To begin with, those are the abbreviations used in the sheet and what does each stand for:

1. EDV: end diastolic volume
2. ESV: end systolic volume
3. EDP: end diastolic pressure
4. SV: stroke volume
5. NE: norepinephrine
6. E: epinephrine
7. SR: sarcoplasmic reticulum
8. F-S relationship: Frank-Starling relationship
9. AV valve: Atrioventricular valve
10. EW: external work
11. PE: potential energy
12. KE: kinetic energy
13. SM: skeletal muscle
14. CO: cardiac output
15. MAP: mean arterial pressure
16. RAP: right atrial pressure
17. TPR: total peripheral resistance

-In this lecture we will be talking about the cardiac cycle, but before that there are some concepts from the previous lecture we have to keep in mind:
1) preload: is the amount of tension in the heart before it contracts.
(Measuring the preload; you can take into consideration either the EDV or the EDP) (As mentioned before the EDV and the EDP are proportional (so taking either won't be any different) since increasing blood volume increases the pressure it exerts on the muscular walls of the heart, and the higher those (EDV or EDP) are the higher the preload is the higher the SV (of course here up to a limit which is the optimal length, where exceeding it is going to cause lower SV with increasing EDV, this is a state of heart failure))

2) Afterload: the end load (amount of tension) that the ventricles produce to eject blood out of the heart into the arterial system. It is worth mentioning here that the pressure at which the ventricles eject blood with should be higher than that of the diastolic aortic pressure; hence, opening the semilunar valves, and that increasing the afterload decreases the stroke volume (given that energy stays the same (we will come to this point later on in the sheet)).

3) Contractility: the intrinsic ability of the heart (myocardium) to contract. (So in other words it is measurement of the effectiveness of the heart). As we know it is hard to measure the

contractility; however, we can obtain an estimation of it by calculating the maximal change in pressure over time.

-Now let's begin with today's lecture shall we:

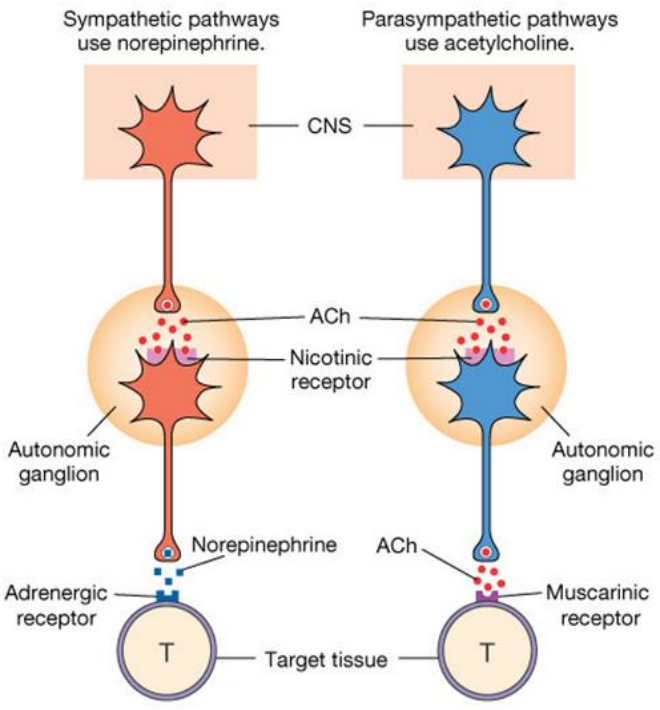
So the doctor started talking about the dominant type of adrenergic receptors in the heart which is the beta-1 receptors. (An easier way to memorize this would be (as the doctor suggested) that we have two lungs; therefore, the dominant type is the beta-2 receptors and only one heart so beta-1 receptors).

Chatecholamines (the signaling molecules for the beta-1 receptors) come in contact with their beta-1 receptors (after being secreted by sympathetic postganglionic fibers), and the beta-1 receptor is coupled with a G-protein which is activated and in turn activates adenylate cyclase that produces cAMP, an intracellular signaling molecule that activates protein kinase A (cAMP dependent protein kinase) where it is going to phosphorylate Phospholamban (can be phosphorylated by any of the three (A,B and C) protein kinases).

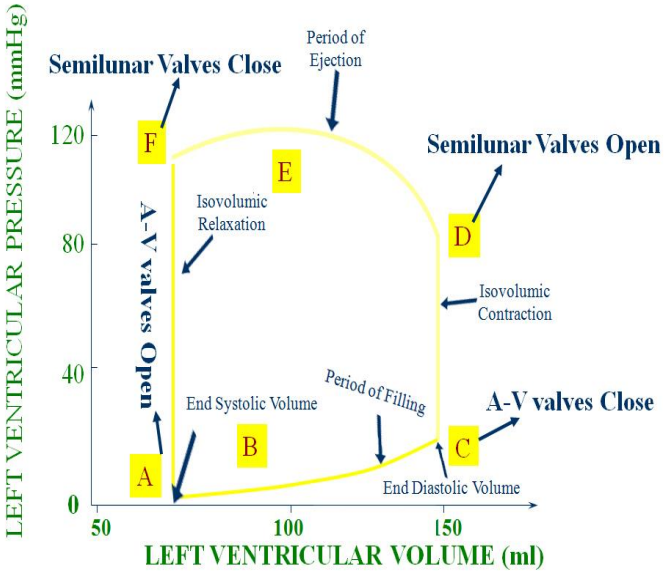
Phospholamban will accelerate the uptake of Ca2+ by the SR by activating the uptake channels, this shortens diastole, decreasing the time needed for relaxation of the cardiac muscle to occur, and that will increase the heart rate. This is the mechanism the positive chronotropic effect (Caused by NE and E) follows.

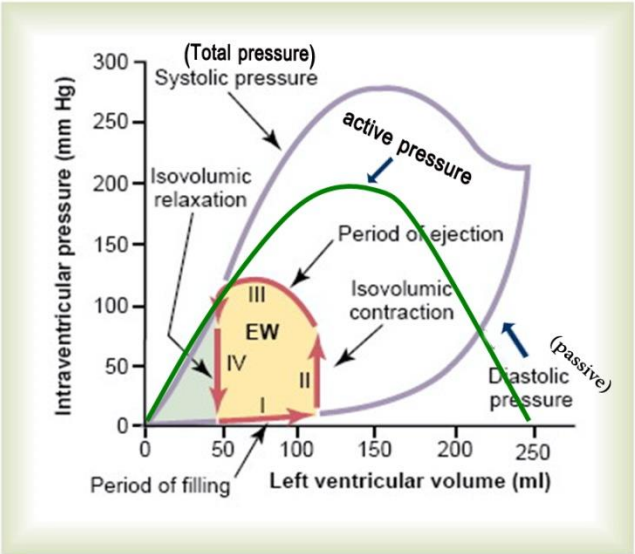
-Now increasing the uptake of Ca2+ by the SR, not only increases heart rate (as a positive chronotropic effect is not the only effect NE and E have on the heart), but will also increase contractility of the myocardium (increased force of contraction which is a positive ionotropic effect). This occurs in the cycle following what just happened (increased uptake of Ca2+ by the SR), where higher uptake of Ca2+ means higher concentration of Ca2+ in SR, so a much greater release of Ca2+ in the cycle that follows the greater uptake. This increased release will cause greater force of contraction.

-The doctor quickly revised the sympathetic and parasympathetic neurotransmitters in pre/post ganglionic fibers.



Let’s take a look on the following graphs:





-Those graphs are a represntaion of the cardiac cycle (F-S relationship which relates the length to the tension).

-Since the graphs represent the relatioship between the tension and the length, the doctor explained why we are using pressure and volume at both axes.

-It goes as follows: the EDV is proportional to the length of the muscle (so volume is used instead of the length), and the tension is proportional to the pressure (so pressure is used instead of the tension).

-the doctor went on from there to explain what are the stages in the cycle and what are their indications on the graph:

- The cardiac cycle begins with the end systolic volume (approximatly 50ml) and opening of the AV valve, followed by filling of ventricles with blood (which is stage I on the graph). Here the increase In volume causes very small increase in pressure because the chambers of the heart are complaint since they are elastic. At the end of stage I the AV valves close; hence, causing the first heart sound.
- Stage II: is the systole, the isovolumic contraction phase of systole. You can notice how the line in the graph goes directly upwards, indicating that there is no change in volume only an increase in pressure. The pressure inside the ventricles keep on increasing until it becomes higher than the diastolic aortic pressure (the afterload) opening the semilunar valves (at the end of this stage).

- Stage III: is the ejecting blood phase of systole, so volume is decreasing (line going backwrds), but increased pressure (line going upwards at the same time). Here you would expect the pressure to decrease (as volume is decreasing), but the pressure increases, and that is due to the pressure produced by the contraction of the ventricles overriding the effect of decreased volume, maintaining the ejection of blood through the whole phase (at the end of this stage semilunar valves close causing the second heart sound).
- Stage IV: is the first phase of diastole, the isovolumic relaxation. Please notice here once again the straight line going downwards indicating the decrease in pressure, with no change in volume. This decreased pressure in the ventiricles opens the AV valve as it becomes less than that of the atrial pressure repeating the cycle once again and it goes on from there.

-Now the doctor took the following scenraios and discussed them broadly where they will be disccused again thouroughly later in the lecture:

1) if we shift the curve to the right (take the line of stage II and shift it to the right while maintaining the line of stage IV in it's original position (unchanged stage IV means fixed ESV)):

The EDV increases, and the SV follows it's footsteps (increasing as well) (this is the F-S relationship).

2) if we shift the curve to the left (take the line of stage IV and shift it to the left while maintaining the line of Stage II in it's original position (unchanged stage II means fixed EDV)):

This will decrease the ESV increasing the SV. This would happen due to the increase in contractility (↑ contractility causes ↓ESV).

-The doctor very briefly talked about the diastolic pressure line (passive tension), the Active tension line, and the systolic pressure line (Total tension):

- The total tension and the active tension increase coordingly until they reach a maximum (the optimal length) after which (exceeding it) the passive tension starts increasing rapidly while both the total and the active tension decrease, until the passive tension meets the total tesnion (the point on the graph where both the systolic pressure and the diastolic pressure meet) at which the difference between them is eqaul to zero, there: the value of the active tension aproaches zero (the acive tension line is very close to the x-axis) here the SV=zero (a state of heart failure) this is because the heart goes

beyond the limit of it's complaince (loosing it's elasticity) and becomes unable to receive any larger volume of blood, nor able to pump it out.

-We come now to the area under the graph (maths and physics,as the doctor described it):

- Area under the graph,represnting the 4 stages of the cardiac cycle we talked about earlier, is equal to the EW of the heart (this is the main form of energy spent by the heart to move the blood inside the circulation) :
  the area under the graph=EW=volume(stroke volume) x Pressure
- Where the volume here is equal to:

EDV-ESV (which is the volume represented by stage II – the volume represented by stage IV)

And the pressure is equal to:

Mean systolic pressure – mean diastolic pressure (the mean here isn't calculated simply as: (value 1 - value 2)/ 2 because the diastole takes more time (0.5 sec) than the the systole (0.3 sec) so we use the integration of the change in pressure over the change in time (dv/dt) to calculate the mean of the pressure).

-As you can see there is an area under the curve (the traingle to the left of the line representing stage IV) that represents the PE which is the stored energy in this system used when the SV is increased (fixed EDV and decreased ESV) (shifting line of stage IV to the left)

-There is a third type of of energy which is the KE (but normally it is very small, less than 1%, so negligible) and is equal to ½ m v^2. This is used to accelerate the blood in the vessels, for e.g. in aortic valve stenosis huge energy is needed to compensate for the blood to counter this descreased valve cross-section, so KE increases to about 50% of the energy used (we said that EW is the main energy, but in such a case KE is) which is a huge burden on the heart, this increases it's demand for O2.

-In SM the increased O2 demand can be met by increased extraction ratio (the difference between the concentration of O2 in the arterial side of the capillaries and the venous side- ateriovenous difference) so SM gets higher O2 meeting it's greater energy consumption due to incrased work (contraction). But as far as it goes for the cardiac muscle, the extraction ratio is already at it's maximum (75%) -during rest- so the only way to meet this demand (increased KE) is by increasing blood flow.

-If the O2 demand of the cardiac muscle is not met (due to coronary artery problem), this will mimic the effects ischemia

CDF (systole) is short (0.3 sec) when compared to ABC (diastole) (0.5 sec) in terms of time, as on the previous graph only pressure and volume are present, which might show the opposite.

has on the heart, so we might develop angina pectoris and if the condition worsens any further MI could occur damaging the heart muscles. That's why people with aortic stenosos are prone to MI.

-the only extra note the doctor made on slide #30 is that the papillary muscles are attached to the ventricular muscles so they contract as a unit, otherwise he only read this slide.

-He only read slide #31 as well, but said that the area under the curves are affected by the preload and the afterload.

-slide #32 shows the 4 stages in their normal positions.

-slide #33 shows what occurs when the preload is increased:

- As the preload increases the SV will increase becaue of an increase in the EDV (which causes greater pressure in the ventricles, F-S law), in other words shifting the line representing stage II (increasing the EDV) will increase the difference between the EDV and the fixed ESV and hence increasing the SV. Now we said preload is the tension in the heart before it contracts so increased preload means increased pressure which is brought by increased EDV. This is intrinsic regulation (no sympathetic or parasympathetic).

-slide #34 shows what occurs when the afterload is increased:

- When afterload (aortic pressure) increases we are increasing the pressure in the ventricles but keeping the EW the same (same area under the graph) and this brings about the increased ESV, so pressure increases but EDV and EW stays fixed (since W is fixed contractility is fixed), this will cause the ESV to increase decreasing the SV.
- Now to keep the SV as it is or even increase it, we need to decrease the ESV (shift line of stage IV to the left, while with increased afterload comes increased pressure) this is achieved by increasing the energy used (and therefore increase contractility), but this comes on the expense of the PE stored in the system where in this case it is used to increase area under graph and hence keep the SV the same or in some cases increasing it. This causes larger O2 demand and the same thing we talked about previosly may occur here as well (ischemia, angiana pectoris and MI)

-slide #35 shows what occurs when the contractility increases:

- Here as you can see the EDV is fixed so what birngs about the increased SV is the decreased ESV. This is a positive ionotropic effect. The pressure here is increased because of increased contractility and not because of increased EDV.

-slide #36 shows the three cases we talked about before, so you can compare what happens to the pressure, EDV, ESV, and SV within each case.

-slide #37 in this slide we see the relation between the SV and the EDV, so as the EDV increases the SV increases up to a certain limit (optimal length or optimal value, yet again :P) and here we repeat the previous F-S relationship scenario where exceeding the limit causes increased EDV while SV decreases, and here the heart filled with fluid (cardiomegaly) it's ability to contract decreases and goes into a heart failure state.

-slide #38 the doctor only read it.

-slide #39 the doctor read it but also said that the sympathetic innervation dominates in contractility and the parasympathetic innervation dominates in heart rate (where stimulating the parasympathetic causes what we call the vagal tone. Now as a side note, cut both, and you'll get an increased heart rate (opposite to the parasympathetic innervation) and decreased contractility (opposite to sympathetic innervtion).

-slide #40 the doctor read it but added that the increased blood volume in the right atrium will cause it to stretch further causing increased pressure over the SA node stimulating it and casusing increased heart rate (atrial (Bainbridge) reflex)

-slide #41 talks about the hormones acting on the heart:

- The first one being thyroxin (as in thyrotoxicosis) which when increases causes rapid increase in heart rate and therefore tachycardia.
- Second one is adrenaline and it stimulates the sympathetic innervation and hence both postitive ionotropic and chronotropic effects as we said earlier.

-Also the concentration of certain ions and how they affect the heart like Ca2+ and K+, but the doctor only concentrated on Ca2+ where it's increased concentration causes a postitive chronotropic effect.

-The doctor here said that the following information are an introduction to the next lecture:

And he started by mentioning Ohm's law where the current is equal to the change in the voltage over the resistance.

-the current here (being electrical flow) is equivalent to the cardiac output which is the blood flow against the peripheral resistance, and the difference in voltage is equivelant to the pressure gradient In our bodies. So the CO equals the change in pressure over the total peripheral resistance:

CO= change in pressure/TPR

So the change in pressure= MAP – RAP

And the mean arterial pressure= (1/3 systolic pressure + 2/3 diastolic pressure)/2

That's because of the difference in timing between systole and diastole, that's why we cant say (systole+diastole)/2, we have to consider that diastole is longer than systole in duration.

-as RAP is equal to zero , so the MAP =CO *TPR. (here if you want to change the MAP you can either change the CO or the TPR or both e.g when a patient arrives at the hospital with increased MAP you can decrease it by as we said changing the CO or the TPR or both, and since it's a linear realtioship (from the equation)decreasing the CO or the TPR will decrease the MAP)

-slide #43 represnts the CO curves:

- As the EDV increases the EDP increases which increases the RAP (that's why we put RAP on the x axis, because its proportional to EDV), and increased RAP increases CO and that is why the curves look like that.
- When the RAP is zero the CO is 5 liters.
- As for all previous cases we have a limit (as the normal curve shows it is 15L of blood according to F-S), now normally it's only 5L (the doctor said for simplicity here) but due to extrinsic regulators it goes up to 15L.
- It is also worth mentioning here that the reserved CO is equal to 10L which is the differene between the maximal CO (15L) and the normal CO (5L).
- In athletes the CO can reach a maximal value of 25L because of increased effectivness (hypereffective) of the heart (this is extrinsic factors plus F-S relationship)

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