Factors that control the stroke volume are divided into:
1- Intrinsic factors represented by frank-starling law.
2- Extrinsic factors.

Some terms have been mentioned in the previous lecture with further clarification:
- Preload: the amount of tension found in the ventricle before it contracts.
  The measurement of preload is proportional to the EDV (which represents the passive tension) or EDP.
  Whether we said it is proportional to EDV or EDP doesn't matter bcz EDV and EDP are proportional that as the volume of blood increases at the end of diastole, the pressure will increase at the end of diastole.
  The higher the preload, the higher the stroke volume up to physiological limits (optimal length). Once the optimal length has been exceeded, an increase in the EDV will be accompanied by decrease in the SV (a state of heart failure).

- Afterload: the amount of tension (pressure) that the ventricle has to develop to eject blood.
  For example, the left ventricle, has to develop pressure equals to or higher than the aortic pressure during diastole.
  As the afterload is increasing, the SV will be decreased, and that's why hypertension is a dangerous condition.
  So in a hypertensive patient who has a diastolic pressure (120 mmHg), the left ventricle must develop a pressure equal to or higher than 120 which is too high. In such a case, the heart demands of oxygen, blood, energy…will be increased to exert such a force.
  Unfortunately, this hypertensive patient, if he has coronary artery disease, aortic stenosis, he might end up with MI or angina pectoris which is a life threatening state.
  Nevertheless, if he has the capacity to introduce these demands, by increasing the work, ejection takes place but with lower SV and so less CO.

- Contractility: a measure of how effective the heart is.
  The measurement of contractility is difficult. It is proportional to the change in pressure overtime. And it is not changed significantly, so we take the maximal change in pressure overtime.
  When we talked about the cardiac cycle, the pressure during the isovolumetric contraction was increasing steeply so we can take the slope,
  The slope = the change in pressure over time.
  The slope is the maximum dP / dt (the maximum change in pressure over time).
So the instruments that are used to measure the contractility will calculate the maximum $dP/dt$.
And maximum $dP/dt$ is used as an index to study the changes in the cardiac contractility as I have read in the net.
This is have been quoted from the net also:

<table>
<thead>
<tr>
<th>LV $dP/dt$ Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>This is an index that is used clinically to characterize the contractile ability of the heart. It is believed that maximum $dP/dt$ is a reasonable index of the initial velocity of myocardial contraction. The maximum left ventricular $dP/dt$, which is normally about 1600 mm Hg/sec, tends</td>
</tr>
</tbody>
</table>

When we talk about the myocardial contractility, the EDV must be fixed and the stroke volume can be changed.
So let us see the effect of different agents on the myocardial contractility:

- **+ve ionotropic agents**
  They increase the contractility by decreasing the ESV and we know that the EDV is constant so SV will be increased. (what is taken from ESV is pumped with SV)

- **-ve ionotropic agents**
  They decrease the contractility by increasing the ESV.
  So contractility is measured when EDV is fixed.
  Manipulation of EDV does not refer to contractility. It refers to Frank starling mechanism which is an intrinsic property of the heart.

**Venous return**
It is the amount of blood that returns to the heart through the venous system PER minute.
Keep in mind that the blood whether oxygenated or deoxygenated returns to the heart via the venous system, oxygenated to the left atrium through pulmonary veins, deoxygenated to the right atrium through SVC and IVC.

**Effect of HR, blood loss and exercise on SV**

1- **slow heart rate**
It increases the time for diastole as a result, increasing the time for filling of the heart with blood so increasing the venous return.
Now high venous return will increase the EDV and according to frank starling SV will be increased

2- **exercise**
During exercise, the sympathetic system is stimulated leading to increase contractility of the heart.
Another mechanism is the muscle system pump. Peripheral veins, particularly in the legs and arms, have one-way valves that direct flow away from the limb and toward the heart. Veins physically located within large muscle groups undergo compression as the muscles surrounding them contract, and they become decompressed as the muscles relax. This increases the venous return and so SV.

3- blood loss
Blood loss decreases blood volume which is associated with decrease in venous return >> decrease EDV and consequently decrease SV.

4- rapid HR
It decreases the diastolic period (time for filling) and so the EDV and subsequently SV are decreased.

Factors Affecting Stroke Volume

- **Preload** – amount ventricles are stretched by contained blood
- **Contractility** – cardiac cell contractile force due to factors other than EDV
- **Afterload** – back pressure exerted by blood in the large arteries leaving the heart

Frank-Starling Law of the Heart

- **Preload**, or degree of stretch, of cardiac muscle cells before they contract is the critical factor controlling stroke volume
- **Slow heartbeat and exercise increase venous return to the heart**, increasing SV
- **Blood loss and extremely rapid heartbeat decrease SV**

Regarding the drawing below
a- preload: tension in the ventricle before it contracts.
b- Afterload: tension to exert contraction.

If the pressure in the ventricle is less than diastolic pressure either in aorta or pulmonary trunk, the semilunar valve will not open and no ejection will take place. This is bcz the afterload has not been overcome.
Phases of the Cardiac Cycle

Extrinsic Factors Influencing Stroke Volume

- Contractility is the increase in contractile strength, independent of stretch and EDV
- Increase in contractility comes from:
  - Increased sympathetic stimuli which has +ve chronotropic effect.
  - Certain hormones like thyroxine, angiotensinII and dopamine. All of which have +ve chronotropic as well as +ve ionotropic effect.
  - Ca2+ and some drugs
- Agents/factors that decrease contractility include:
  - Acidosis by inhibition of cardiac muscle contraction.
– **Increased extracellular K+** (when we think of K, we must think of nurst equation...so it causes the RMP to be more – ve), this is what has been said by the Dr.

What is mentioned in GUYTON is the following:
High extracellular K concentration partially depolarizes the cell membrane, causing the membrane potential to be LESS negative. (you can refer to page 112 to read more)
And if we apply the nurst equation:
EMF = -61 * log (K inside / K outside)
Let us consider Ki = 140 and Ko = 4, the EMF will be around -90
If Ko has become 6 for ex. This value (K inside / K outside) will be decreased and so the product will be less – ve.

Q. Does hyperkalemia affect phase 3??
Yes, it decreases phase 3 as well as phase 2. All in all, it will decrease the duration of the whole action potential and so decreases the contractility.

– **Calcium channel blockers** that cause decrease Ca influx by blockage of slow voltage gated Ca channals.

Blockage of Ca influx has 2 effects:

1- Decrease intracellular Ca.
2- Decrease Ca release from the SR bcz of Ca induced Ca release mechanism of the heart.

**How epinephrine/NE work as +ve ionotropic agents??**

EP/NE are neurotransmitters that bind to beta1 adrenergic receptors on the heart. This receptor is coupled to G-protein system which will activate the nearby adenylate cyclase that in turn will convert ATP to cAMP. The later will activate protein kinase A (cAMP-depedent protein kinase). PKA will phosphorylate phospholambin protein on the SR. Once it is phosphorylated, it will activate the Ca pump in SR, increasing the Ca uptake and so concentration of Ca inside SR is increased. As we have seen NE decreases the time of diastole as a result of lowering intracellular Ca.
In conclusion, the effect of NE:
1- Increasing HR by decreasing diastolic period.
2- Increasing contractility
As we said NE increases the Ca uptake so higher Ca is built up inside the SR. In the next beat, upon induction of Ca release from what has been entered, higher amounts of Ca will be released into the cytoplasm causing +ve inotropic effect.
Also, PKA might phosphorylate Ca channals causing higher influx.

Mathematical representation of cardiac cycle according to length-tension relationship curve.

This contains 3 curves:
1-passive tension curve which is the amount of tension that is found in the muscle before it contracts
2-Active tension
3-Total tension

If we stretch a rubber, a tension will be stored inside it before it contracts, this is the passive tension. When the tension on it has ended, firstly, it overcomes the tension applied on it then contraction takes place (total tension). Active tension is the difference btwn the total and passive tension.

When we come to the heart, we can't talk about length, we talk about volume.
So in the diagram below, the x axis will be the volume and the y axis is the intraventricular pressure (left ventricular volume in your diagram).

Intraventricular pressure: is the pressure that develops in the ventricle during contraction.
This pressure firstly has to overcome the passive tension then it has to be sufficient to perform ejection.
As you see in the diagram, the higher the volume in the ventricle, the higher the pressure develops until reaching the optimal length (physiological limit). At this point, the maximum tension has been developed (both active and total tension).

Any further increase in the volume will be accompanied by decrease in the stroke volume and cardiac output because of decreased active and total tension. However, the passive tension (diastolic pressure) will be increased dramatically to the extent that the total tension (systolic pressure) just overcomes the passive and the difference between them is zero and no stroke volume at this point.

*At the point where total and passive tension, the active tension approaches zero.

Diastolic pressure (in the ventricle) = passive tension = preload

Total tension is the pressure that develops in the ventricle to overcome the contraction.

In the x axis 50 ml represents the ESV. Here, the AV valves open >> filling of the ventricles >> AV valves close >> end of diastole >> isovolumetric contraction (constant volume with rapid increasing pressure until it becomes higher than diastolic aortic pressure) >> opening of semilunar valves >> ejection >> end of systole >> isovolumic relaxation at the early diastole (constant volume with rapid decrease in pressure until it becomes lesser than atria) >> opening of AV valves.
There are 3 kinds of energy in this system, one of which is the **external work**. External work is the work (energy, force) that is done by the heart to move the blood inside the circulation and it is the major work done by the system. It equals the area under the curve (yellow-colored)

How to calculate the area under this curve??

1. By integration.
2. By multiplication of the SV (horizontal line that is the difference btwn the EDV and ESV) by the avg of the pressure (vertical line that is the difference btwn the systolic mean pressure and diastolic mean pressure).

- considering that the area is a rectangle.

Note; there is a difference in the pressure during systole and diastole. The difference is in timing of the diastole and timing of systole so the mean pressure is the integration of the area but to make it easy, we consider it a rectangle.

The mean pressure is affected by diastole more than systole bcz the higher period of diastole.

Another kind of energy done by the system is the **kinetic energy**. Kinetic energy is the amount of energy that is spent to accelerate the blood through the semilunar valve.

\[ KE = \frac{1}{2} * m * v^2 \]
Normally, our system spends less than 1% of kinetic energy. However, in some situations when the aortic valve is narrowed (aortic stenosis), the KE might contribute to more than 50% of the energy because the heart needs to develop too much energy to keep the SV so here most of the energy is spent as KE not as EW.

How can frank starling law be presented on this curve??

Shifting the EDV to the right leading to increase in the SV as well as the EW.

How can I increase the contractility of this system??

The EDV is fixed so we apply the shift to the ESV by shifting it to the left (decreasing it). When doing this, part of the potential energy has been used.

PE is normally stored in the system to be used when we need to increase contractility.

What is the effect of increasing afterload??

It causes a decrease in the SV, keeping in mind that the EW remains the same.

Note; if the SV remains constant in a hypertensive pt, the EW is needed to be increased.

- Refer to slide 28, 31

The pressure at point D is called the afterload. After this point is the ejection.

Which is the longer period, from (A to C) or from (C to F)??

Absolutely, it is from A to C because it represents the diastolic period. Otherwise, the same information is repeated.

Valvular Function
➢ To prevent back-flow.
➢ Chordae tendineae are attached to A-V valves.
➢ Papillary muscle, attached to chordae tendineae, contract during systole and help prevent back-flow.
➢ Because of smaller opening, velocity through aortic and pulmonary valves exceed that through the A-V valves.
➢ Most work is external work or pressure-volume work.
➢ A small amount of work is required to impart kinetic energy to the heart (1/2 mV2).
➢ What is stroke-volume in previous figure?
➢ External work is area of Pressure-Volume curve.
➢ Work output is affected by “preload” (end-diastolic pressure) and “afterload” (aortic pressure).

Refers to slide (32-35) all of them have been discussed.

Length tension relationship (slide 36)

-X axis is the length represented by EDV.
-Y axis is the SV which represents the active tension (stoke volume).
-As the EDV is increasing, the SV is increasing until reaching the optimal length (maximal SV is achieved bcz of the optimal alignment of actin and myosin), when it is exceeded, a decrease in the SV will be observed (heart failure).

Regulation of Heart Rate

● Positive chronotropic factors increase heart rate (sympathetic)
● Negative chronotropic factors decrease heart rate (parasympathetic)

Regulation of Heart Rate: Autonomic Nervous System

● Sympathetic nervous system (SNS) stimulation is activated by stress, anxiety, excitement, or exercise
● Parasympathetic nervous system (PNS) stimulation is mediated by acetylcholine and opposes the SNS
● PNS dominates the autonomic stimulation, slowing heart rate and causing vagal tone.

The predominant effect for HR is caused by the parasympathetic and the predominant effect for contractility is the sympathetic.
So if we cut both, the HR will be increased and the contractility will be decreased.
Atrial (Bainbridge) Reflex

- Atrial (Bainbridge) reflex – a sympathetic reflex initiated by increased blood in the atria
  - Causes stimulation of the SA node
  - Stimulates baroreceptors in the atria, causing increased SNS stimulation

Atrial Bainbridge reflex states that an increase in the blood volume in the right atrium will increase the HR due to the stimulation of the SA node.

Chemical Regulation of the Heart

- The hormones epinephrine and thyroxine increase heart rate
- Intra- and extracellular ion concentrations such as Ca must be maintained for normal heart function.

Hyperkalemia and hypocalcemia, both decrease the HR.

Important Concepts About Cardiac Output (CO) Control

- **Cardiac Output is the sum of all tissue flows and is affected by their regulation** so if the blood flow for one of the tissue has been increased, the CO will be increased. \( CO = 5 \text{L/min, cardiac index} = 3 \text{L/min/m}^2 \text{ (surface area in m}^2) \).
- CO is proportional to tissue O2 use.
- CO is proportional to 1/TPR when AP is constant.
- \( CO = \frac{(MAP - RAP)}{TPR} \)

CO is the amount of blood ejected by either ventricle per minute. Cardiac index has been created to standardize the cardiac output (bcz it differs according to gender, it is higher in males than females, and from individual to another). And it is the product of division of the CO on the surface area of the body. By this, the CO is equal to all individuals bcz we are different in terms of surface area but CO is also different.

CO is FLOW, it is the amount of blood flowing per minute. This is the same concept of flow of current, for instance. As it is represented by Ohm's law
Current = change in voltage / resistance.

But here we are talking about the flow of blood (F)

F = change in pressure / resistance.

And when we talk about CO in which the change in pressure is between the aorta and the right atrium and the resistance is the total peripheral resistance, the equation will be:

\[ CO = \frac{(MAP - RAP)}{TPR} \]

MAP > mean arterial pressure

RAP > right atrium pressure

TPR > total peripheral resistance

But the RAP normally equals zero so the resultant equation will be:

\[ CO = \frac{MAP}{TPR} \]

Best of luck 😊

Done by:

Anonymous 😄