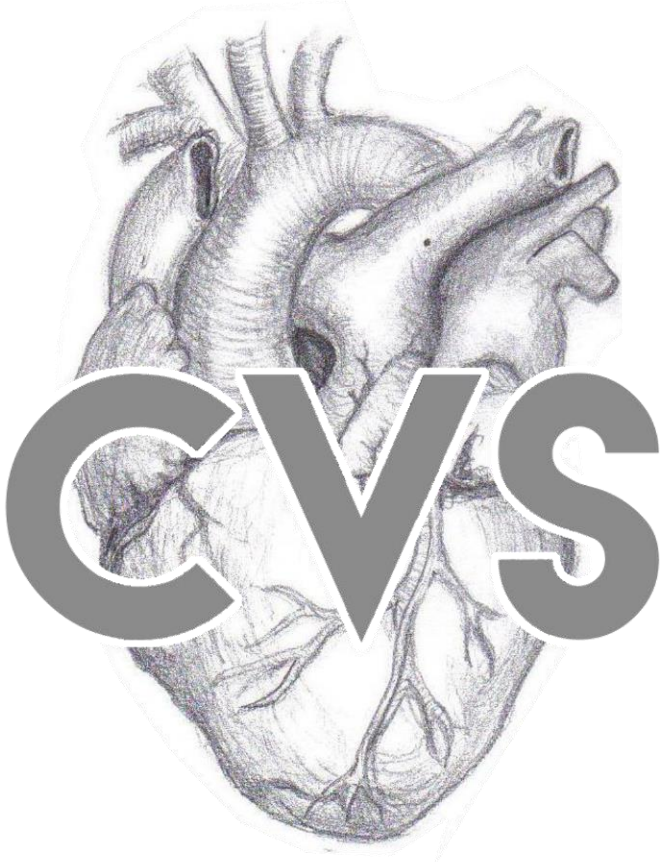

CVS

ANATOMY / HISTOLOGY

✓ Sheet ○ Slide ○ Handout

Number

2

Subject

Cardiac histology & Blood Flow

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Date: 18/10/2016

Price:

In this sheet we will continue talking about blood vessels, discuss the cardiac muscle histology, and lastly discuss the blood circulation.

❖ Medium size veins:

Main features:

- Minimal amount of smooth muscles in the tunica media. Resulting in low resistance.
- Tunica adventitia is the largest layer, containing high amount of collagen. This amount of collagen makes the vein highly compliant (مطاوع).

Compliance (المطاوعة): Is an important feature in veins. It means that the vein can expand and expand when it is filled with blood with very little recoil. In contrast to the elastic tissue that expand during systole and then recoil during diastole.

This feature permits the veins to store a large amount of blood under low pressure. And this is clearly demonstrated in **Figure 1**.

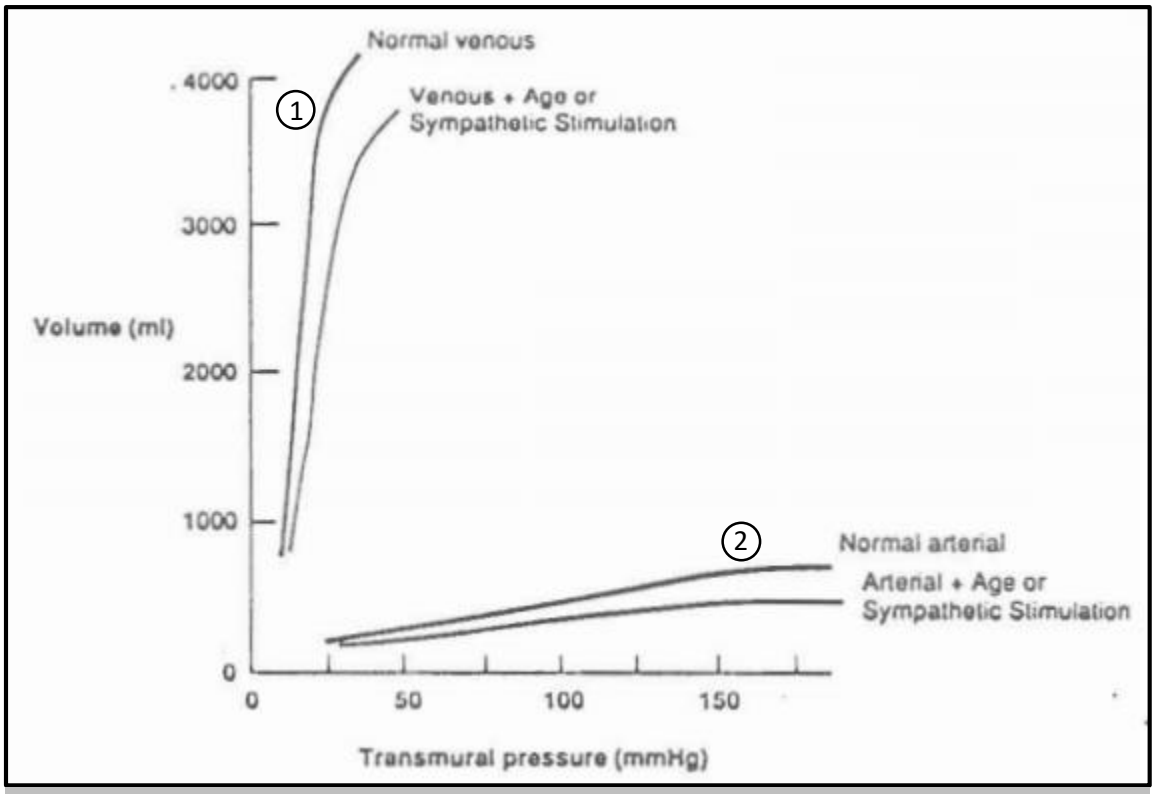


Figure 1: The relationship between Blood Volume (ml) and Transmural Pressure (mmHg).

Look at **Figure 1**. In case of venous circulation ①, we increased the blood volume as far as 4 liters and the blood pressure reached around 20 mmHg only. Whereas in the arteries ② if you put less than 1 liter, the pressure will increase as far as 200 mmHg.

This compliance results in the fact that 60% of the blood is in veins, and the pressure hardly reaches 18 mmHg, allowing the blood to reach the heart easily.

So veins are described as **Low resistant collecting system** or **Low pressure storage system**.

- Compliance $C = \Delta V/\Delta P_{TM}$ = Slope of the curve
  (This equation wasn't mentioned by the doctor but it is in the handout).

Note: As you may notice in the figure, we measure the Transmural blood pressure. And this is the real pressure. **Transmural pressure (الضغط عبر الجدار)** is the difference in pressure between the two sides of a vessel wall (so it's the effect of the blood from inside and the vessel's environment outside).

❖ Arterioles:

- A small arteriole has single layer of smooth muscles.
- A large arteriole has 3-4 layers of smooth muscles.

Normally there is a partial contraction (partial constriction) of the smooth muscles in the wall of an arteriole. This feature is called **vascular tone**.

The significance of this tone: It permits the arteriole to induce more constriction or induce more dilation. If the tone was absent, the arteriole can't induce more dilation, it can only constrict.

The vascular tone is a result of two mechanisms:

1- Myogenic activity: a **spontaneous** depolarization of the muscle membrane resulting in a contractile characteristic in the muscle that doesn't need a stimulus.
2- Sympathetic stimulation. (This is opposed by the **local metabolites** of an organ; as local metabolites dilate the arteriole. And this makes sense because highly metabolic organ needs more blood supply)

We can divide the factors that can influence the level of contractile activity in arteriolar smooth muscle into:

- Intrinsic factors: Local metabolites.
- Extrinsic factors: Mainly the sympathetic stimulation.

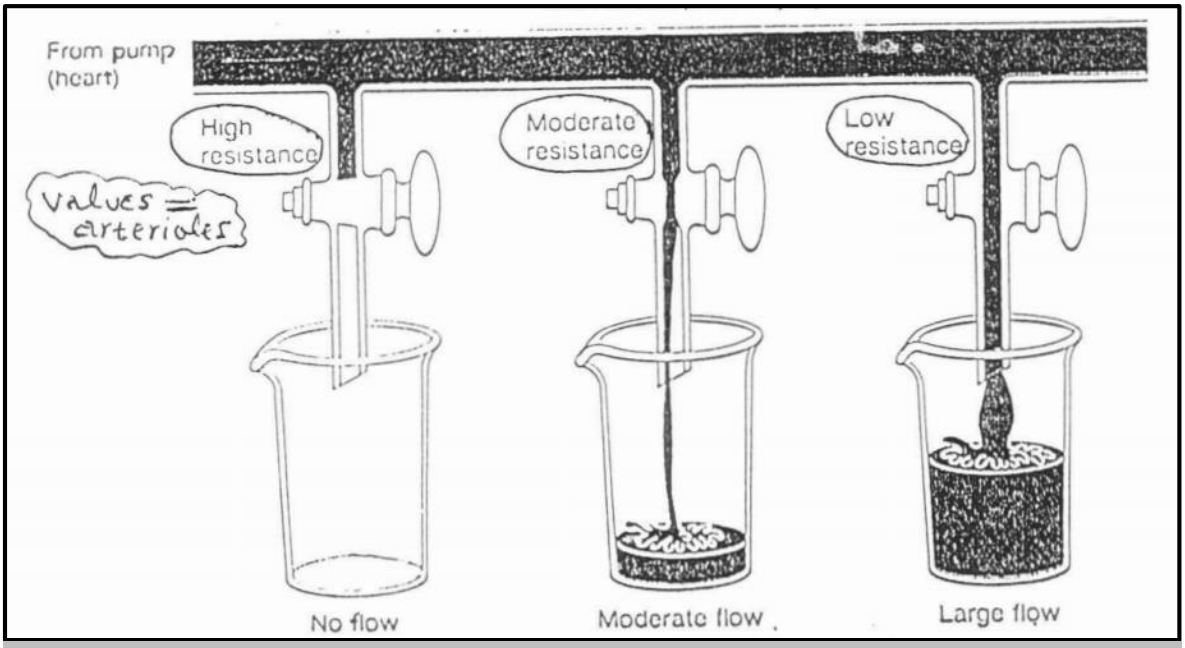


Figure 2: The relationship between Blood flow and peripheral resistance.

In a state of generalized sympathetic induced vasoconstriction, we suppose that the blood flow to the organs will be reduced. But at the same time the vasoconstriction elevates the mean arterial blood pressure which means **increasing the main driving force for blood flow to all organs**. After that each organ will receive blood according to its local metabolites.

So the sympathetic vasoconstriction came with the benefit of increasing the driving force. And at the organs level the blood flow is proportional to its metabolic activity as the local metabolites override the sympathetic constrictor effect.

Examples on some local metabolites:

- Coronary circulation: Adenosine (a metabolite in the cardiac muscle) as well as hypoxia induce vasodilation and increase coronary blood flow.
- CO_2 is a very important metabolite that cause vasodilation in the brain.
- Lactic acid in the skeletal muscles.

❖ Cardiac Muscle:

(We will discuss cardiac muscle histology and compare it with skeletal muscle at the same time.)

A cardiac muscle fiber = **Group of cells** joined by special junctions called intercalated discs.
A skeletal muscle fiber = **One cell**. The cell is multinucleated, nuclei situated at the periphery of the cell beneath the sarcolemma (sarcolemma = cell membrane).

Cardiac muscle exhibits **functional syncytium** as a result of gap junctions that transmit the action potential to all cardiac fibers. So the cardiac fibers act as one unit.
Skeletal muscle doesn't exhibit functional syncytium.

Atrial muscle fibers have its own syncytium and ventricular muscle fibers have its own syncytium, but there is no syncytium between the atria and the ventricles directly; because they are separated by a fibrous ring, **except for a small muscle that transports action potentials from atria to ventricles called AV Bundle or Bundle of His.**

Both cardiac muscle and skeletal muscles exhibit **cross striations**.
Cross striations indicate that actin and myosin fibrils are organized as **sarcomeres** (The functional unit in a muscle cell).

The sarcomere is subdivided into A band, I band and Z line.

Skeletal muscle fibers have T tubules (Transverse tubules). These are invaginations of the cell membrane inside the muscle fibers. Its function is to transmit action potentials deep inside the muscle fiber.
In each side of the T tubule there are enlarged areas of the sarcoplasmic reticulum that accumulate Ca^{+2} called Terminal cisternae. These with the T tubule form a **triad** (Terminal cisternae - T tubule - Terminal cisternae).

T tubules are located at the junction between A and I bands.

Cardiac muscle also exhibits T tubules. However, these are located at the level of Z lines. And the sarcoplasmic reticulum doesn't form terminal cisternae, it ends with

expansions beside the T tubule forming **diad**
(Sarcoplasmic reticulum expansion - T tubule).

- Sarcoplasmic reticulum is more developed in skeletal muscle fibers.
- Cardiac muscle fibers are more vascularized, and have more mitochondria.
- Cardiac muscle fibers have intercalated discs between cells, skeletal fibers don't.

Mechanism of contraction:

- Cardiac Muscle:

(Note: Contractility of cardiac muscle directly proportional with intracellular Ca^{+2} concentration which is stored in the sarcoplasmic reticulum.)

When an action potential starts, depolarization will spread across the cell membrane and enters inside the T tubule. T tubule contains a receptor called DHP receptor (dihydropyridine receptor), this receptor has a slow voltage gated Ca^{+2} channel. When the DHP receptors depolarize the channels will open and the Ca^{+2} will enter inside the cells from the extracellular compartment.

When Ca^{+2} ions enter, they open Ca^{+2} channels in the membrane of the sarcoplasmic reticulum called ryanodine receptors (they are channels actually, but called receptors because they open when exposed to ryanodine in vitro), then the Ca^{+2} stored in the sarcoplasmic reticulum will diffuse to the sarcoplasm and cause contraction
This phenomenon is called [**Ca^{+2} induced Ca^{+2} release**].
(There is two sources of Ca^{+2} for contraction, but the extracellular is the main one)

- Skeletal Muscle:

Here DHP receptor is linked with a molecule called foot process that blocks the Ca^{+2} channels (ryanodine receptors).

When DHP receptors depolarize, conformational changes will occur and it will pull the foot process and this opens Ca^{+2} channels, then Ca^{+2} accumulated in the terminal cisternae will diffuse into the sarcoplasm.

Skeletal muscles don't show Ca+2 induced Ca+2 release. (Because it doesn't need extracellular Ca^{+2})

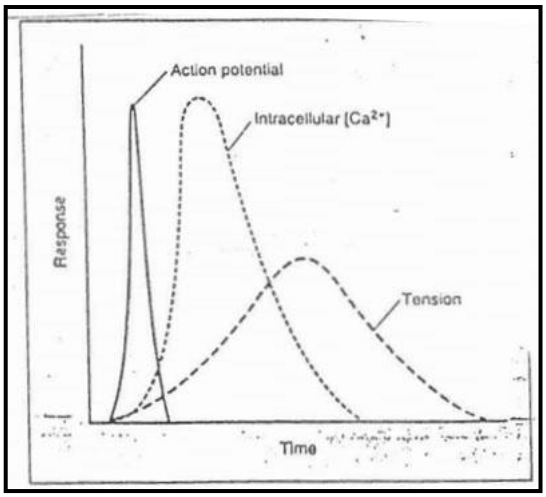


Figure 3: Temporal sequence of events in excitation-contraction coupling in a muscle.
The muscle action potential precedes a rise in intracellular [Ca^{+2}], which precedes contraction.

End of comparison

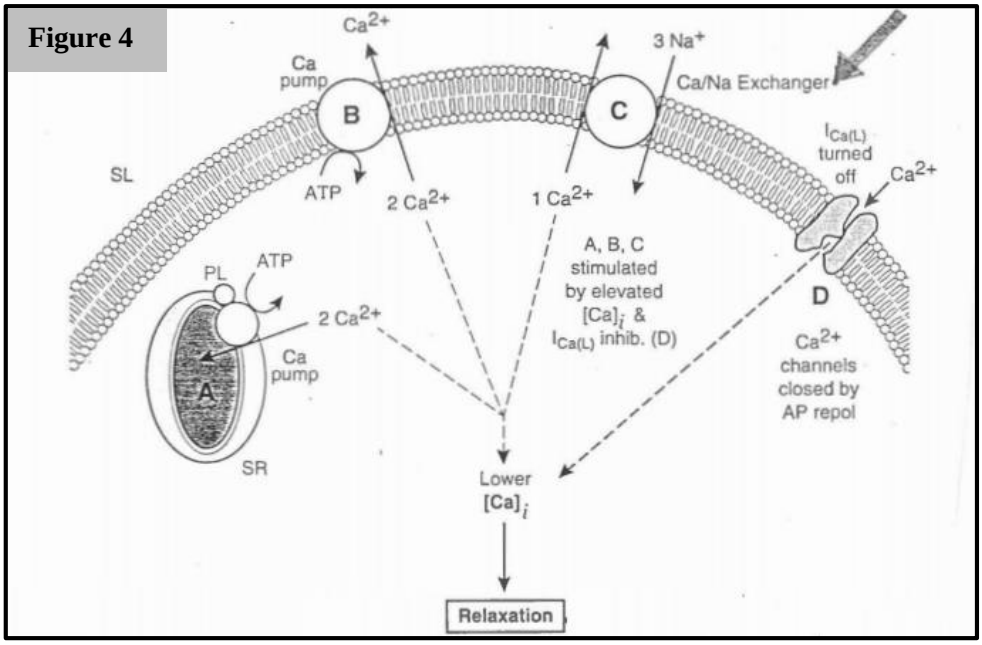
Mechanism of relaxation in cardiac muscle:

4 events involved (**Figure 4**):

A- Ca^{+2} ATPase pumps at the membrane od the sarcoplasmic reticulum, restore Ca^{+2} inside the sarcoplasmic reticulum.
B- Ca^{+2} ATPase pumps at the sarcolemma, pump Ca^{+2} outside.
C- Na^{+} - Ca^{+2} Exchanger at the sarcolemma, 3 Na^{+} ions exchanged with one Ca^{+2} ion.
D- And finally closure of slow voltage gated ca channels when the action potential repolarizes.

Note: A + B need ATP as they pump Ca^{+2} against its gradient. C doesn't need ATP as Na^{+} diffuse down its gradient.

Figure 4



Contents of the intercalated disc (the barrier between cardiac muscle cells):

1- Macula adherence (Desmosome)
2- Zonula adherence
3- Gap junction: an area of low electrical resistance which allow the spread of action potential from one cell to another which results in a functional syncytium.

Cardiac muscle cells are of two types; the first type is the contractile type that we were discussing it. The second is the conductive type which is a special type that transports action potential throughout the muscle called **Purkinje fibers**.

As you know from physiology the action potential starts in the SA node and then reaches the AV node then go through the AV bundle it reaches the ventricle, and in order to reach to the whole cardiac muscle we need specialized muscle fibers and these are the well conductive Purkinje fibers.

Purkinje fibers are larger than normal cardiac muscle cells, located beneath endocardium, have little myofibrils (actin and myosin) and a lot of glycogen, have desmosomes and obviously gap junctions between each other (intercalated discs), and don't have a T tubule system.

❖ Blood flow and Cardiac output:

We can view the heart as two halves; right half and left half.

Blood circulates across the body and then come back to the heart via superior vena cava and inferior vena cava and enters the right atrium, then the tricuspid valve will open and the blood moves to the right ventricle that will pump this blood through the pulmonary trunk to the lungs.
Lungs returns the blood to the left atrium through the valve-less pulmonary veins, then, through the bicuspid valve, blood enters the left ventricle that will pump the blood through the aorta to the whole body arteries (except the lungs).

[Right half for pulmonary circulation | Left half for systemic circulation]

Note: Indirectly, the left half of the heart receives blood from the right half. So if the blood volume pumped by right ventricle decreases, the volume pumped from the left half will also decrease.

In the vascular system, vessels constriction or dilation has an important role in:

- Regulate arterial blood pressure.
- Alter blood flow within organs.
- Regulate capillary blood pressure.
- Distribute blood volume within the body.

In order to blood flow reaches organs, it needs pressure (a driving force). In our body this pressure is generated from **two events:**
- Pumping action of the heart
- Peripheral resistance.

- If a patient developed allergy from a drug or any allergen, histamine released during allergy will cause vasodilation, this will reduce the peripheral resistance so the blood pressure falls. This example illustrates that the blood pressure is not only determined by the pumping activity of the heart but also peripheral resistance is a must.

During diastole the whole heart is filled with blood and during systole the blood is pumped to the pulmonary trunk from the right side and to the aorta from the left side.

Blood pressure near the heart (at the beginning of the systemic circulation) equals 93 mmHg, this pressure is called **Mean arterial blood pressure (متوسط الضغط الشرياني)**

When blood reaches arterioles in organs, it will face resistance from the arterioles (because they are narrow) so the pressure will decrease to 37 mmHg. This difference in pressure is called pressure gradient and represents a driving force because fluids move from the higher pressure to the lower pressure.
[So, as discussed in page 3, the narrowing of the vessels seems to reduce blood flow to organs but actually it is increasing the driving force and maintains the pressure gradient]

Normal blood pressure values:

During systole, the highest blood pressure in the lungs (from the right ventricle) equals 25 mmHg, this is called (systolic pulmonary blood pressure).
When blood spread inside the lungs, the pressure will fall as low as 10 mmHg which is called diastolic (pulmonary blood pressure).

Whereas the left ventricle pumps the blood against more resistance in the systemic circulation. So the systemic systolic blood pressure = 100-140 mmHg and the diastolic blood pressure = 70-90 mmHg.

Cardiac output (C.O):

Now we will discuss some definitions used in the CVS.

Cardiac output is the amount of blood pumped by each ventricle per minute.
(so it is also called minute volume)

Normally, output of both ventricles is equal.

How its calculated:

Cardiac output (liters/min) = Stroke volume (liters/beat) x Heart rate (beat/min)

With each beat the ventricle pumps 70-80 ml of blood, called stroke volume (SV).

Heart rate = 70 beats/minute.

So normal C.O is about 5.5 liters/minute.

If the right ventricular output is greater than the left output, blood will accumulate in lungs.
If the left ventricular output is greater than the right output, blood will accumulate in systemic circulation.

Note: Generally, cardiac output is equal in both sides even if it value was not normal (below 5.5 for example). Because if the volume pumped by the right ventricle decreases the left ventricle output will also decrease because the volume entering it is decreased.
In the consequences above, C.O was different in each side as a result in a problem in the heart, higher rate in one side for example. Always remember that the cardiac output depends in the volume as well as the rate.

After diastole each ventricle is filled with **130 ml** of blood called **end diastolic volume (EDV)**.

In systole it will not pump all the blood, it pumps the stroke volume (80 ml) and remains about **50 ml** called **end systolic volume (ESV)**.

$$SV = EDV - ESV$$

To determine myocardial contractility, we calculate something called Ejection fraction EF (determined by echocardiography).

$$EF = SV/EDV \times 100\%$$

Normally 60-65%

If it was low, 40% for example, we say the heart is weak.

Blood flow:

Flow of any fluid in any pipe is directly proportional with pressure gradient ΔP at each end of the pipe and is inversely proportional with the resistance.

So,

Flow (Q) = ΔP / R

In the case of the human body the fluid is the blood and the pipes are the vessels and resistance is found in any vessel containing smooth muscles.

And in this equation, we can replace the flow with cardiac output as they are the same. And we get:

C.O = ΔP/TPR

ΔP in our body is the difference in pressure between the area near the heart (in the aorta) and the right atrium (the end of the pipe).

So, ΔP = Mean atrial blood pressure - Right atrial pressure

In the right atrium, blood pressure is atmospheric and equals 0 mmHg. So,

ΔP = Mean atrial blood pressure

TPR is the Total peripheral resistance. (called total because any vessel that has smooth muscles resist flow. However, it is the most in arterioles)

So,

C.O = Mean atrial blood pressure / TPR

In another way,

Mean atrial blood pressure = C.O x TPR

This is the most important equation in the CVS.

This equation shows that the blood pressure, as said before, depend on the pumping of the blood per minute (C.O) and the peripheral resistance.

Low C.O will decrease blood pressure and low resistance will decrease blood pressure.

So if you have a patient with low blood pressure, it may be because a low C.O or a low resistance. So it's not always right to give vasoconstrictors (increasing resistance) to rise blood pressure as it may be cause by weakness in the heart (low C.O) or it may be bleeding (low blood volume and hence low C.O).