Cardio-Vascular System

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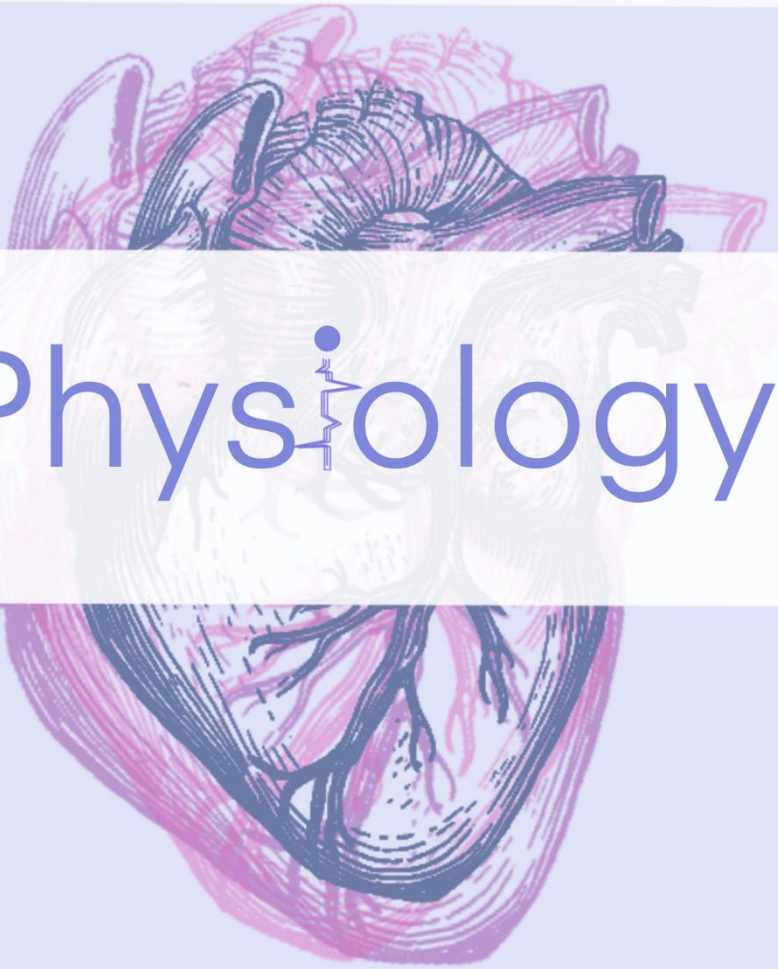

Physiology

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Review

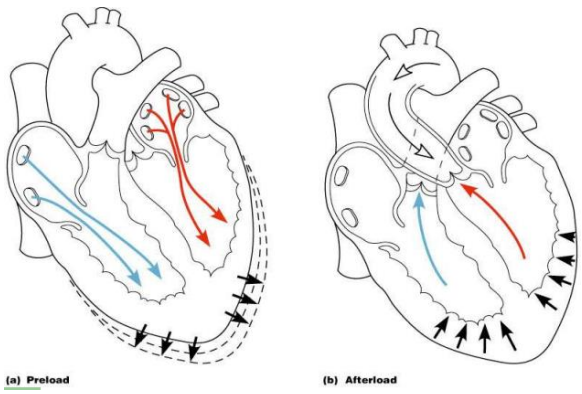
Last time we discussed the control of stroke volume and cardiac output.

Three factors control the stroke volume:

1. Preload, or the degree of stretch, of cardiac muscle cells before they contract.
   a. The Frank-Starling Law states that, within **physiological limits**, the higher the preload the higher the stroke volume. This can be stated in another way: an increase in the length of the muscle before it contracts (resting length, passive length, passive tension) increases the force of contraction. However, we cannot measure the length in the heart, but we can measure the volume of the ventricle before it contracts (diastolic volume), and this is what we refer to as the preload.
   b. Preload is affected by the heart rate and blood volume.
2. Contractility
3. Afterload

The left figure indicates the **preload**, the amount of blood found in the ventricle before it contracts. The ventricles are dilated and full of blood.

The right figure indicates the **afterload**, the force that the ventricle has to exert to open the semilunar valves. To do so, the force that has to develop in the right and left ventricles should be higher than the diastolic pressure in the pulmonary artery and aorta, respectively.



Cardiac Output

There are different mechanisms that ultimately lead to an increase in cardiac output. The cardiac output increases with increasing stroke volume, heart rate, or both.

As we discussed earlier, three factors can increase the stroke volume:

1. **Increased Preload**
   a. Within physiological limits, cardiac muscle fibers contract more forcefully with stretching (Frank-Starling Law of the heart).
2. **Increased Contractility**
   a. Positive inotropic agents such as increased sympathetic stimulation, catecholamines (E and NE, postganglionic neurotransmitters in the SNS), glucagon (an endocrine hormone secreted by the pancreas), thyroid hormones in the blood (T3 and T4), and increased Ca^{2+} in extracellular fluid increase the contractility by increasing the force of contraction at all physiological levels of stretch.

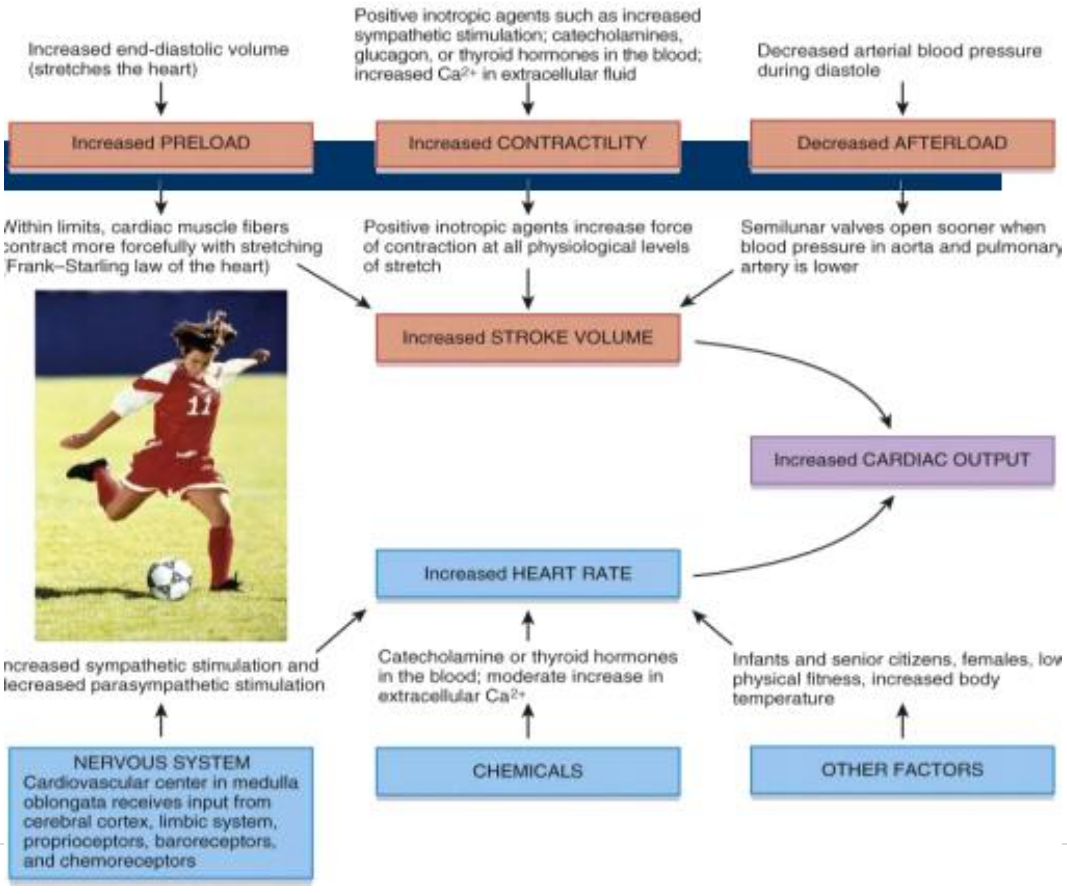
3. **Decreased Afterload**
   a. Decreased arterial blood pressure (in the aorta and pulmonary artery) during diastole decreases afterload and therefore the semilunar valves open sooner.

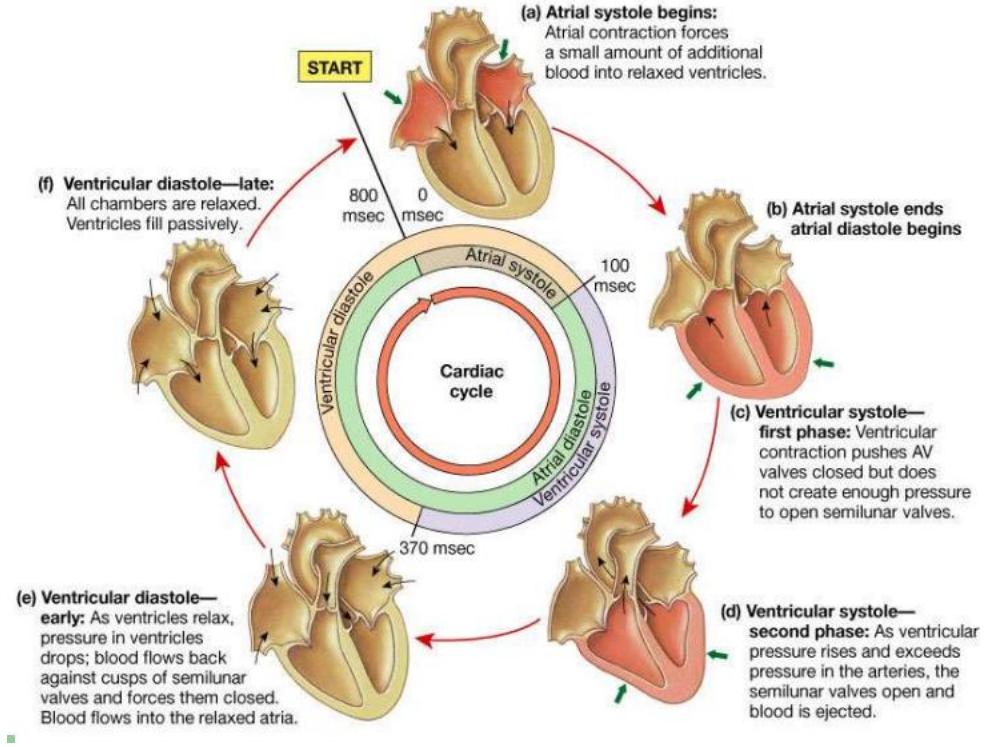
There are also three factors that increase **heart rate**:

1. The Nervous System
   a. Increased sympathetic stimulation and decreased parasympathetic stimulation increase heart rate.
   b. The cardiovascular center in the medulla oblongata receives input from the cerebral cortex, limbic system, proprioceptors, baroreceptors, and chemoreceptors.
2. Chemicals
   a. Catecholamines or thyroid hormones in the blood and moderate increases in extracellular Ca^{2+} increase heart rate.
      i. Patients with hyperthyroidism have tachycardia.
      ii. Patients who are nervous (=increased sympathetic stimulation) also have increased heart rate.
   b. Other factors
      i. Infants and senior citizens, females, low physical fitness, and increased body temperature (patients with fever have higher heart rate, which sometimes may lead to lower stroke volume by decreasing the ventricular filling time, which results in lower diastolic volume (preload)).

Recall that when you multiply heart rate and stroke volume you get the cardiac output.

This figure restates everything that we have discussed:





Note on the image above: (the professor read every word in the figure)

The atrial systole only imparts less than 25% of the ventricular volume. This means that the volume of blood pumped by contraction of the atria is less than 25% of the final blood volume of the ventricles. This is because the AV valves remain open before the atrial contraction, so even if the atria do not contract a large amount of blood still reaches the ventricles. In fact, atrial systole is not essential for the normal functioning of the heart.

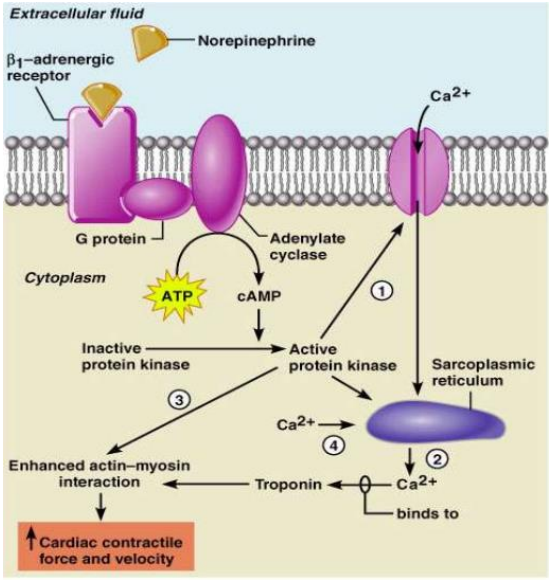
Extrinsic Factors Influencing Stroke Volume

Contractility *(extra: Contractility refers to the innate ability of the myocardial cells to contract.)* is independent of stretch and EDV (end diastolic volume). We already discussed the factors that increase contractility, such as increased sympathetic stimuli, certain hormones (T3, T4, and glucagon), Ca^{2+}, and some drugs (such as digoxin, a positive inotropic agent).

Other factors *decrease* contractility:

1. Acidosis – Decreased pH inhibits cellular enzymes and this will cause a depression in cellular activity.
2. Increased Extracellular K^{+} (hyperkalemia)
3. Calcium channel blockers – By blocking calcium influx through the slow calcium channels, intracellular calcium levels will decrease and this lowers the force of contraction.

Contractility and Norepinephrine



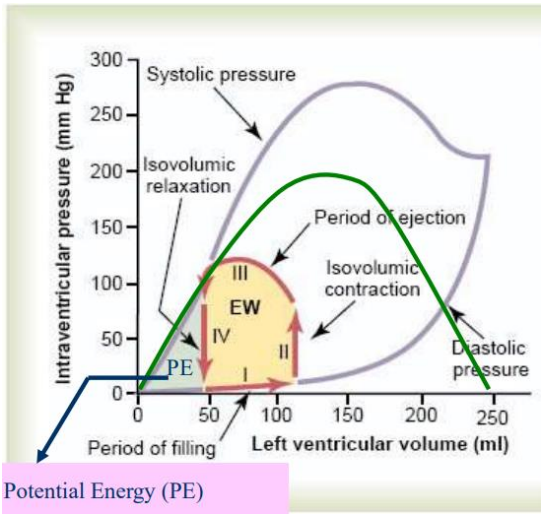
The sympathetic nervous system has positive inotropic and chronotropic effects. Catecholamines act on the heart by binding to their **β_1 receptors**. These receptors are G-protein coupled receptors, and when bound by norepinephrine, the alpha subunit of the G protein dissociates. The alpha subunit then activates adenylate cyclase (a membrane enzyme), which converts ATP to cAMP. cAMP activates **PKA**, a cyclin-dependent protein kinase.

How is the **inotropic effect** then caused? The activated PKA causes multiple effects:

1. It activates calcium channels to increase influx of Ca^{2+}. More Ca^{2+} influx leads to higher contractility.
2. It enhances the actin-myosin interaction, which increases cardiac contractility.
3. More Ca^{2+} influx means more Ca^{2+} release from the sarcoplasmic reticulum, which leads to a higher force of contraction.

Recall when we took the **chronotropic effect** caused by catecholamines. Activated PKA phosphorylates phospholamban, a sarcoplasmic reticulum protein. This leads to quicker uptake of Ca^{2+} through the SR Ca^{2+} pump. This shortens the time for relaxation, which increases the heart rate.

Left Ventricular Pressure/Volume (P/V) Loop



We will now look at the cardiac cycle, and the control of the cardiac cycle, through a mathematical presentation.

Let's begin by understanding the components of the left ventricular pressure/volume graph:

The left ventricular volume is plotted on the x-axis, while the intraventricular pressure (tension) is plotted on the y-axis.

The diastolic pressure line indicates the changes in passive tension and end-diastolic pressure that can occur. The systolic pressure line indicates the changes in total tension, and the green line indicates the active tension.

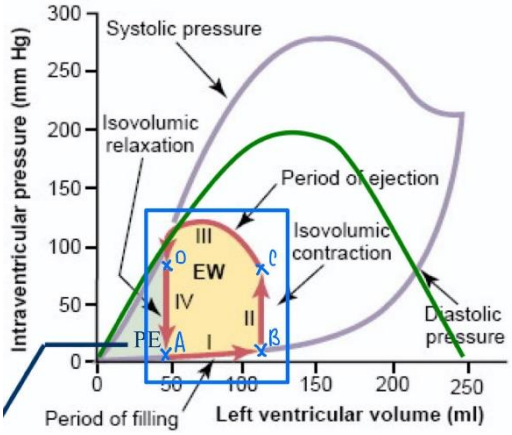
(Active Tension = Total Tension – Passive Tension)

The entire figure is drawn to represent the ability of the heart to change its resting, active, and total tension.

Extra clarification from the textbook:

The diastolic pressure curve (lower purple line) is determined by filling the heart with progressively greater volumes of blood and then measuring the diastolic pressure immediately before ventricular contraction occurs, which is the end-diastolic pressure of the ventricle.

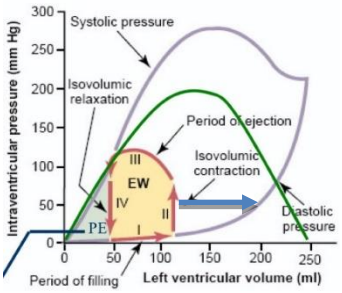
The systolic pressure curve (upper purple line) is determined by recording the systolic pressure achieved during ventricular contraction at each volume of filling.



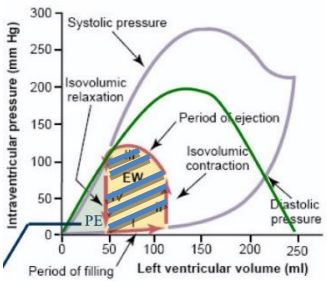
Next, we will draw our focus to the left ventricular P/V loop, which is outlined by the blue box. This part of the figure illustrates the cardiac cycle:

- Point A: AV valve opens. Here we can see the value of the end-systolic volume (ESV).
- Phase I: Period of blood filling in the ventricle. There is little increase of pressure.
- Point B: AV valve closes (Sound 1). Here we see the EDV.
- Phase II: Isovolumic contraction – No change in volume, there is only change in pressure.
- Point C: Semilunar valve opens.
- Phase III: Period of Ejection – During ejection there is increase in pressure and decrease in volume of the ventricle.
- Point D: Semilunar valve closes. (Sound 2)
- Phase IV: Isovolumic relaxation – No change in volume with decrease in pressure.

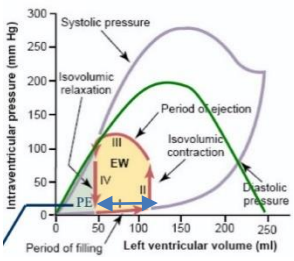
Diastole is phases I and IV (mostly I, since IV is short). Systole is phases II and III. In fact, the time for phase I is greater than the times of phases II, III, and IV combined.



This curve (or loop) represents one cardiac cycle. This cardiac cycle can however change, for example the end-diastolic volume can increase (indicated by the blue arrow).



The area under the curve (shaded with blue lines) is the energy that can be used to move the blood inside the circulation. This is called the **external work (EW)**. *(or, as the textbook defines it, the work needed to move blood from the low pressure-veins to the high-pressure arteries).*



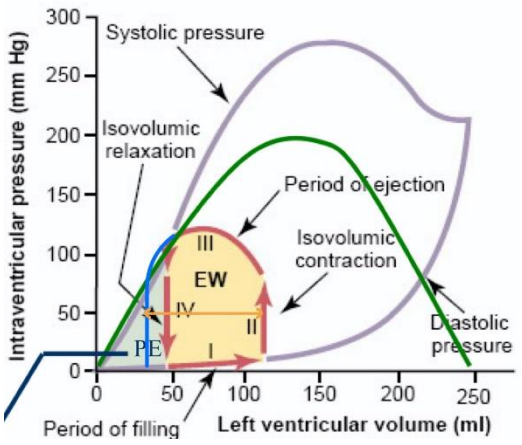
EW = Stroke Volume x Pressure

Pressure = Mean change in systolic pressure - Mean change in diastolic pressure.

Also recall that the stroke volume = EDV-ESV. The length of the double-sided arrow in the graph indicates the stroke volume.

We can also see the graph illustrates the potential energy (PE). This is the energy stored in the system that can be used to increase the stroke volume without increasing the EDV. *(or, as the textbook defines it, the PE represents additional work that could be accomplished by contraction of the ventricle if the ventricle should completely empty all the blood in its chamber with each contraction)*

As shown in the figure, the curve will extend to where the PE is utilized (decreasing the ESV by shifting it to the left). In this case, where the EDV is fixed but the stroke volume increased, there is an increase in contractility. There is also an increase in the ejection fraction.



Increase in contractility = Use part of the PE stored in the system.

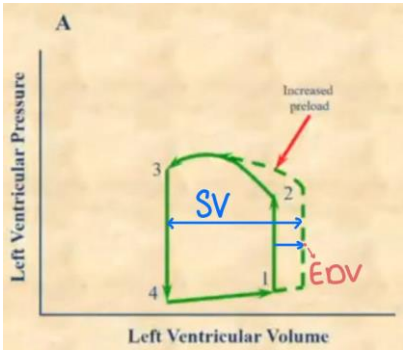
(Added explanation: Stroke volume = EDV – ESV, so when we lower the ESV this increases the stroke volume)

Valvular Function

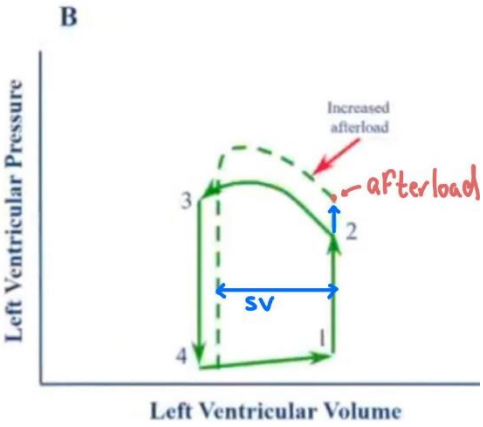
- The function of valves is to prevent back-flow of blood.
- The back-flow of blood to the atria is prevented by the chorda tendineae, which are attached to the AV-valves. The chorda tendineae, in turn, are attached to the papillary muscles, which contract when the ventricles contract (during systole).
- Because the openings of the semilunar valves are smaller than those of the AV valves, the velocity of blood ejection through the aortic and pulmonary valves is far greater than that through the AV valves.
- Most of the work output of the heart is the external work (also known as pressure-volume work).
- A small amount of work is required to impart kinetic energy to the heart ($\frac{1}{2}mv^2$). This KE is normally negligible. However, this KE becomes important when there is aortic stenosis- to the point that the KE will form more than 50% of the total work output). This is because in aortic stenosis the aortic valve is narrowed, and to move the same amount of blood through the narrower valve needs a larger amount of KE. This can be very dangerous, especially if the orifice is extremely narrowed, because the left ventricle has to spend a lot of energy to move the blood through the orifice.
- External work is the area of the pressure-volume curve.
- Work output is affected by preload (end-diastolic pressure) and afterload (aortic pressure).

Pressure/Volume Relationships Under Different Conditions

Here we can see a shift in the isovolumetric curve to the right, indicating an increase in the EDV. This leads to an increase in the SV. Increased EDV indicates increased preload.



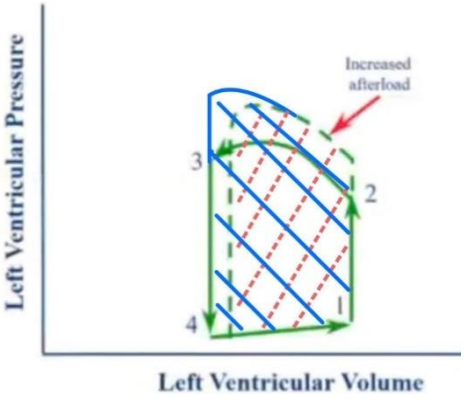
Conclusion: Increased preload = Increased SV (Frank-Starling Law)

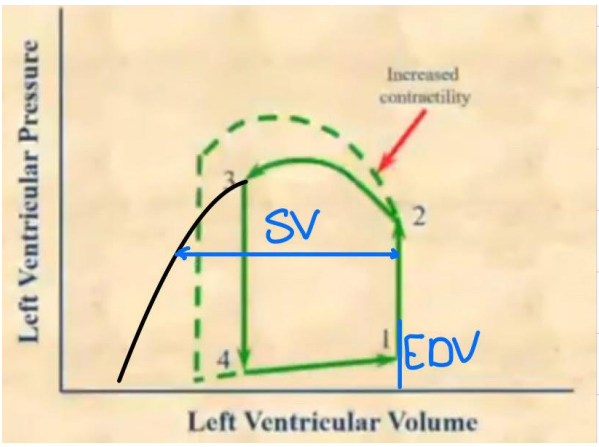


Here we can see a shift in the pressure curve upwards. This means the arterial diastolic pressure, or the afterload, shifts upward. To keep the external work (area) the same, there must be a decrease in the stroke volume.

However, the SV can be maintained if the energy (to convert to work) is increased. This is the danger of hypertension. With arterial hypertension, there is increased diastolic and systolic pressure. If you increase the arterial diastolic pressure, the heart has to spend more energy than before to keep the stroke volume the same (more energy is needed to overcome the pressure in aorta that keeps the aortic valve closed *and* pump the same amount of blood).

This can be seen in the graph, where the stroke volume is maintained if the area increased (blue lines), indicating more work than if the stroke volume had lowered (pink dashed lines). If the heart is unable to meet the demand of the increased workload, then stroke volume, and therefore cardiac output, decreases and the amount of blood pumped may not be enough to supply the tissues.





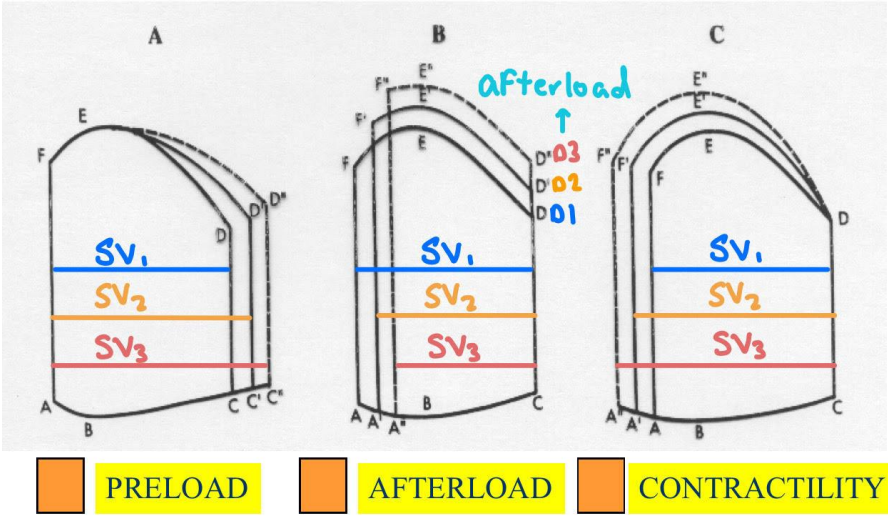
Here, we have increased contractility by using a portion of the potential energy (black curve). Therefore, there is an increase in SV but the EDV remains the same. This is done by positive inotropic agents.

The next figure summarizes what we've discussed:

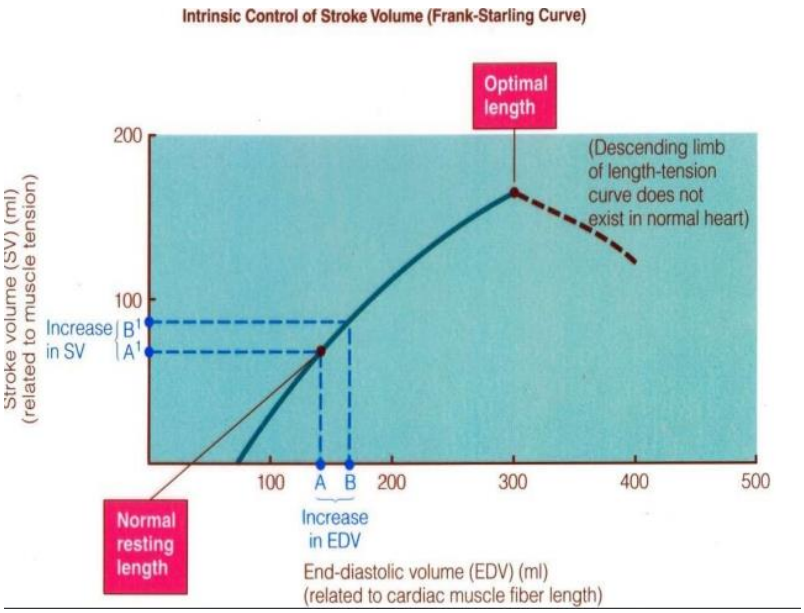
Graph A: With successfully increasing preload there is increased stroke volume.

Graph B: With increasing afterload, SV decreases (this will ensure that the work (area) is the same for all three curves).

Graph C: EDV remains the same. Increasing SV indicates increasing contractility. (positive inotropic action)



This graph plots EDV on the x-axis and SV on the y-axis. As you can see, this is a representation of the Frank-Starling law. The higher the EDV the higher the SV up to the physiological limit (the optimal length). After this length, although the EDV increases the SV decreases. This indicates heart failure.



Regulation of Heart Rate

- Positive chronotropic factors increase heart rate. (ex: sympathetic nervous system [SNS])
- Negative chronotropic factors decrease heart rate. (ex: parasympathetic nervous system [PNS])

Autonomic Nervous System Regulation

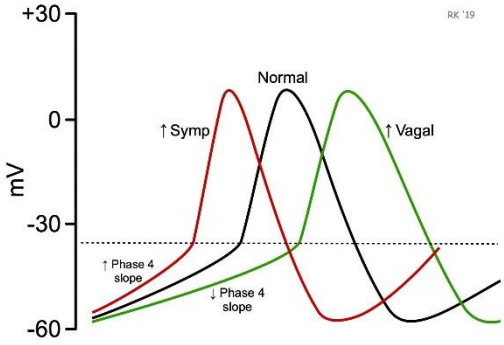
- SNS stimulation is activated by stress, anxiety, excitement, or exercise.
- PNS stimulation is mediated by acetylcholine and opposes the SNS.
- The PNS dominates the autonomic stimulation of the heart rate, slowing it down and causing vagal tone.
- The SNS dominates the autonomic stimulation of contractility.

→ What would happen if the parasympathetic and sympathetic fibers to the heart were cut?

The heart rate would increase (due to loss of parasympathetic innervation) and the contractility would decrease (due to loss of sympathetic innervation).

The Atrial (Brainbridge) Reflex (Brainbridge was a scientist)

The atrial (Brainbridge) reflex is a sympathetic reflex initiated by increased blood in the atria (specifically the right atrium). Increased right atrial pressure presses on the SA node, increasing its permeability to sodium and calcium. This will affect the SA node depolarization curve by making the resting membrane potential less negative and by increasing the slope (red curve), which will lead to increased heart rate.



Increased blood in the atria also stimulates baroreceptors in the atria, causing increased SNS stimulation.

Chemical Regulation

- The hormones epinephrine and thyroxine increase heart rate.
- Intracellular and extracellular ion concentrations must be maintained for normal heart function.
    - Hypercalcemia leads to increased heart rate.

Important Concepts About Cardiac Output Control

- Cardiac output (CO) is the sum of all tissue flows and is affected by their regulation. CO = 5L/min (all blood that leaves the heart from the aorta goes to the tissues, so the sum of all blood flows to the tissues equals the cardiac output).
- CO varies between individuals due to size and gender. Therefore, another measure used is the **cardiac index**. Cardiac index = CO/Surface area(m^2) (unit is L/min/m^2). So, it is better to compare individuals with their cardiac index and not their cardiac output.
- CO is proportional to tissue O_2 use.
    - The higher the exercise level of an individual, the higher their O_2 use, and the higher their CO.

The cardiac output can also be thought as the flow of blood from the aorta to the right atrium. We can calculate CO through the equation:

$$CO = Flow = \frac{\Delta P}{R} = \frac{(Mean\ arterial\ pressure) - (Right\ atrial\ pressure)}{Total\ peripheral\ resistance}$$

CO is proportional to 1/TPR (total peripheral resistance) when arterial pressure is constant. Why do we only refer to arterial pressure? It's because the right atrial pressure is zero, so the equation can also be written as:

$$CO = Flow = \frac{\Delta P}{R} = \frac{(Mean\ arterial\ pressure)}{Total\ peripheral\ resistance}$$

Goodluck!