

Introduction to CV Pathophysiology

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Introduction to Cardiovascular Pathophysiology

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1. Basic Anatomy

Please review basic anatomy from relevant textbooks. The heart consists of four chambers; two thin walled chambers the **atria** and two muscular chambers the **ventricles**. The left ventricle is conical in shape, the right ventricle has a semilunar morphology on cross section. The left ventricular wall is three times as thick as the right ventricular wall measuring 9-11 mm.

The atria and ventricles are separated by the **AV groove** and the **AV valves**; the **tricuspid** valve on the right and the **mitral** valve (two leaflets) on the left. These valves are tethered to the ventricular cavity via the **chordae tendinae** to three papillary muscles on the right and two larger **papillary muscles** in the left (the anterolateral and posteromedial papillary muscles). These valves prevent the return of blood backwards to the atria when the ventricles contract is systole.

The semilunar valves are tricuspid and separate the ventricular cavities from the vessels they contract into. The **pulmonic** valve separates the right ventricle from the pulmonary artery, the **aortic** valve the left ventricle from the aorta. These valves prevent the return of blood from the great vessels (pulmonary artery, aorta) back the ventricles (right and left ventricles) in diastole.

The myocardium is perfused by three principle coronary arteries; the **left anterior descending** artery (LAD), **left circumflex** (CX) and the **right coronary artery** (RCA). The **left main** coronary artery originates from the **ascending aorta** at the left **sinus of valsalva**. It runs between the left atrium and the pulmonary artery and at the level of the AV groove divides into the left anterior descending (LAD) and left circumflex (CX). The LAD courses along the anterior interventricular groove between the right and left ventricles and runs towards the apex. It supplies blood to the **interventricular septum** via **septal branches** and the anterolateral wall of the left ventricle via the **diagonal**

branches. The CX runs along the left atrioventricular groove. Its branches are the **obtuse** marginal branches that perfuse the lateral wall of the left ventricle.

The right coronary artery originates from the ascending aorta at the level of the right sinus of valsalva. It runs along the right atrioventricular groove towards the apex of the heart. Along its course it gives off **right ventricular branch(es)**. Once it reaches the inferior interventricular groove it gives off the **posterior descending artery (PDA)** that perfuses the inferior interventricular septum. In 90% of individuals the **AV nodal artery** originates close to the origin of the PDA. The coronary anatomy of such individuals is described to have a “**right dominant**” circulation. In 5% the AV nodal artery comes off the left circumflex and patients are described as having a “**left dominant**” system whereas in 5% the AV node is perfused by both and the system is described as “**co dominant**.”

The heart’s “pacemaker,” the **Sinus Node**, is located in the supero lateral right atrium at the site of its junction with the superior vena cava. Impulses are generated in the sinus node, the atrium is activated and the impulse conducts to the AV node located antero medially in the right atrium superior to the origin of the septal tricuspid valve leaflet. After a brief delay, the impulse is conducted down to the His-Purkinje through the **right and left bundle branches** to the right and left ventricles respectively initiating ventricular systole.

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In addition to the myocardial muscles, the coronary arteries perfuse the papillary muscles and the electrical system of the heart. Ischemia of the papillary muscles may result in functional mitral regurgitation. Ischemia of the AV node and the bundle branches can cause conduction delays or “blocks.”

2. Excitation-Contraction Coupling

The myocardial cells’ (cardiomyocyte) most important function is contraction. The **myofibrils** are the contracting elements of the cardiomyocyte. The myofibrils contain the two chief contractile proteins; the thick **myosin** and the thin **actin**. The **sarcomere** is the contracting unit of the myofibril and contains the two overlapping proteins; actin and myosin. The myofibrils consist of a series of linked sarcomeres. Myocardial contraction occurs as a result of the coupling of actin and myosin. The myocardial cell wall is called the **sarcolemma**. A characteristic of myocardial cells is the invagination of the cell membrane into the cell called the **transverse tubular system (T tubules)**. The **sarcoplasmic reticulum** is a series of intracellular tubules that communicate with the T tubules. They serve to store and release Ca^{++} coupling membrane depolarization to mechanical contraction of the sarcomere.

Tropomyosin is a protein that is intertwined with actin and inhibits contraction by hiding the binding receptor sites. The **troponin complex** is connected to actin and consists of an inhibitory component, **Troponin I**, a Ca^{++} binding component **Troponin C** and a binding

component **Troponin T** that binds the troponin complex to actin. Contraction is due to cross bridging between the globular head of myosin to actin.

The entry of Ca^{++} into the myocyte during **phase 2 of the monophasic action potential** through the L-type Ca^{++} channel results in further Ca^{++} release from the sarcoplasmic reticulum through **ryanodine receptors**. Calcium binds to Troponin C inhibiting Troponin I. Tropomyosin is displaced to expose the binding sites which require ATP to bind with the myosin head. Conformational changes to the myosin head after hydrolysis of ATP results in contraction, pulling actin inwards. When Ca^{++} is reuptaken and the concentration of Ca^{++} begins to fall, actin and myosin uncouple and **Diastole** begins.

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3. The Cardiac Cycle

Defining the components of the cardiac cycle differs according to whether one looks at the physiologic or the mechanical components of the cycle. From a mechanical point of view the ventricular cycle can be divided into systole and diastole; the forceful expulsion of blood and the process of refilling before the next expulsion respectively. From an electrical point of view, the myocardium is either depolarizing (phase 0 of the monophasic action potential), repolarizing (phases 1-3 of the monophasic action potential) or in the resting (phase 4) phase of the monophasic action potential. If the cell being considered is one capable of spontaneous depolarization (**automaticity**) the membrane potential spontaneously begins to move to the threshold potential to depolarize in phase 4 of MAP. If the cell being considered does not possess automaticity, it remains at the resting membrane potential awaiting for an electrical impulse to depolarize it.

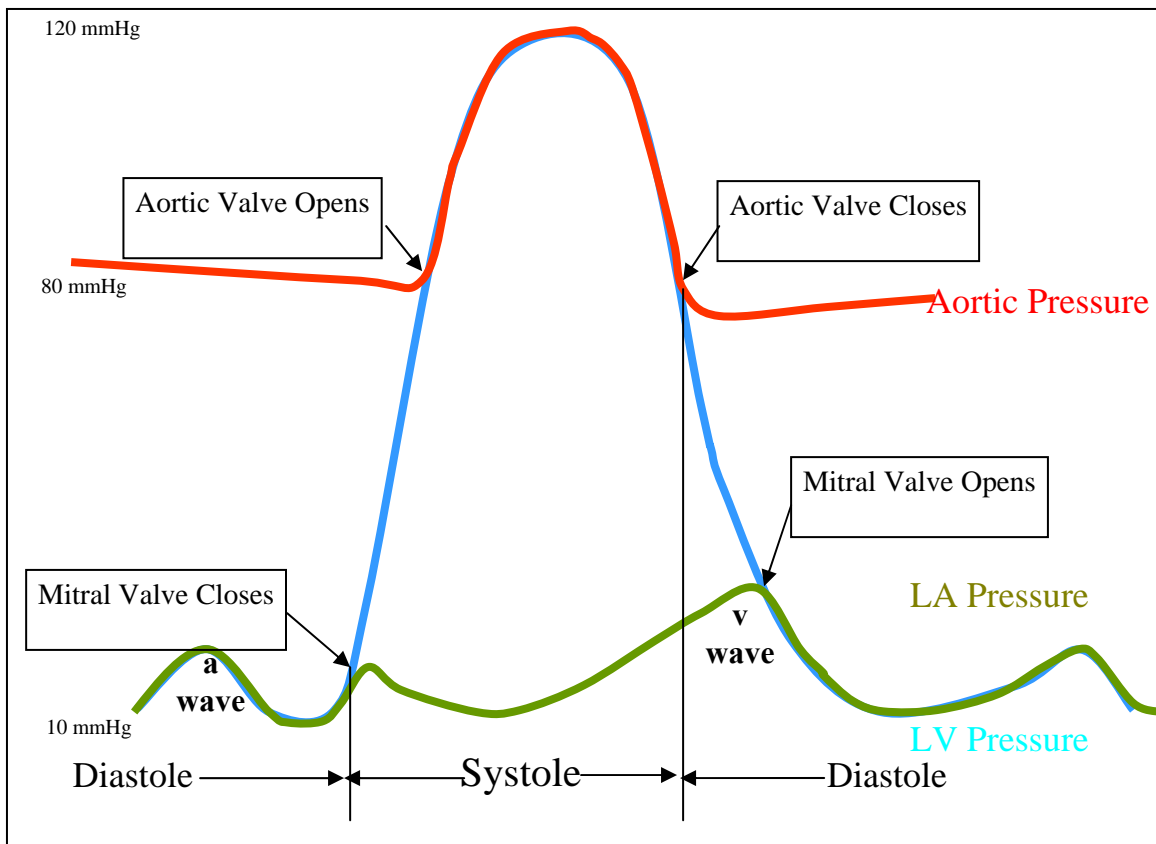
Classically, the cardiac cycle consists of ventricular contraction and ventricular relaxation. Once the electrical signal arrives at the myocyte, **depolarization** begins. Ca^{++} is released into the myocyte triggering the **actin-myosin interaction** (excitation-contraction coupling; see above). As pressure builds up in the left and right ventricles, the mitral and tricuspid valves are shut generating the **first heart sound S1**. S1 consists of M1 and T1; closure of the mitral and tricuspid valves respectively. Pressure continues to build up until the aortic and pulmonic valves are forced open. The time between the closure of the mitral and tricuspid valves and the opening of the aortic and pulmonic valves is called **isovolumic contraction**. Contraction is occurring but blood is not being ejected across the semilunar valves yet. **Systole** (Greek for contraction) begins when the aortic and pulmonic valves open and blood begins to flow across them. The volume of blood ejected with each cycle is the **Stroke Volume** which averages $45 \pm 13 \text{ mL/M}^2$ body surface area. The rate of ejection is determined by the pressure gradient across the valve.

When Ca^{++} levels in the myocardial cells begin to fall as a result of Ca^{++} reabsorption, the strength of contraction begins to diminish and intracavitary pressures begin to decline. Once the pressure in the aorta and pulmonary artery begin to exceed the pressures in the left and right ventricular cavities respectively, the aortic and pulmonic valves will shut. This generates the **second heart sound S2**. S2 consists of A2 and P2, the sequential

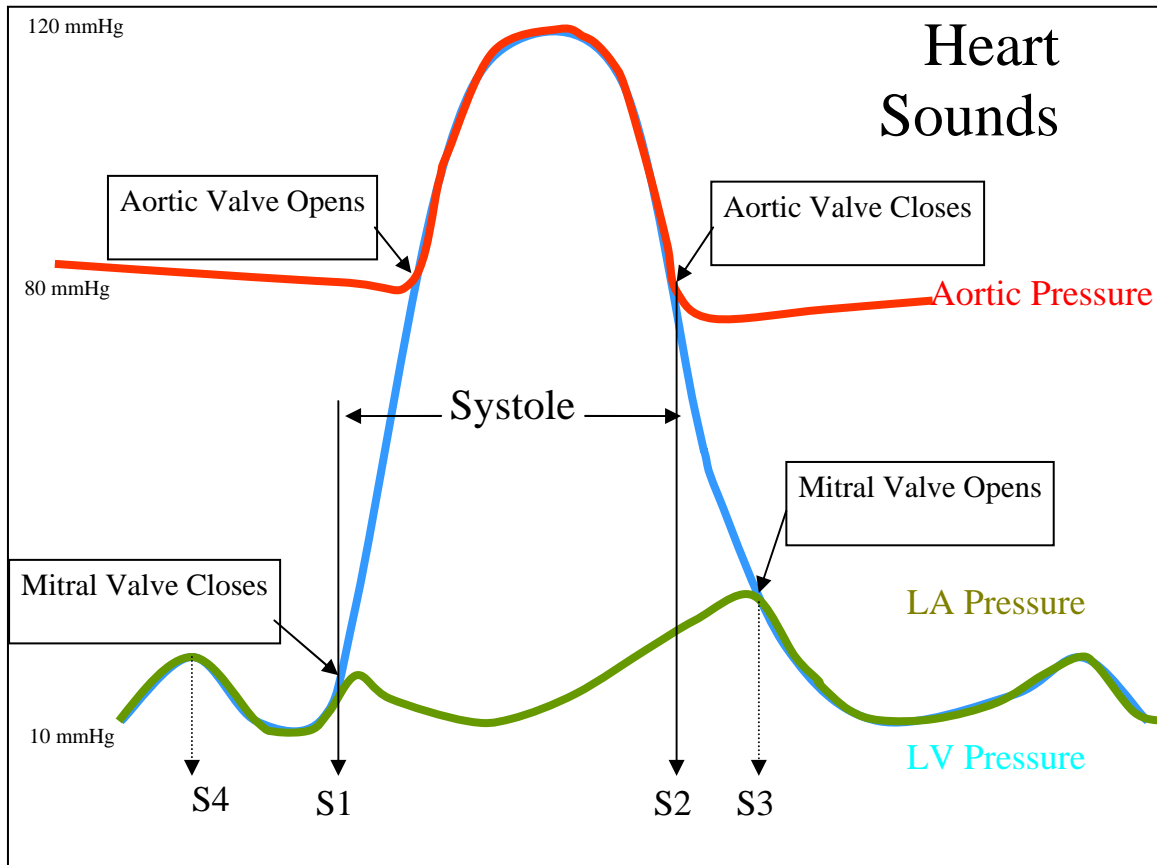
closure of the aortic and pulmonic valves. The ventricle continues to relax without further changes in volume until the pressure falls below left and right atrial pressures. This phase is called the **isovolumic relaxation phase**. S2 signals the beginning of **diastole**.

During ventricular systole, when the mitral and tricuspid valves are closed, the atria (left and right) are filling up with blood and their pressures are rising. When the left and right atrial pressures exceed the left and right ventricular pressure, the mitral and tricuspid valves open and the first (or early) rapid filling phase begins. The early rapid filling phase accounts for most (80%) of diastolic ventricular filling and may generate a heart sound known as **S3**. **Atrial systole** represents the second rapid filling phase of diastole accounting for 15% of diastolic filling and completes filling of the right and left ventricles before ventricular systole commences. The interval between these two rapid filling phases is called **diastasis** (Greek for separating apart). Five percent of diastolic ventricular filling occurs during this phase.

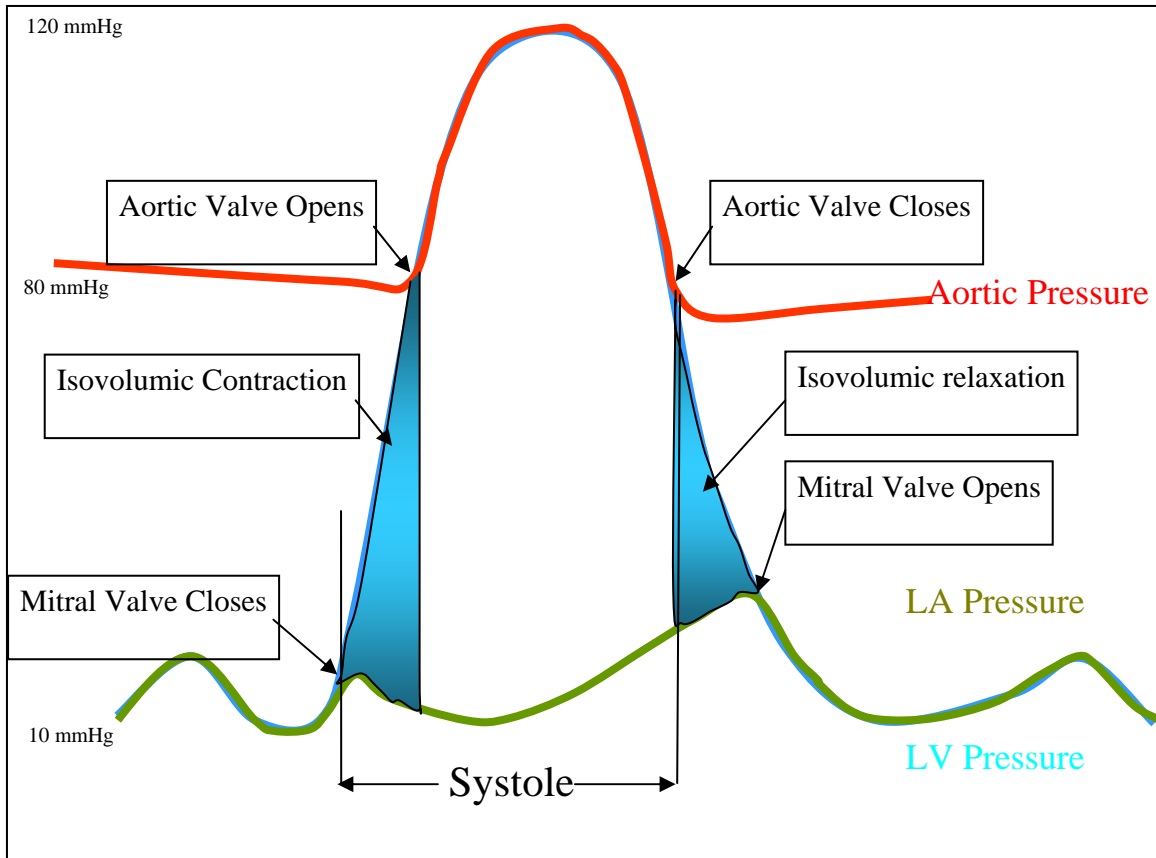
Intra atrial pressure recordings reveal two peaks and two descents. The **a wave** is the atrial pressure generated during atrial systole immediately preceding ventricular systole. The peak atrial pressure recorded during ventricular systole before the tricuspid and mitral valves open is the **v wave**.



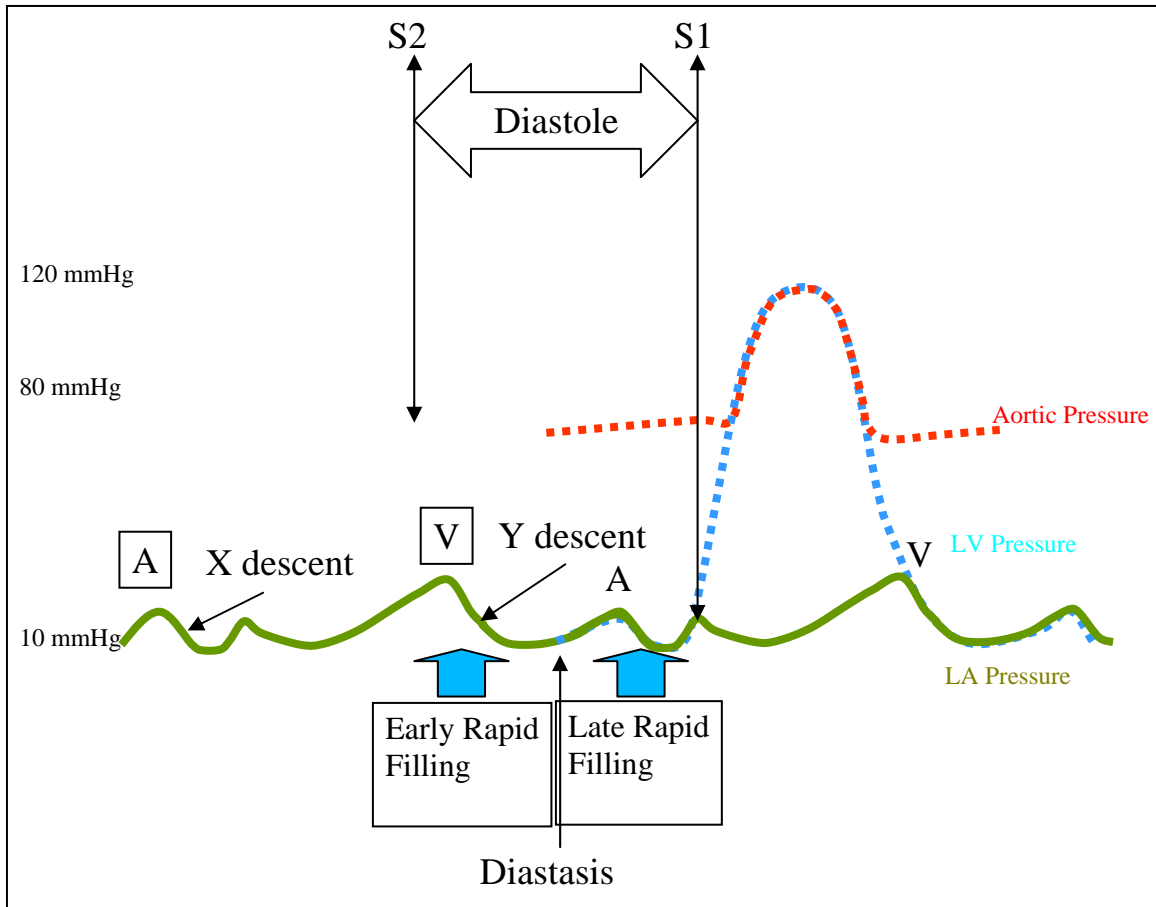
The Cardiac Cycle. Definition of Systole and Diastole. Opening and Closure of the Aortic and Mitral Valves.



Superimposed are the left atrial pressure tracing (green), the left ventricular pressure tracing (blue) and the aortic pressure tracing. S1 occurs when the mitral and tricuspid valves close at the onset of systole. When pressure in the LV cavity falls below aortic pressure at the end of systole, the aortic pulmonic valves close and generate S2. The mitral valve opens when LA pressure exceeds left ventricular pressure. S3 can normally be heard in individuals without heart disease up to the age of 40 and occurs when blood rushes into the left ventricle (first rapid filling phase) after the mitral valve opens in diastole. An S4 is usually an abnormal finding and occurs at the time of the second rapid filling phase of the left ventricle. It remains debatable if a “normal” S4 occurs in the elderly particularly after exercise.



The Isovolumic Phases of the Cardiac Cycle. Left ventricular contraction begins when the mitral valve shuts (S1) however it is only when the LV cavity pressure exceeds aortic pressure that the actual ejection of blood occurs. The period in between is the isovolumic contraction. The isovolumic relaxation time is the time between the closure of the aortic valve (S2) and the opening of the mitral valve at the onset of the first rapid filling phase.



Two successive cycles are shown. The cycle on the left has only the atrial tracing displayed while the tracing on the right has superimposed left ventricular and aortic pressure tracings to demonstrate the relationship between the atrial cycle and the ventricular cycle. Towards the end of diastole, the atrial pressure immediately preceding the opening of the mitral and tricuspid valves is the **V wave**. The opening of the tricuspid and mitral valves lead to the **first rapid filling phase**, during which most of ventricular filling occurs. The **A wave** is generated by the contraction of the atrium expelling blood from the atria to the ventricles during the **second rapid filling phase** of ventricular diastole. The period separating the first and second rapid filling phases of the ventricle is called **diastasis**. In practice, measured atrial pressure is a mean of the recorded atrial pressures.

4. Intra Cardiac Pressures

Many factors play a role in generating intra cardiac pressures. Recording intra cardiac pressures help distinguish various pathophysiologic states from each other. This would determine the type of therapy the patient receives. A patient with a low blood pressure and low right and left filling pressures probably suffers from dehydration whereas a low blood pressure with high filling pressures would point to cardiogenic shock. Therapy in the former would consist of fluid resuscitation whereas in the latter, would consist of positive inotropic agents.

Although the atrial waveforms have two peaks and troughs per cycle, their pressures are often described as one mean value. In the ventricles and the main arteries (aortic and pulmonary) pressures are described in systolic and diastolic phases of each cycle. In diastole and in the absence of stenosis of the AV valves (tricuspid and mitral) right atrial and left atrial pressures are equal to right and left ventricular diastolic pressures respectively.

Mean RA pressure = RV diastolic pressure

Mean LA pressure = LV diastolic pressure

In systole and in the absence of stenosis of the pulmonic or aortic valves, right ventricular systolic pressure equals pulmonary artery systolic pressure and left ventricular systolic pressure equals aortic systolic pressure.

RV systolic pressure = PA systolic pressure

LV systolic pressure = Ao systolic pressure

In aortic stenosis, for example, the classical finding on cardiac catheterization is an LV systolic pressure > aortic systolic pressure. The tight aortic valve fails to transmit LV pressure to the aorta.

Preload is one of the main determinants of LV (cardiac) stroke volume. Left ventricular preload is measured as the left ventricular end-diastolic pressure. This is the pressure at the end of diastole measured in the LV after it has filled up with blood from the left atrium. Elevated end-diastolic pressure is consistent with heart failure and a low pressure with volume depletion such as with dehydration or significant hemorrhage. The left ventricular end-diastolic pressure, *in the absence of mitral stenosis*, is equal to the left atrial pressure. The left atrial pressure can be indirectly measured by wedging a catheter in the distal pulmonary artery. This catheter is introduced from a systemic vein such as the internal jugular, subclavian or femoral vein and is advanced across the tricuspid and pulmonary valves. Once the catheter tip has been wedged and its location confirmed radiographically, by oximetry and waveform, the pressure is used to reflect the left ventricular end diastolic pressure (filling pressure). This pressure is called the pulmonary capillary wedge pressure (PCWP). In the absence of pulmonary vascular disease, the pulmonary artery diastolic pressure is equal to the PCWP.

LVEDP = LA pressure = PCWP = PA diastolic pressure*

* In the absence of mitral stenosis and pulmonary vascular disease.

RA	RV	PA	LA	LV	Ao
2-6	15-30/2-6	15-30/6-12	6-12	100-140/6-12	100-140/60-80

Above are representative intra cardiac pressures in mmHg

In **mitral stenosis** the classical hemodynamic change seen is an LA pressure > LV end diastolic pressure. Blood is impeded in its flow across the mitral valve in diastole hence the differences in diastolic pressure. In **aortic stenosis**, LV systolic pressure > aortic systolic pressure. The narrowed aortic valve impedes flow from the LV into the aorta in systole

5. Cardiac Output

Cardiac output is heart rate (HR) X stroke volume (SV). Stroke volume is the volume of blood ejected during each cardiac cycle. **Stroke volume = End-diastolic volume (EDV) – End-systolic volume (ESV).** A normal stroke index is 45 +/- 13 mL/M² body surface area. The determinants of cardiac output are **Preload, Contractility** and **Afterload.**

Preload refers to the degree the ventricle is distended (extent of myofibrillar stretch) before systole occurs. The Frank-Starling law states that within limits stroke volume is greater the more distended the ventricle is (the greater the degree of stretch) at the end of diastole. Hence, the greater end-diastolic volume is the greater stroke volume is. Patients who are dehydrated or have suffered significant hemorrhage have lower cardiac outputs despite having a normal ventricle because they have lower preload. This is rectified by increasing their preload with the administration of fluid or blood.

At a fixed preload and afterload, the **contractility** of the myocardium can vary. The greater the degree of inotropy (contractility; in Latin; *ino* is “fiber” and *tropy* “to move”) the more forceful the contraction, the higher the ensuing stroke volume. In the Frank-Starling curve different degrees of inotropy are represented by different curves. These curves plot preload against the generated cardiac output at that specific level of contractility. A ventricle with greater contractility will have a curve shifted upward and to the left hence generating a higher cardiac output at the same preload (and afterload). A failing heart will have a curve shifted to the bottom and to the right.

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The **left ventricular ejection fraction (LVEF)** is an indicator of left ventricular systolic function. It represents the ratio of ejected blood to the volume of blood immediately before the aortic and pulmonic valves open. Normally the left ventricular ejection fraction is 67% +/- 8%. A ventricle that has suffered irreversible damage (e.g. after a myocardial infarction) typically has a depressed contractility.

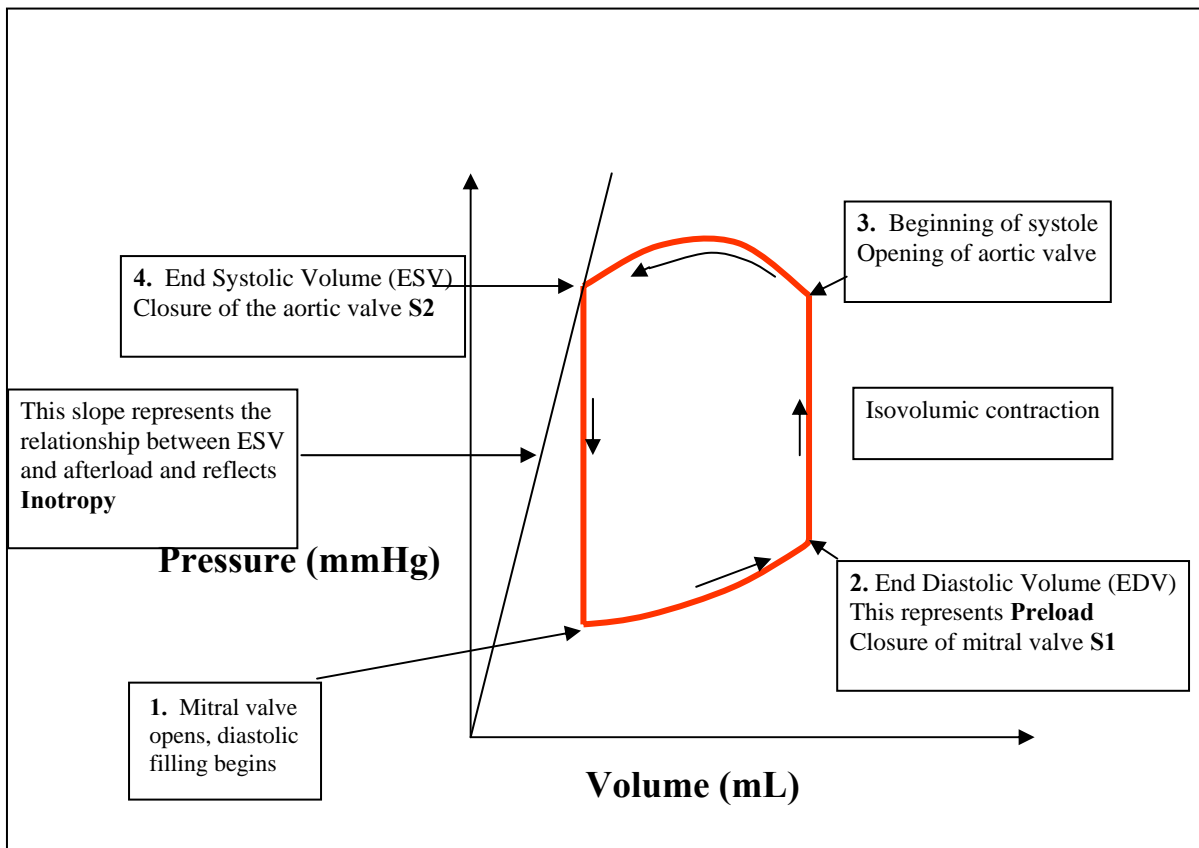
$$\text{LVEF} = \text{Stroke volume} / \text{End diastolic volume}$$

Afterload is the force against which the heart has to pump. **Ventricular wall stress** best represents afterload and is formally defined by **Laplace's law**;

$$\text{Wall stress } (\sigma) = \text{Pressure} \times \text{Ventricular Radius} / 2 \times \text{wall thickness}$$

Practically afterload is represented by the aortic systolic pressure. The relationship between cardiac output and afterload is inverse; the greater the afterload, the lower the cardiac output. Examples of increased afterload include hypertension and aortic stenosis. The increase in wall thickness that develops with time in these two conditions (left ventricular hypertrophy) leads to a decline in wall stress.

Another way of looking at cardiac output and its main determinants is the Pressure-Volume loop. This graph plots the pressures in the ventricle against the volume of that ventricle.



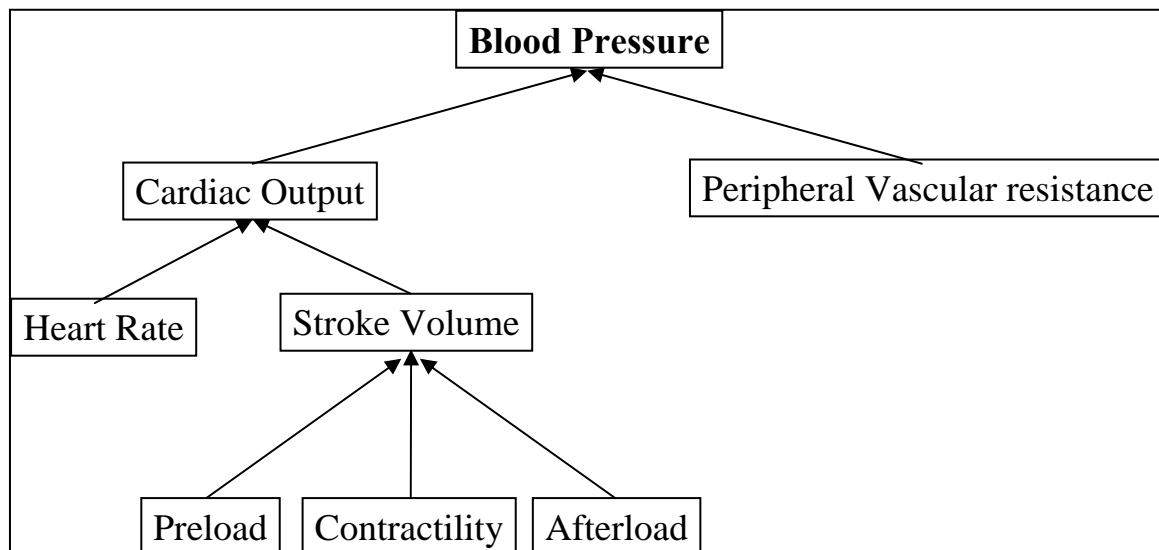
We can begin at any point. If we begin at point **1**, where the ventricle now begins to fill after the tricuspid and mitral valves open, the filling pressure is seen to rise (from left to right) until it reaches the end-diastolic pressure (EDP or end diastolic volume EDV) at **2**. The pressure (and volume) at this point represents **Preload**. Point **2** represents the beginning of systole, pressure is rising, the aortic and pulmonic valves have not yet opened, and the ventricular volumes remain unchanged. This phase is the **isovolumic contraction phase**. Once intracavitary pressures exceed pressures in the aorta and pulmonary artery the aortic and pulmonic valves open at point **3** and the ejection of blood begins. At point **4**, intracavitary pressures begin to fall and the aortic and pulmonic valves

close creating S2. The ventricular pressures decline with no change in volume, this is the **isovolumic relaxation phase**.

6. Systemic and pulmonary pressure and resistance

The heart pumps blood into two arterial systems, the right heart into the pulmonary vascular system and the left ventricle into the systemic vascular system. While normally the cardiac output of both sides of the heart is the same, the resistance of their respective arterial system and the pressures within these systems are different. The resistance of the pulmonary vascular system is $1/17^{\text{th}}$ of the systemic vasculature.

As systemic pressure and its determinants remain poorly understood, the causes of hypertension remain poorly defined. Systemic pressure is determined by cardiac output, which has been extensively discussed, and peripheral resistance. Peripheral resistance is the vascular tone maintained by the arterial system in the body. The vascular tone helps maintain perfusion and assists in maintaining a homeostatic blood pressure. When cardiac output goes down, for example, vascular tone increases to maintain blood pressure in the face of a declining cardiac output. Changes in blood pressure due to changes in peripheral vascular resistance are unusual. Examples include excessive vasodilation from anti-hypertensive medications, and vasodilation from anaphylactic shock. Measurement of peripheral vascular resistance can help distinguish different types of shock. In anaphylactic shock and septic shock, peripheral vascular resistance is typically low in the early stages. In cardiogenic shock and hypovolemic shock, peripheral vascular resistance is elevated in the body's attempt to maintain the blood pressure and hence perfusion, to vital organs.



Although cardiac output is **pulsatile** the calculation of vascular resistance uses a modification of Ohm's law used for continuous flow. Resistance is the ratio between the

pressure differential across the vascular system being studied and cardiac output. The units are either dynes-sec-cm⁻⁵ or if divided by 80, Wood units.

$$\text{Resistance} = \text{Pressure Gradient} / \text{Cardiac Output (CO)}$$

$$\text{Pulmonary Vascular Resistance} = (\text{Mean PA pressure} - \text{LA pressure}) / \text{CO}$$

$$\text{Systemic Vascular Resistance} = (\text{Mean Aortic pressure} - \text{RA pressure}) / \text{CO}$$

$$\text{Mean Pulmonary pressure} = (\text{Systolic pressure} + 2 \text{ Diastolic pressure}) / 3$$

$$\text{Mean Arterial pressure} = (\text{Systolic pressure} + 2 \text{ Diastolic pressure}) / 3$$

The **mean arterial pressure (MAP)** of an individual with a BP 120 / 80 mmHg is $(120 + 2 \times 80) / 3 = 93$ mmHg. Normal systemic vascular resistance is 2130 ± 270 dynes-sec-cm⁻⁵, normal pulmonary vascular resistance is 123 ± 54 dynes-sec-cm⁻⁵. Systemic vascular resistance is elevated in low cardiac output states such as congestive heart failure and hypovolemic shock. Resistance is low when patients are in the early stages of septic shock and in high cardiac output states such as arteriovenous fistulas, anemia and Paget's disease. Elevated pulmonary vascular resistance may be fixed or reversible. Reversible causes include hypoxia and hypercarbia. Irreversible causes include Eisenmenger's syndrome and recurrent pulmonary embolism.

Cardiac Output is measured in one of two ways. The easiest and most popular method is the thermodilution method. Using a balloon tipped Swan-Ganz catheter inserted via a systemic vein such as the internal jugular or subclavian vein, the tip of the catheter contains a thermistor that is advanced to the pulmonary artery. Cold saline with a measured temperature is injected via a proximal port. The thermistor at the tip of the catheter measures the temperature and the change in temperature is plotted versus time. The area under the curve represents cardiac output. This method is not reliable in the presence of tricuspid valve regurgitation or when cardiac output is low.

The second method, the Fick method, requires measurement of total O₂ consumption, arterial and venous O₂ content. Cardiac Output is measured as

$$\text{Total O}_2 \text{ Consumption} / \text{Arterio-Venous O}_2 \text{ difference (vol\%)} \times 10$$

Patients with low cardiac output have a low systemic venous O₂ content. The body is trying to extract as much O₂ as possible to make up for the reduced delivery of O₂. Hence the returning venous O₂ content is low. Cardiac output is often normalized to body surface area and is described as **Cardiac Index**.

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In practice, measurement of right and left filling pressures and cardiac output (using the thermodilution method) is performed using a **Swan-Ganz catheter**. This balloon tipped

catheter is introduced from a systemic vein (jugular, subclavian or femoral vein). Once the balloon is inflated, the tip is advanced into the right atrium, across the tricuspid valve into the right ventricle and then across the pulmonary vein into the pulmonary artery. The catheter tip is then wedged into a distal pulmonary arteriole. The pressure recorded in the wedged position represents left atrial pressure and is called the **pulmonary capillary wedge pressure (PCWP)**. In the absence of mitral stenosis, this pressure reflects left ventricular diastolic pressure (the filling pressure of the left ventricle). Advancement of the catheter tip is either performed by observing the morphology of the recorded pressure waveform, under fluoroscopy or both. Determining this pressure helps distinguish between different causes of hypotension. In cardiogenic shock and pericardial tamponade the PCWP is elevated and the systemic pressure is low. In dehydration and critical hemorrhage, the PCWP is low.