such as non-adrenergic, non-cholinergic (NANC) autonomic nerves that innervate penile erectile tissues and other specialized tissues in the body to produce vasodilation.

Under normal, basal conditions in blood vessels, NO is continually being produced by cNOS. The activity of cNOS is calcium and calmodulin dependent. There are two basic pathways for the stimulation of cNOS, both of which involve release of calcium ions from subsarcolemmal storage sites. First, shearing forces acting on the vascular endothelium generated by blood flow causes a release of calcium and subsequent cNOS activation. Therefore, increases in blood flow stimulate NO formation (**flow-dependent NO formation**). Second, endothelial receptors for a variety of ligands stimulate calcium release and subsequent NO production (**receptor-stimulated NO formation**). Included are receptors for acetylcholine, bradykinin, substance-P, adenosine, and many others vasoactive substances. In the late 1970s, Dr. Robert Furchgott observed that acetylcholine released a substance that produced vascular relaxation, but only when the endothelium was intact. This observation opened this field of research and eventually led to his receiving a Nobel prize. Initially, Furchgott called this substance

endothelium-derived relaxing factor (EDRF), but by the mid-1980 he and others identified this substance as being NO.

The other isoform of endothelial NOS is iNOS. It differs, in part, from cNOS in that its activation is calcium independent. Under normal, basal conditions, the activity of iNOS is very low. The activity of iNOS is stimulated during inflammation by bacterial endotoxins (e.g., lipopolysaccharide) and cytokines such as tumor necrosis factor (TNF) and interleukins. During inflammation, the amount of NO produced by iNOS may be a 1,000-fold greater than that produced by cNOS.

Intracellular Mechanisms

When NO forms, it has a half-life of only a few seconds, in large part because [superoxide anion](#) has a high affinity for NO (both molecules have an unpaired electron making them highly reactive). Therefore, superoxide anion reduces NO bioavailability. NO also avidly binds to the heme moiety of hemoglobin (in red blood cells) and the heme moiety of the enzyme **guanylyl cyclase**, which is found in vascular smooth muscle cells and most other cells of the body. Therefore, when NO is formed by vascular endothelium, it rapidly diffuses into the blood where it binds to hemoglobin and subsequently broken down. It also diffuses into the vascular smooth muscle cells adjacent to the endothelium where it binds to and activates guanylyl cyclase. This enzyme catalyzes the dephosphorylation of GTP to **cGMP**, which serves as a second messenger for many important cellular functions, particularly for signalling smooth muscle relaxation.

Cyclic GMP induces smooth muscle relaxation by multiple mechanisms including

1. increased intracellular cGMP, which inhibits calcium entry into the cell, and decreases intracellular calcium concentrations ([click here for details](#))
2. activates K⁺ channels, which leads to hyperpolarization and relaxation
3. stimulates a cGMP-dependent protein kinase that activates [myosin light chain phosphatase](#), the enzyme that dephosphorylates myosin light chains, which leads to smooth muscle relaxation.

Because of the central role of cGMP in NO-mediated vasodilation, drugs (e.g., Viagra®) that inhibit the breakdown of cGMP ([cGMP-dependent phosphodiesterase inhibitors](#)) are used to enhance NO-mediated vasodilation, particularly in penile erectile tissue in the treatment of erectile dysfunction. Increased cGMP also has an important anti-platelet, anti-aggregatory effect.

Vascular Effects of NO

Vascular actions of NO include the following:

- Direct vasodilation (flow dependent and receptor mediated)
- Indirect vasodilation by inhibiting vasoconstrictor influences (e.g., inhibits [angiotensin II](#) and [sympathetic vasoconstriction](#))
- Anti-thrombotic effect - inhibits platelet adhesion to the vascular endothelium
- Anti-inflammatory effect - inhibits leukocyte adhesion to vascular endothelium; scavenges superoxide anion
- Anti-proliferative effect - inhibits smooth muscle hyperplasia

Because of the above actions of NO, when its production is impaired or its bioavailability is reduced, the following can result:

- Vasoconstriction (e.g., coronary vasospasm, elevated systemic vascular resistance, hypertension)
- Thrombosis due to platelet aggregation and adhesion to vascular endothelium
- Inflammation due to upregulation of leukocyte and endothelial adhesion molecules
- Vascular hypertrophy and stenosis

Diseases or Conditions Associated with Abnormal NO Production and Bioavailability

- Hypertension
- Obesity
- Dyslipidemias (particularly hypercholesterolemia and hypertriglyceridemia)
- Diabetes (both type I and II)
- Heart failure
- Atherosclerosis
- Aging
- Cigarette smoking

Active Hyperemia

Active hyperemia is the *increase in organ blood flow (hyperemia) that is associated with increased metabolic activity of an organ or tissue*. An example of active hyperemia is the increase in blood flow that accompanies [muscle contraction](#), which is also called **exercise or functional hyperemia** in skeletal muscle. Blood flow increases because the increased oxygen consumption of during muscle contraction stimulates the production of vasoactive substances that dilate the resistance vessels in the skeletal muscle. Other examples include the increase in gastrointestinal blood flow during digestion of food, the increase in coronary blood flow when heart rate is increased, and the increase in cerebral blood flow associated with increased neuronal activity in the brain. The figure shows that there is a resting flow associated with the basal oxygen consumption of the tissue. As the oxygen consumption increases, there is generally a near-linear increase in blood flow until the vessels begin to achieve a maximally dilated state.

The magnitude of active hyperemia responses differ among organs because of the relative changes in metabolic activity from rest and their vasodilatory capacity. Active hyperemia can result in up to a 50-fold increase in muscle blood flow with maximal exercise, whereas cerebral blood flow may only increase 2-fold with increased neuronal activity.

Active hyperemia can also be influenced by competing vasoconstrictor mechanisms. For example, [sympathetic activation](#) during exercise can reduce the maximal skeletal muscle active hyperemia compared to what would occur in the absence of sympathetic activation.

Active hyperemia may be due to a combination of [tissue hypoxia](#) and the generation of vasodilator metabolites such as [potassium ion](#), [carbon dioxide](#), [nitric oxide](#), and [adenosine](#).

Coronary Anatomy and Blood Flow Oxygen Supply

Oxygen is supplied to the myocardium by the [coronary circulation](#). [Coronary blood flow](#) is determined by [hemodynamic factors](#) such as perfusion pressure and vascular resistance. The latter is determined by vascular anatomy and structure, as well as by changes in diameter of the vascular lumen resulting from contraction and relaxation of vascular smooth muscle ([local regulation of blood flow](#)).

The delivery of oxygen to the myocardium (oxygen supply) is determined by two factors: coronary blood flow (CBF) and the oxygen content of the blood (AO_2).

$$\mathbf{O_2\ Delivery = CBF \times AO_2,}$$

where CBF = ml/min and AO_2 = ml O_2 /ml blood

Therefore, the units for O_2 delivery are ml O_2 /min. The normal content of oxygen in arterial blood is about 20 ml O_2 /100 ml blood (0.2 ml O_2 /ml blood), or 20 vol %. CBF, expressed per 100g of tissue weight is about 80 ml/min per 100g at resting heart rates. Therefore, the oxygen delivery to the heart under resting conditions is about 16 ml O_2 /min per 100g.

Ordinarily, the oxygen content of arterial blood changes relatively little. Therefore, the primary determinant of oxygen delivery in the absence of [hypoxemia](#) is coronary blood flow.

In coronary artery disease, a number of factors can reduce coronary blood flow. [Stenotic lesions](#) cause a narrowing of vessel, particularly the large epicardial coronaries (e.g., left anterior descending or circumflex arteries). The stenosis may be at a specific site, or it may diffuse along the length of the vessel. In either case, the stenosis can limit maximal coronary flow (decreased coronary flow reserve). Maximal flow is reduced because the the fixed stenosis is [in-series](#) with the distal microcirculation. Diseased coronary vessels are more susceptible to [vasospasm](#), which can lead to a temporary restriction of coronary flow at rest. This can occur during stressful conditions or during exercise in susceptible individuals. Finally, thrombus formation, particularly at the site of a ruptured atherosclerotic plaque, can partially or completely occlude a coronary vessel causing [unstable angina](#) or [myocardial infarction](#).

Myocardial Oxygen Extraction

The amount of [oxygen delivered](#) to the myocardium is greater than the amount that is actually taken up ([oxygen consumed](#)) by the myocardium to support oxidative metabolism. Typically, the myocardium extracts about 50% of the oxygen supplied by the arterial blood. This oxygen extraction is determined by the ratio of [oxygen consumption](#) to [coronary blood flow](#) as described by the [Fick Principle](#). Oxygen extraction is, by definition, the difference between the arterial and venous contents of oxygen ($AO_2 - VO_2$).

Compared to most organs of the body (see table below), the oxygen extraction of the heart is relatively high. The AO_2-VO_2 of the heart is typically 10-12 vol % (ml O_2 /100 ml blood).

Organ	AO_2-VO_2 (vol %)
heart	10-12
skeletal muscle (resting)	2-5
kidney	2-3
intestine	4-6
skin	1-2

Theoretically, the maximal amount of oxygen that can be extracted is 20 vol %. In reality, however, the maximal oxygen extraction is around 15-16 vol % because of the kinetics of oxygen dissociation from hemoglobin. Therefore, the heart is extracting at least two-thirds of the physiologically available oxygen under normal operating conditions. Because of this, the heart must tightly couple oxygen supply and demand in order to ensure adequate tissue oxygenation. In the absence of coronary artery disease (CAD), coronary blood flow increases almost proportionately to increases in MVO_2 thereby preventing tissue hypoxia and functional impairment. [Local regulation](#) of blood flow is responsible for adjusting coronary blood flow to the metabolic demands of the contracting myocardium.

In the presence of CAD, coronary blood flow may not be able to supply adequate oxygen to meet metabolic demands of the contracting heart. This will increase the oxygen extraction and decrease the venous oxygen content. This leads to tissue [hypoxia](#) and [angina](#). If the lack of blood flow is due to a [fixed stenotic lesion](#) in the coronary artery (because of atherosclerosis), blood flow can be improved within that vessel by 1) placing a stent within the vessel to expand the lumen, 2) using an intracoronary angioplasty balloon to stretch the vessel open, or 3) bypassing the diseased vessel with a vascular graft. If the insufficient blood flow is caused by a blood clot (thrombosis), a [thrombolytic drug](#) that dissolves clots may be administered. Anti-platelet drugs and aspirin are commonly used to prevent the reoccurrence of clots. If the reduced flow is due to coronary [vasospasm](#), then coronary vasodilators can be given (e.g., [nitrodilators](#), [calcium-channel blockers](#)) to reverse and prevent vasospasm.

Oxygen Demand

Oxygen demand is a concept that is closely related to the oxygen consumption of an organ. The two terms are often used interchangeably although they are not equivalent. Demand is related to need, whereas consumption is the actual amount of oxygen consumed per minute. Under some conditions, demand may exceed consumption because the latter may be limited by the [delivery of oxygen](#) to the myocardium. The following discussion focuses on the oxygen demand by the heart.

Highly oxidative organs such as the heart [see [cardiac metabolism](#)] have a high demand for oxygen and therefore have a relatively high oxygen consumption (MVO_2) is required to regenerate ATP that is utilized by membrane transport mechanisms (e.g., [Na⁺/K⁺-ATPase pump](#)) and by myocyte contraction and relaxation (e.g., [myosin ATPase](#)). The following tables give MVO_2 values and compares these with the oxygen consumption of other organs:

Cardiac State	MVO_2 (ml O₂/min per 100g)
Arrested heart	2
Resting heart rate	8
Heavy exercise	70

By comparison, the oxygen consumption (ml O₂/min per 100g) for other organs is:

Organ	O₂ Consumption (ml O₂/min per 100g)
Brain	3
Kidney	5
Skin	0.2

Resting muscle	1
Contracting muscle	50

The above tables show that the heart has a wide range of MVO_2 values that depends on the state of mechanical activity. Skeletal muscle, like the heart, has a wide range of values for oxygen consumption depending on its level of mechanical activity. The MVO_2 in the arrested heart represents basal ATP utilization, primarily by membrane transport systems. The additional increase in MVO_2 above this basal level is that required to support myocyte contraction and relaxation.

In order to support MVO_2 , particularly during times of increased oxygen demand (e.g., during exercise), the heart must extract oxygen from the arterial blood supplying the myocardium (see [Oxygen Supply](#)).

There is a unique relationship between MVO_2 , coronary blood flow (CBF), and the extraction of oxygen from the blood ([arterial-venous oxygen difference](#), $AO_2 - VO_2$). This relationship is an application of the **Fick Principle**:

$$MVO_2 = CBF \times (AO_2 - VO_2),$$

where CBF = coronary blood flow (ml/min), and $(AO_2 - VO_2)$ is the arterial-venous oxygen content difference (ml O_2 /ml blood). For example, if CBF is 80 ml/min per 100g and the A- VO_2 difference is 0.1 ml O_2 /ml blood, then the $MVO_2 = 8$ ml O_2 /min per 100g.

Another way of expressing this relationship is:

$$MVO_2 = (CBF \cdot AO_2) - (CBF \cdot VO_2),$$

where $CBF \cdot AO_2$ is the [oxygen supply](#) (or delivery) to the myocardium and $CBF \cdot VO_2$ is the unextracted oxygen leaving the heart via the venous circulation. The difference between the oxygen that enters the heart and that which leaves the heart per minute is the oxygen consumption of the heart.

Oxygen consumption by the heart can be estimated in humans by utilizing the Fick Principle; however, that requires catheterization of the coronary sinus to measure venous oxygen saturation and coronary blood flow. Relative changes in MVO_2 can be estimated by using an indirect index such as the **pressure-rate product**. There are different variations of this index, but one method simply multiplies the aortic systolic pressure by the heart rate. This can be useful, for example, in clinical trials to determine if a drug reduces oxygen demand. The pressure-rate product is based on the observation that MVO_2 is closely related to [ventricular wall tension](#).

Myocardial Oxygen Balance

Myocardial oxygen balance is determined by the ratio of [oxygen supply](#) to [oxygen demand](#) as shown in the figure. Increasing oxygen supply by increasing either arterial oxygen content or coronary blood flow leads to an increase in tissue oxygen levels (usually measured as the partial pressure of oxygen, pO_2). Increasing oxygen demand alone (i.e., myocardial oxygen consumption) decreases tissue oxygen levels. Normally, when oxygen demand increases there is a proportionate increase in coronary blood flow and oxygen supply so that tissue oxygen levels are maintained during times of increased oxygen demand. This increase in blood flow is performed by [local regulatory mechanisms](#). This tight coupling between oxygen demand and coronary blood flow is impaired in coronary artery disease because [oxygen supply](#) is limited by vascular [stenosis](#). If the oxygen supply/demand ratio is reduced either by a decrease in oxygen delivery relative to demand, or by an increase in demand relative to supply, then tissue [hypoxia](#) results.

A reduced oxygen supply/demand ratio is the cause of chest pain ([angina](#)) associated with coronary artery disease. These patients are treated with [antianginal drugs](#) such as [beta-blockers](#), [calcium-channel blockers](#), [nitrodilators](#) that improve this ratio.

Ischemia and Hypoxia

Ischemia is insufficient blood flow to provide adequate oxygenation. This, in turn, leads to tissue **hypoxia** (reduced oxygen) or **anoxia** (absence of oxygen). Ischemia always results in hypoxia; however, hypoxia can occur without ischemia if, for example, arterial hypoxia occurs.

The most common causes of ischemia are acute arterial thrombus formation, chronic narrowing ([stenosis](#)) of a supply artery that is often caused by atherosclerotic disease, and arterial [vasospasm](#). As blood flow is reduced to an organ, [oxygen extraction](#) increases. When the tissue is unable to extract adequate oxygen, the partial pressure of oxygen within the tissue falls (hypoxia) leading to a reduction in mitochondrial respiration and oxidative metabolism.

Electrophysiological Changes During Cardiac Ischemia

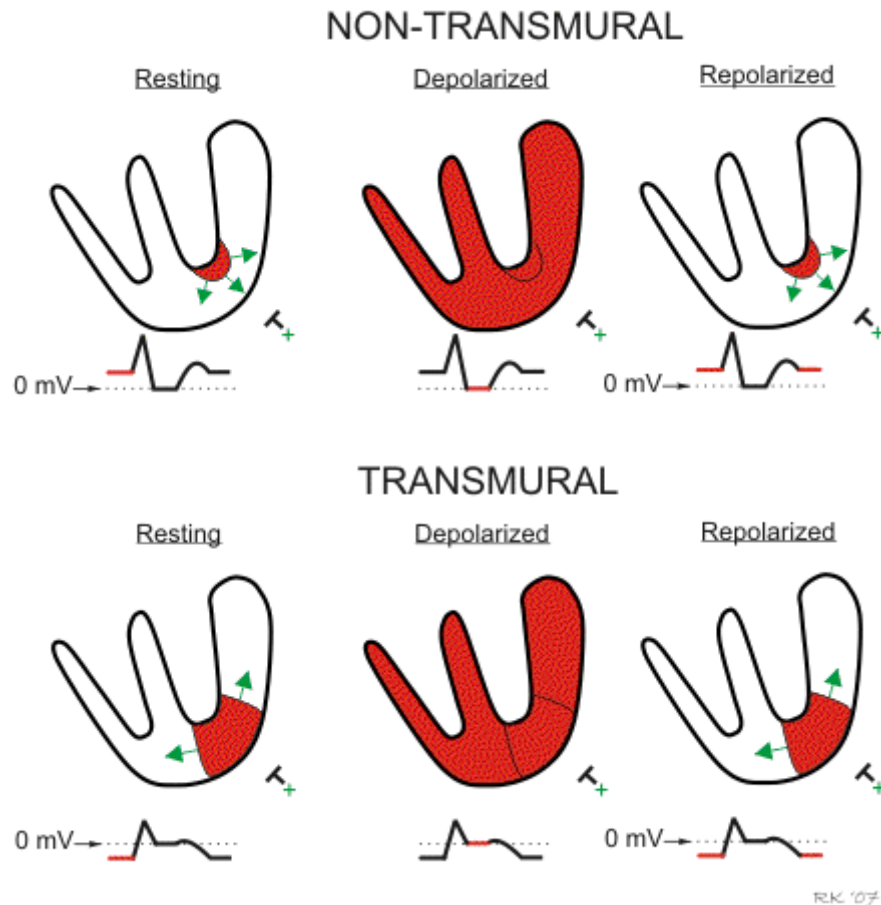
Ischemia/hypoxia causes an elevation in extracellular K^+ . This occurs because K^+ leaks out through [K_{ATP} channels](#) (normally inhibited by ATP) and because of decreased activity of the [Na⁺/K⁺-ATPase pump](#). These changes occur because [ATP levels decline in hypoxic cells](#).

Increases in extracellular K^+ cause [membrane depolarization](#) in accordance with the [Nernst equation](#) (although very small increases in extracellular K^+ may cause hyperpolarization by increasing g_K). Depolarization will inactivate fast [Na⁺⁺ channels](#) and thereby decreased action potential upstroke velocity ([fast Na⁺ channels](#) inhibited). This will lead to decreased [conduction velocity](#). These changes often lead to [arrhythmias](#) that may require the use of [antiarrhythmic drugs](#).

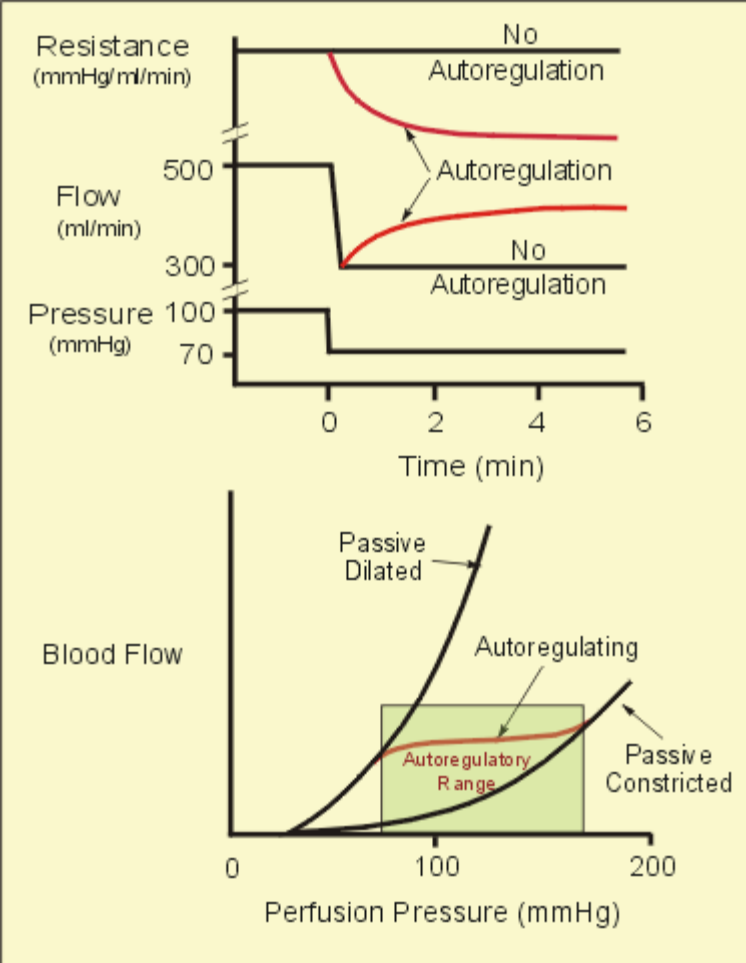
Injury currents flowing from the depolarized ischemic regions to normal regions result in the appearance of [ST segment](#) elevation or depression, depending upon whether the ischemic region is non-transmural, subendocardial (ST depression) or transmural (ST elevation). The former is usually associated with [demand ischemia](#) (e.g., exertional angina), whereas the latter is associated with [supply ischemia](#) (e.g., coronary occlusion).

For non-transmural ischemia, the ST segment depression occurs because when the ventricle is at rest and repolarized states, the depolarized, ischemic region generates electrical currents that are recorded by an overlying electrode. If the depolarizing currents are traveling toward the positive electrode, the baseline voltage prior to the [QRS complex](#) (which is normally isoelectric - i.e., zero volts) will be elevated. In contrast, when the ventricle becomes depolarized, all the muscle is depolarized so that zero voltage is

recorded by the electrode as usual. Therefore, the net effect of the elevated baseline voltage is that the ST segment appears to be depressed relative to the baseline.



For transmural ischemia, the ST segment elevation occurs because when the ventricle is at rest and repolarized, the depolarized, ischemic region generates electrical currents that are traveling away from the positive electrode; therefore the baseline voltage prior to the QRS complex will be depressed. When the ventricle becomes depolarized, all the muscle is depolarized so that zero voltage is recorded by the



electrode. Therefore, the net effect of the depressed baseline voltage is that the ST segment appears to be elevated relative to the baseline.

Autoregulation

Autoregulation is a manifestation of local [blood flow regulation](#). It is defined as the intrinsic ability of an organ to maintain a constant blood flow despite changes in perfusion pressure. For example, if perfusion pressure is decreased to an organ (e.g., by partially occluding the arterial supply to the organ), blood flow initially falls, then returns toward normal levels over the next few minutes. This autoregulatory response occurs in the absence of neural and hormonal influences and therefore is intrinsic to the organ. When perfusion pressure (arterial minus venous pressure, $P_A - P_V$) initially decreases, blood flow (F) falls because of the following relationship between [pressure, flow and resistance](#):

$$F = \frac{(P_A - P_V)}{R}$$

When blood flow falls, arterial resistance (R) falls as the [resistance vessels](#) (small arteries and arterioles) dilate. Many studies suggest that that [metabolic](#), [myogenic](#) and [endothelial](#) mechanisms are responsible for this vasodilation. As resistance decreases, blood flow increases despite the presence of reduced perfusion pressure.

This autoregulatory response is shown in the top panel of the figure. For example, if perfusion pressure is reduced from 100 to 70 mmHg, this causes flow to decrease initially by approximately 30%. Over the next few minutes, however, flow begins to increase back toward control if the organ is capable of autoregulating (red lines). This occurs because vascular resistance falls. If autoregulation does not occur, the flow will remain decreased.

If an organ is subjected to an experimental study in which perfusion pressure is both increased and decreased over a wide range of pressures, and the steady-state autoregulatory flow response measured, then the relationship between steady-state flow and perfusion pressure can be plotted as shown in the bottom panel of the figure. The red line represents the autoregulatory responses in which flow changes relatively little despite a large change in perfusion pressure. If a vasodilator drug is infused into an organ so that it is maximally dilated and incapable of autoregulatory behavior, the curve labeled "Passive Dilated" is generated as perfusion pressure is changed. It is non-linear because blood vessels passively dilate with increasing pressures, thereby reducing resistance to flow. If a vasodilator is not infused so that the organ can undergo autoregulation, then there will be a range of perfusion pressures where flow will not follow the "Passive Dilated" curve. In fact, the flow over a particular range of perfusion pressures (i.e., autoregulatory range) may change very little as shown in this example (e.g., as found in coronary and cerebral circulations). The "Passive Constricted" curve represents the pressure-flow relationship when the vasculature is maximally constricted. The bottom panel also shows that there is a pressure below which an organ is incapable of autoregulating its flow because it is maximally dilated. This perfusion pressure, depending upon the organ, may be between 50-70 mmHg. Below this perfusion pressure, blood flow decreases passively in response to further reductions in perfusion pressure. This has clinical implications for coronary, cerebral, and peripheral arterial disease. There is an upper limit to the autoregulatory range; however, this upper limit is seldom reached physiologically.

Different organs display varying degrees of autoregulatory behavior. The renal, cerebral, and [coronary](#) circulations show excellent autoregulation, whereas skeletal muscle and splanchnic circulations show moderate autoregulation. The cutaneous circulation shows little or no autoregulatory capacity.

Under what conditions does autoregulation occur and why is it important? A change in systemic arterial pressure, as occurs for example with hypotension caused by hypovolemia or circulatory shock, can lead to autoregulatory responses in certain organs. In hypotension, despite [baroreceptor reflexes](#) that constrict much of the systemic vasculature, blood flow to the brain and myocardium does not decline appreciably (unless the arterial pressure falls below the autoregulatory range) because of the strong capacity of these organs to autoregulate. Autoregulation, therefore, ensures that these critical organs have an adequate blood flow and [oxygen delivery](#).

There are situations in which arterial pressure does not change, yet autoregulation is very important. Whenever a distributing artery to an organ becomes narrowed (e.g., atherosclerotic narrowing of

lumen, vasospasm, or partial occlusion with a thrombus) this can result in an autoregulatory response. Narrowing (see [stenosis](#)) of distributing arteries increases their resistance and hence the pressure drop along their length. This results in a reduced pressure at the level of [smaller arteries and arterioles](#), which are the primary vessels for regulating blood flow within an organ. These resistance vessels dilate in response to reduced pressure and blood flow. This autoregulation is particularly important in organs such as the brain and heart in which partial occlusion of large arteries can lead to significant reductions in oxygen delivery, thereby leading to tissue [hypoxia](#) and organ dysfunction.

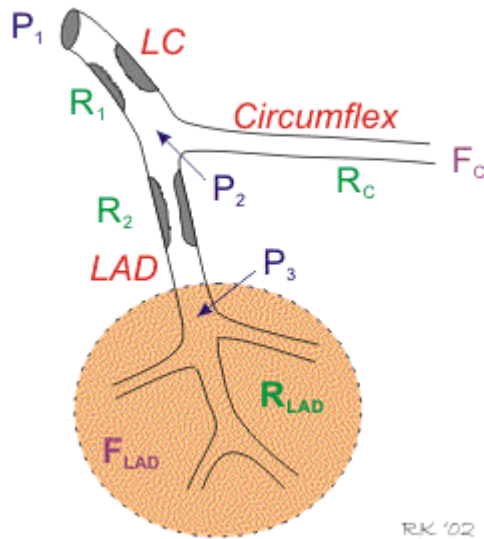
Critical Stenosis

The term "**stenosis**" can refer to an abnormal narrowing of an artery, usually of a discrete segment. Stenosis can also refer to a reduced cross-sectional area of a heart valve when it opens. In the case of an artery, stenosis most commonly occurs in large distributing arteries such as coronary, renal, cerebral, iliac and femoral arteries. The narrowing commonly results from a chronic disease process - atherosclerosis. Sometimes a vessel can become acutely stenotic due to focal vasospasm. But in general, stenosis results from chronic vascular disease.

Stenosis increases the vascular resistance as described by [Poiseuille's equation](#), which says that resistance is inversely related to the radius to the fourth power. Therefore, if the radius (or diameter) of a vascular segment is reduced by one-half, the resistance within that narrowed segment increases by 16-fold. If this vascular segment were being perfused in isolation, the flow would be decreased 16-fold if perfusion pressure is held constant. However, in vivo this degree of stenosis would have relatively little effect on flow because the vessel is coupled in-series with other resistance vessels ([CLICK HERE](#) for more information). If we consider the renal artery and kidney circulation, the renal artery contributes to only a small fraction (<1%) of the total renal vascular resistance. Therefore, the renal artery needs to be narrowed considerably before overall renal vascular resistance is increased enough to significantly decrease renal blood flow. This is also true for other organ circulations such as the heart, limbs and brain.

The term "**critical stenosis**" refers to a critical narrowing of an artery (stenosis) that results in a significant reduction in maximal flow capacity in a distal vascular bed. A critical stenosis may or may not reduce resting flow depending on the organ's capacity to [autoregulate](#) its blood flow and the development of [collateral blood flow](#), both of which serve to reduce the overall resistance in the smaller

resistance vessels. Clinically, a critical stenosis typically is thought of in terms of a 60-75% reduction in the diameter of the large distributing artery. This explains why interventional measures such as balloon angioplasty, stent placement, or arterial bypass surgery are not usually conducted in patients until there is at least a 75% reduction in vessel diameter.



Vascular Steal

presence of multiple vessel stenotic lesions can lead to a condition called "vascular steal." This occurs when dilation of one vascular network (e.g., during exercise or vasodilator therapy) "steals" blood flow from another region within the organ that is already maximally dilated because of the presence of proximal lesions.

Vascular steal can occur in the coronary vasculature, in the [lower limb vasculature](#), or in any vascular network when specific conditions are met. The model described below is for the coronary vasculature.

Conditions:

1. [Clinically significant lesions](#) in left main coronary artery (LC) and left anterior descending artery (LAD), R_1 and R_2 , respectively.

2. The pressure distal to the LAD lesion (P_3) divided by resistance of the vasculature supplied by the LAD (R_{LAD}) determines blood flow in the LAD-supplied distal vascular beds (F_{LAD}). The vascular bed supplied by the LAD is maximally dilated (i.e., at minimal resistance, R_{LAD}) due to [autoregulation](#) in response to the large reduction in pressure distal to the LAD lesion (P_3) caused by the combined LC and LAD stenotic lesions (R_1 and R_2 , respectively).
3. Blood flow in the circumflex-supplied vascular beds (F_C) is determined by P_2 divided by the resistance of the distal vascular beds supplied by the circumflex artery (R_C). If the LC lesion does not reduce P_2 to a value below the autoregulatory range of the circumflex vascular beds, then these beds will not be maximally dilated and therefore can still decrease their resistance (R_C) in response to increased metabolic demand by the heart or to vasodilator drugs.

In the above example, vasodilator stimuli (e.g., exercise or drugs) will decrease R_C and increase F_C . When this increase in circumflex blood flow occurs, the increased flow across R_1 will further decrease P_2 . This, in turn, will cause P_3 to decrease, thereby reducing the perfusion pressure to the LAD vascular beds. When this occurs, F_{LAD} will decrease. Remember that R_{LAD} is already minimal (i.e., maximally dilated) due to the low P_3 and therefore is incapable of dilating further in response to a vasodilator stimulus. The net result is that circumflex blood flow increases while LAD blood flow decreases (i.e., vascular steal). This redistribution of flow leads to [ischemia](#) and [hypoxia](#) (especially during augmented oxygen demand) in the myocardium supplied by the LAD.

Analogous situations in the iliac and femoral circulations of the lower limb can lead to vascular steal during exercise. This is termed "[intermittent claudication](#)" and results in ischemic pain during walking.

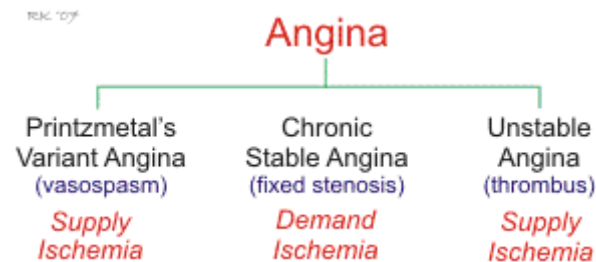
Angina

Angina is chest pain caused by an imbalance between [oxygen supply](#) (decreased coronary blood flow) and [oxygen demand](#) (increased myocardial oxygen consumption), which leads to a decrease in the [oxygen supply/demand ratio](#) and myocardial [hypoxia](#). The decreased flow can result from coronary

artery vasospasm, [fixed stenotic lesions](#) (chronic vessel narrowing), or from a blood clot (thrombus) that incompletely (non-occlusive thrombus) or completely occludes a coronary artery (occlusive thrombus). Oxygen consumption can be elevated by increased heart rate, contractility ([inotropy](#)), [afterload](#) and [preload](#).

Type of Angina

There are three types of angina: Prinzmetal's variant angina, chronic stable angina, and unstable angina. All three forms are associated with a reduction in the oxygen supply/demand ratio.



Variant (Prinzmetal's) angina results from coronary vasospasm, which temporarily reduces coronary blood flow (i.e., produces [ischemia](#) by reducing oxygen supply; "**supply ischemia**"), thereby decreasing the oxygen supply/demand ratio. Enhanced sympathetic activity (e.g., during emotional stress), especially when coupled with a dysfunctional coronary vascular endothelium (i.e., reduced endothelial production of the vasodilators [nitric oxide](#) and [prostacyclin](#)) can precipitate vasospastic angina. This form of angina is treated with drugs that reverse or inhibit coronary vasospasm. These drugs include [calcium-channel blockers](#) and [nitrodilators](#). These drugs also reduce oxygen demand to further improve the [oxygen supply/demand ratio](#).

Chronic stable angina is caused by a chronic narrowing of coronary arteries due to atherosclerosis. This narrowing is readily observed in the large epicardial arteries by an angiogram; however, narrowing also occurs in smaller branches that cannot be visualized angiographically. When a coronary artery is narrowed beyond a critical value ([critical stenosis](#)), the myocardial tissue perfused by the artery will not receive adequate blood flow because [coronary flow reserve](#) (i.e., maximal flow capacity) is limited. This results in the tissue becomes ischemic and hypoxic, particularly during times of increased [oxygen demand](#) (e.g., during physical exertion). Therefore, in this type of angina, relative ischemia occurs when the oxygen

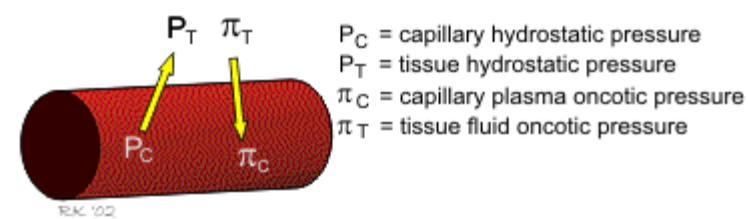
demand increases, so this is referred to as "**demand ischemia**." This leads to anginal pain during physical exertion (**exertional angina**). The pain usually is associated with a predictable threshold of physical activity. Other conditions that cause myocardial oxygen demand to increase, such as a large meal or emotional stress, can also precipitate pain. This form of angina is most commonly treated with drugs that reduce oxygen demand. These drugs include [beta-blockers](#), [calcium-channel blockers](#), [nitrodilators](#). They act by decreasing heart rate, contractility, afterload and preload.

Unstable angina is caused by transient formation and dissolution of a blood clot (thrombosis) within a coronary artery. The clots often form in response to plaque rupture in atherosclerotic coronary arteries; however, the clot may also form because diseased coronary artery endothelium ([endothelial dysfunction](#)) is unable to produce [nitric oxide](#) and [prostacyclin](#) that inhibit platelet aggregation and clot formation. When the clot forms, coronary flow is reduced, leading to a reduction in the oxygen supply/demand ratio ("**supply ischemia**"). If the clot completely occludes the coronary artery for a sufficient period of time, the myocardium supplied by the vessel may become infarcted (**acute myocardial infarction**) and become irreversibly damaged. This form of angina is treated with drugs that reduce oxygen demand (i.e., [beta-blockers](#), [calcium-channel blockers](#), [nitrodilators](#)), but more importantly, this form of angina is treated with drugs that inhibit thrombus formation (e.g., anti-platelet drugs and aspirin).

Angina may also be precipitated by a combination of supply and demand ischemia. For example, diseased, stenotic coronary segments can sometimes undergo vasoconstriction during exercise (healthy arteries dilate). This probably occurs due to the absence of sufficient production of [nitric oxide](#) and perhaps [prostacyclin](#) by the vascular endothelium to counteract normal sympathetic-mediated effects on [vascular alpha-adrenoceptors](#).

A hemodynamic condition may exist that leads to coronary [vascular steal](#). In this condition, multiple fixed stenotic lesions can lead to a redistribution of flow within the major supply arteries of the heart under conditions of exercise or vasodilator therapy. As blood flow increases in one region of the coronary vascular network, blood flow can reciprocally decrease in another region leading to anginal pain.

Physical Factors that Determine Capillary Fluid Exchange



$$\text{NDF} = (P_C - P_T) - \sigma (\pi_C - \pi_T)$$

When $\text{NDF} > 0 \rightarrow$ Filtration

When $\text{NDF} < 0 \rightarrow$ Reabsorption

Hydrostatic (P) and oncotic (π) pressures within the capillary and tissue interstitium (T) determine the net driving force (NDF) for fluid movement into the capillary (reabsorption) or out of the capillary (filtration). The oncotic pressure difference is multiplied by the reflection coefficient (σ) that represents the permeability of the capillary barrier to the proteins responsible for generating the oncotic pressure.

There is a free exchange of water, electrolytes, and small molecules between the intravascular and extravascular compartments of the body. The primary site of this exchange is [capillaries and small post-capillary venules](#) (sometimes grouped together and called "exchange vessels"). Several [mechanisms](#) are involved in this exchange; however, the most important are [bulk flow](#) and [diffusion](#). The rate of exchange, in either direction, is determined by [physical factors](#): hydrostatic pressure, oncotic pressure, and the physical nature of the barrier separating the blood and the interstitium of the tissue (i.e., the permeability of the capillary wall).

There are two important and opposing hydrostatic forces: [capillary hydrostatic pressure](#) (P_C) and [tissue hydrostatic pressure](#) (P_T). Because P_C is normally much greater than P_T , the net hydrostatic pressure gradient across the capillary is positive, meaning that hydrostatic forces are driving fluid out of the capillary and into the interstitium. There are also two opposing oncotic pressures influencing fluid exchange: [capillary plasma oncotic pressure](#) (π_C) and [tissue \(interstitial\) oncotic pressure](#) (π_T). π_C is much greater than π_T , therefore the oncotic pressure gradient across the capillary, if unopposed by hydrostatic forces, would reabsorb fluid from the interstitium into the capillary. The oncotic pressure difference ($\pi_C - \pi_T$) should be multiplied by the [reflection coefficient](#) that represents the permeability of the capillary barrier to the proteins responsible for generating the oncotic pressure. Because both hydrostatic and oncotic forces are normally expressed in units of mmHg. The net driving force (NDF) for fluid movement is the net pressure gradient determined by the sum of the individual hydrostatic and oncotic pressures.

For a given NDF, the amount of fluid filtered or reabsorbed per unit time (**fluid flux**, or J_V) will be determined by the permeability of the capillary barrier and by the surface area available for exchange. The permeability is usually referred to as the filtration constant (K_F), and is determined by the physical properties of the barrier (i.e., size and number of "pores" and the thickness of the barrier). For example, [fenestrated capillaries](#) have a higher K_F than [continuous capillaries](#). Furthermore, substances such as [histamine](#), which are released in response to tissue injury or inflammation, increase K_F . The surface area (A) is related to the length, diameter, and number of capillaries available for exchange. The surface area is dynamic in vascular beds such as skeletal muscle where the number of perfused capillaries increase several-fold during exercise.

To summarize: $J_V = K_F A [(P_C - P_T) - \sigma(\pi_C - \pi_T)]$

The expression in brackets represents the NDF. If this is positive, filtration occurs, and if negative, reabsorption occurs. For a given NDF, the J_V is determined by the product of K_F and A .

In most vascular beds of the body, filtration occurs across the arteriolar end of the capillary and reabsorption occurs across the venular end. In general, there is net filtration across capillary beds (i.e., filtration > reabsorption) that is picked up by the [lymphatics](#). If an imbalance occurs where net filtration exceeds the capacity of the lymphatics, then [edema](#) results. The kidneys are an exception to these generalizations in that renal glomerular capillaries filter large amounts of fluid along their entire length. This results from higher glomerular capillary hydrostatic pressures and higher capillary permeabilities.

Hydrostatic and Oncotic Pressures

Capillary Hydrostatic Pressure (P_C)

This pressure drives fluid out of the capillary (i.e., filtration), and is highest at the arteriolar end of the capillary and lowest at the venular end. Depending upon the organ, the pressure may drop along the length of the capillary (axial pressure gradient) by 15-30 mmHg. The axial gradient favors filtration at the arteriolar end (where P_C is greatest) and reabsorption at the venular end of the capillary (where P_C is the lowest). The average capillary hydrostatic pressure is determined by [arterial](#) and [venous](#) pressures (P_A and P_V), and by the ratio of post-to-precapillary resistances (R_V/R_A). An increase in either arterial or venous pressure will increase capillary pressure; however, a given change in P_A is only about one-fifth as effective in changing P_C as the same absolute change in P_V . Because venous resistance is relatively low, changes in P_V are readily transmitted back to the capillary, and conversely, because arterial resistance is relatively high, changes in P_A are poorly transmitted downstream to the capillary. Therefore, **P_C is much more influenced by changes in P_V than by changes in P_A** . Furthermore, P_C is increased by precapillary vasodilation (particularly by arteriolar dilation); precapillary vasoconstriction decreases P_C . Venous constriction increases P_C , whereas venous dilation decreases P_C .

Tissue (Interstitial) Hydrostatic Pressure (P_T)

This pressure is determined by the interstitial fluid volume and by the [compliance](#) of the tissue, which is related to the ability of the tissue volume to increase. Normally, P_T is near zero. In some tissues it is slightly subatmospheric, whereas in others it is slightly positive. Tissue compliance is generally low; that is, small increases in tissue volume as occurs during states of enhanced filtration or lymphatic blockage result in dramatic increases in P_T . The rise in P_T that occurs with increased interstitial fluid volume decreases the hydrostatic gradient across the capillary thereby limiting filtration.

Capillary Plasma Oncotic Pressure (Π_c)

Because the capillary barrier is readily permeable to ions, the osmotic pressure within the capillary is principally determined by plasma proteins that are relatively impermeable. Therefore, instead of speaking of "osmotic" pressure, this pressure is referred to as the "oncotic" pressure or "colloid osmotic" pressure because it is generated by colloids. Albumin generates about 70% of the oncotic pressure. This pressure is typically 25-30 mmHg. The oncotic pressure increases along the length of the capillary, particularly in capillaries having high net filtration (e.g., in renal glomerular capillaries), because the filtering fluid leaves behind proteins leading to an increase in protein concentration.

Normally, when oncotic pressure is measured, it is measured across a semipermeable membrane – i.e., a membrane that is permeable to fluid and electrolytes but not to large protein molecules. In most capillaries, however, the wall (primarily endothelium) does have a finite permeability to proteins. The actual permeability to protein depends upon the [type of capillary](#) as well as the nature of the protein (size, shape, charge). Because of this finite permeability, the actual oncotic pressure generated across the capillary membrane is less than that calculated from the protein concentration. The effects of finite protein permeability on the physiological oncotic pressure can be determined knowing the [reflection coefficient](#) (σ) of the capillary wall. If the capillary is impermeable to protein then $\sigma = 1$. If the capillary is freely permeable to protein, then $\sigma = 0$. [Continuous capillaries](#) have a high σ (>0.9), whereas [discontinuous capillaries](#) which are very "leaky" to proteins have a very low σ . In the latter case, plasma and tissue oncotic pressures may have a negligible influence on the [net driving force](#).

Tissue (interstitial) Oncotic Pressure (Π_T)

The oncotic pressure of the interstitial fluid depends on the interstitial protein concentration and the reflection coefficient of the capillary wall. The more permeable the capillary barrier is to proteins, the higher the interstitial oncotic pressure. This pressure is also determined by the amount of fluid filtration

into the interstitium. For example, increased capillary filtration decreases interstitial protein concentration and reduces the oncotic pressure. This effect of filtration on protein concentration also serves as a mechanism to limit capillary filtration. In a "typical" tissue, tissue oncotic pressure is about 5 mmHg (i.e., much lower than capillary plasma oncotic pressure).

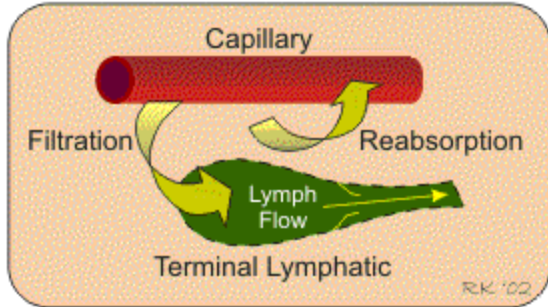
Tissue Edema and General Principles of Transcapillary Fluid Exchange

Edema refers to the swelling of tissues that result from excessive accumulation of fluid within the tissue. Edema can be highly localized as occurs in a small region of the skin subjected to a bee sting. Edema, however, can also comprise an entire limb, specific organs such as the lungs (e.g., [pulmonary edema](#)) or the whole body.

General principles

To understand how edema occurs, it is first necessary to explain the concept of tissue compartments. There are two primary fluid compartments in the body between which fluid is exchanged - the intravascular and extravascular compartments. The **intravascular compartment** contains fluid (i.e., blood) within the cardiac chambers and vascular system of the body. The **extravascular system** is everything outside of the intravascular compartment. Fluid and electrolytes readily move between these two compartments. The extravascular compartment is made up of many subcompartments such as the cellular, interstitial, and lymphatic subcompartments, and a specialized system containing cerebrospinal fluid.

The movement of fluid and accompanying solutes between compartments (mostly water, electrolytes, and smaller molecular weight solutes) is governed by [physical factors](#) such as [hydrostatic](#) and [oncotic](#) forces. These forces are normally balanced in such a manner the fluid volume remains relatively constant between the compartments. If the physical forces or barriers to fluid movement are altered, the volume of fluid may increase in one compartment and decrease in another. In some cases, total fluid volume increases in the body so that both intravascular and extravascular compartments increase in volume. This can occur, for example, when the kidneys fail to excrete sufficient amounts of sodium and water. When the fluid volume within the interstitial compartment increases, this compartment will increase in size leading to tissue swelling (i.e., **edema**). When excess fluid accumulates within the peritoneal space (space between the abdominal wall and organs), this is termed "**ascites**." Pulmonary



The interstitial volume (bounded area) depends on the rates of filtration, reabsorption, lymph flow, and the compliance of the interstitial compartment.

congestion, which can occur in [heart failure](#) as the left atrial pressure increases and blood backs up in the pulmonary circuit, causes [pulmonary edema](#).

A model that helps us to understand what causes edema is shown to the right. **Filtration** is the movement of fluid out of the capillary and **reabsorption** is the movement of fluid back into the distal end of the capillary and small venules. In most capillary systems of the body, there is a

small [net filtration](#) (typically about 1% of plasma) of fluid from the intravascular to the extravascular compartment. In other words, capillary fluid filtration exceeds reabsorption. This would cause fluid to accumulate within the interstitium over time if it were not for the [lymphatic system](#) that removes excess fluid from the interstitium and returns it back to the intravascular compartment. Circumstances, however, can arise where net capillary filtration exceeds the capacity of the lymphatics to carry away the fluid (i.e., net filtration > lymph flow). When this occurs, the interstitium will swell with fluid, thereby become edematous.

Factors Precipitating Edema

- Increased [capillary hydrostatic pressure](#) (as occurs when venous pressures become elevated by gravitational forces, in heart failure or with venous obstruction)
- Decreased [plasma oncotic pressure](#) (as occurs with hypoproteinemia during malnutrition)
- Increased [capillary permeability](#) caused by proinflammatory mediators (e.g., histamine, bradykinin) or by damage to the structural integrity of capillaries so that they become more "leaky" (as occurs in tissue trauma, burns, and severe inflammation)
- Lymphatic obstruction (as occurs in filariasis or with tissue injury)

Prevention and Treatment of Edema

The treatment for edema involves altering one or more of the physical factors that regulate fluid movement. For example, in edema (pulmonary or systemic) secondary to [heart failure](#), [diuretic drugs](#) are given to reduce [blood volume](#) and [venous pressure](#). In heart failure patients, improving cardiac output by using [cardiostimulatory](#) or [vasodilators](#) drugs reduces venous and capillary pressures, thereby decreasing filtration and promoting reabsorption of fluid within tissues ([click here](#) to see why increasing cardiac output decreases venous pressure). If a patient suffers from ankle edema, that

person will be instructed to keep their feet elevated whenever possible (to diminish the effects of [gravity](#) on capillary pressure), use tight fitting elastic hose (to increase [tissue hydrostatic pressure](#)), and possibly be prescribed a [diuretic](#) drug to enhance fluid removal by the kidneys.

