Cardio-Vascular System

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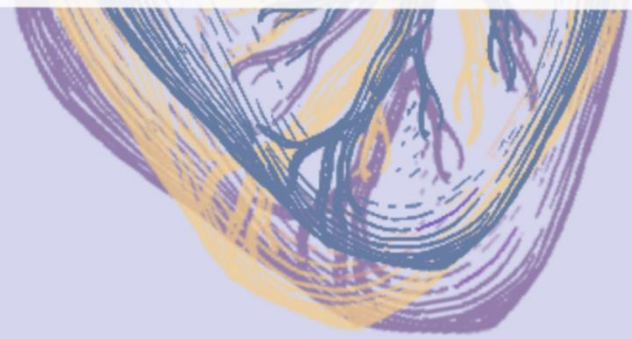
Pathology



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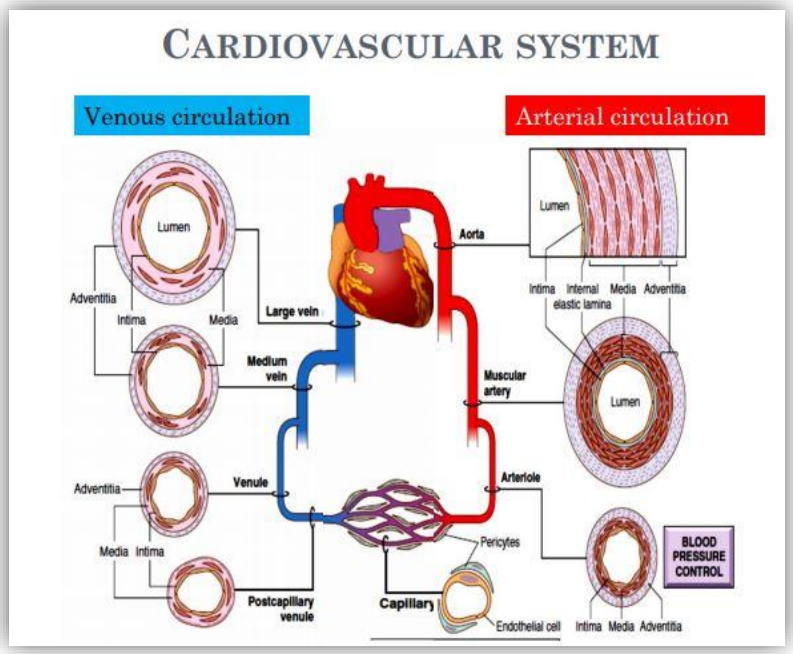
The cardiovascular system consists of the **heart and the blood vessels.** The circulation of the blood through the vascular system can be **functionally as well as histologically** divided into **venous circulation** and **arterial circulation**. In the venous circulation, a specific type of the blood vessels called veins connect the heart with different body tissues, it will return blood from tissues to the heart. It starts with the smallest sized veins that are called venules and then will move into larger sized veins until reach the largest sized veins that are connected directly to the heart.

On the other hand, **arterial circulation** starts with the Aorta (the largest artery in our body), and then moving into smaller and smaller branches until we reach the smallest sized arteries which are called arterioles. Arterioles and Venules will connect together inside the tissues through a certain type of blood vessels called **Capillaries** (network of blood vessels).

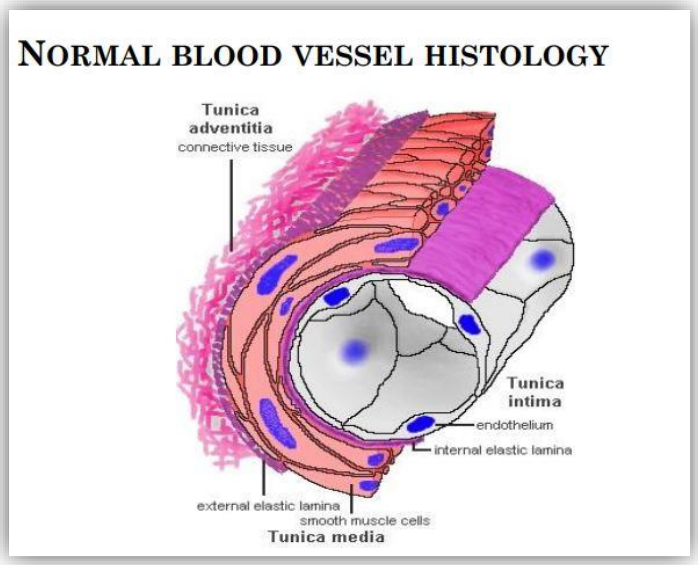
There are certain histological and functional differences between arteries and veins.



Regarding the histology of blood vessel, all types of blood vessels are composed of the same **three layers:** Tunica intima, Tunica media and Tunica adventitia.

Now If we took a cross section through the blood vessel and starting from the inside towards outside, the first layer will be **Tunica intima**.

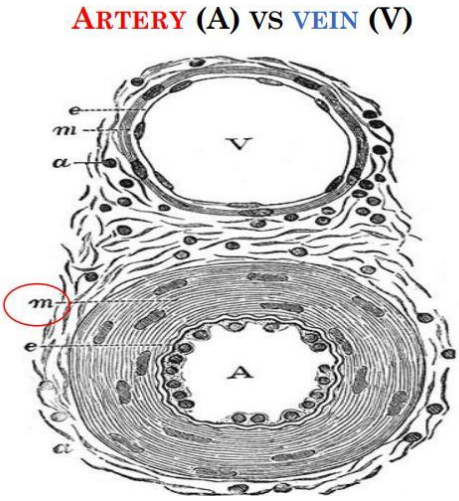
This layer is composed of a specialized type of cells called **Endothelium** or Endothelial cells. Beneath the endothelial cells there is some **delicate connective tissue** that Is bounded by a specific type of connective tissue called internal elastic lamina.



The second layer of the blood vessel is called **Tunica Media**. This layer gives the **thickness** to the wall of the blood vessel, it consists of a **smooth muscle cells**, some elastic fibers and proteins. This layer is very important because it will give the **contractility** to the artery. The **Tunica media** is bounded by external elastic Lamina.

The third layer is called **Tunica adventitia**. It is connective tissue layer that surrounds and supports the blood vessel from the **outside**. It also contains small sized blood vessels that are called **vasa vasorum** and small nerves called **Nervi Vasorum** which give blood supply and nerve supply to the wall of the blood vessel.

- ✓ The major differences between arteries and veins is not in the number of layers that are composing the wall. It's actually in one of the layers, which is the media. As you can see in this picture, both veins and arteries are composed of three layers. We have the endothelial cells and then media and then adventitia, but the media layer in the artery is much thicker than the media layer of the vein, and this is the most important difference between arteries and veins.



- ✓ This difference will also affect the function of the blood vessels. Artery would have a good contractile ability which is needed for its function. The vein will not have the same ability to contract.

Why are we discussing the differences between arteries and veins?

- ✓ Because there are different pathologies or disorders affecting them.

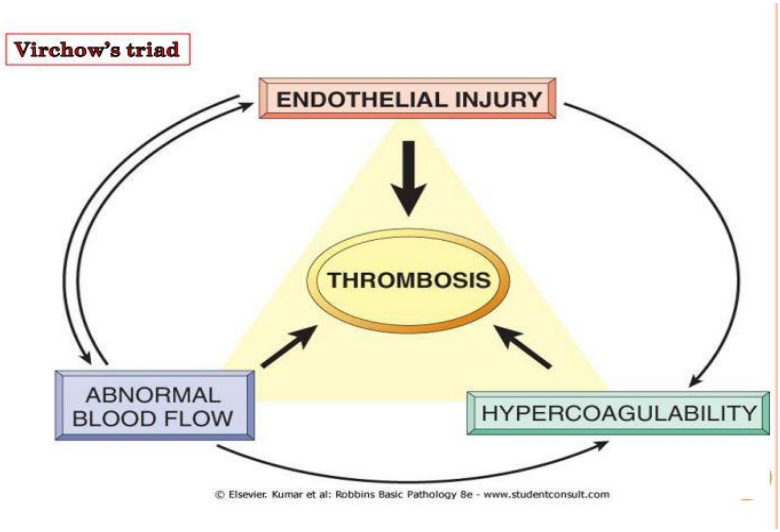
Hemostasis

Hemostasis is the natural, physiological process through which the body protects itself against the adverse consequences of blood loss. This process starts whenever there is vessel injury, the vessel injury will produce certain changes, **cellular as well as vascular changes** in order to prevent the excessive loss of blood through the defect. These responses will include vascular spasm as well as recruitment and activation of certain constituents of the blood like platelets and fibrin in order to form the platelet plug that will close the vascular wall defect.

Blood coagulation is a very important physiological event to protect our hemostasis, and life. However, at certain points, this process can be pathological that may endorse injury

and cause harm to our body. This happens whenever unnecessary blood clotting is activated.
The pathological thrombosis is caused by the presence of at least **one of 3 factors** (together called Virchow's triad).

The word triad means three things, so, there are three factors that contribute to the pathology of thrombosis. These factors include endothelial injury, abnormal blood flow and hypercoagulability.
Each one of those factors can independently lead to thrombosis.

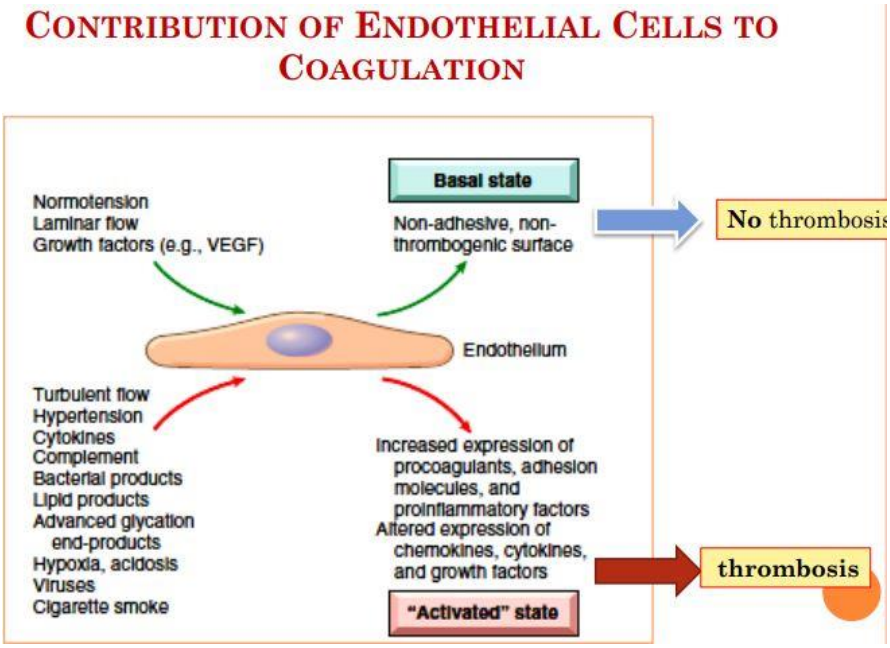


Sometimes at certain circumstances one, two or three of these factors can be happening at the same time. And sometimes one of those factors can lead to the other factor. For example, endothelial cell injury might lead to abnormal blood flow and consequently both of them would be happening at the same location and will lead to thrombosis. Another example is that abnormal blood flow may sometimes lead to local effect of **hypercoagulability** and so on. So, these factors in Virchow's Triad are very important regarding the pathology of thrombosis.

- Endothelial cells are a special type of cells that cover the inside surface of blood vessels and the heart. So, both the heart and the blood vessels are covered from inside by the Endothelial cells. Under normal circumstances, the endothelial cells will prevent or inhibit the process of coagulation inside the vascular space (we mean by normal circumstances the presence of normal blood pressure, laminar blood flow and the presence of certain inhibitory growth factors like **VEGF**).

Under those circumstances, the endothelial cell is called to be in the basal or inactive state, it will have non-adhesive and non-thrombogenic surface.
However, the endothelial cells can be activated or injured. those circumstances include anything that disturbs the blood flow inside the blood vessel like turbulence, hypertension, presence of abnormal amounts of certain cytokines and complements or bacterial products, cigarette smoke as well as other things that are injurious to the surface of endothelial cells. In this case, the endothelial cell is said to be transformed into activated state or the injury of the endothelial cell, both of which are interchangeable terms.

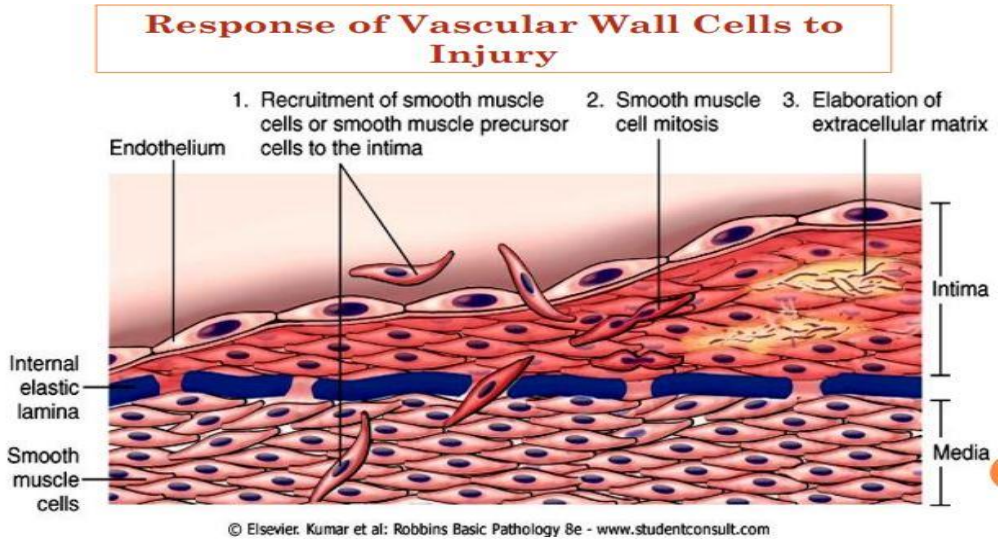
Whenever the endothelial cell is injured, this will lead to increase the expression of certain pro-coagulants and adhesion molecules, and some pro inflammatory factors. All of these will alter the surface of the endothelial cell, and now it will transform from a cell that prevents or inhibits coagulation into a cell that will promote it.



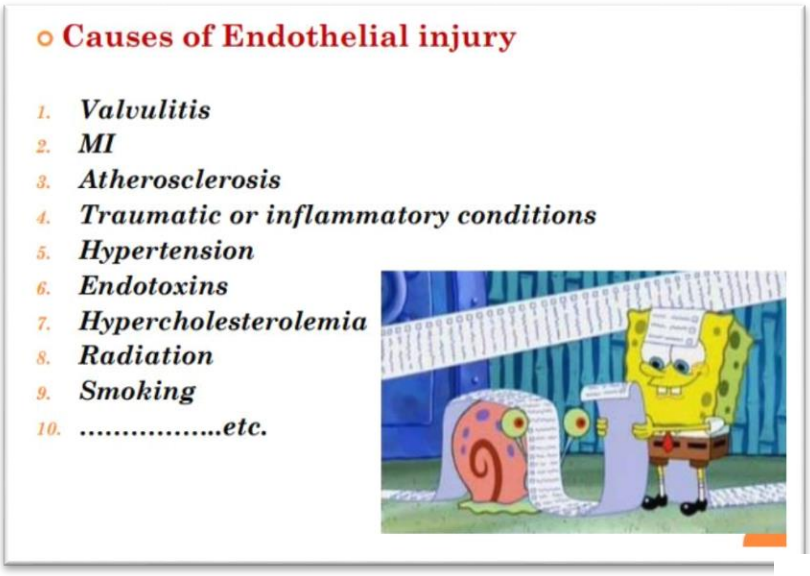
Whenever the endothelial cell injury and activation happens, this will lead to exposure of the subendothelial structures (Subendothelial collagen and other proteins), this will lead to a cascade of events resulting in activation of platelets, adherence of platelets to the site of injury, release of tissue factor, and progression of the coagulation event.

During the process of endothelial injury, there will be certain changes taking place inside the wall of the blood vessel itself. So besides promoting coagulation, the wall of the blood vessel itself will undergo changes. These changes include:

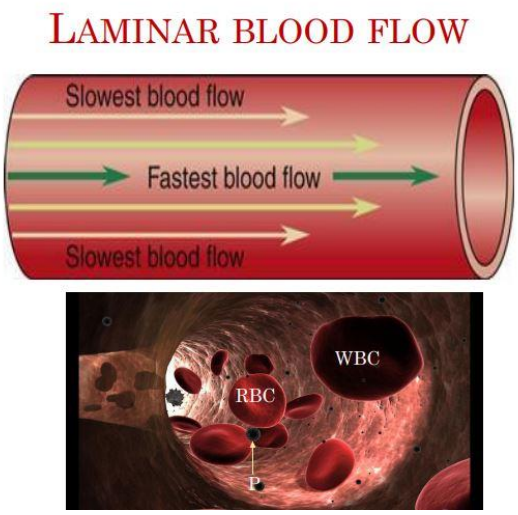
i. Recruitment of **smooth muscle cells** into the **Tunica intima**. So, smooth muscle cells will migrate from their normal habitat (which is the media) towards the intima.
ii. Inside the intima, smooth muscle cells will undergo **mitosis**, so, they will increase in number.
iii. At the same time, they will also elaborate extracellular matrix proteins. So, with time after the onset of injury of the wall of the endothelial cells, the major changes that will be distinct in the wall of the blood vessel is the **abnormal thickening** that will happen in the intima as you can see in this diagram.



Whenever the wall of the blood vessel is injured, it will show a **healing response** regarding this injury. The pathological effect of vascular wall healing is most importantly **excessive thickening of the intima**. This will lead to luminal stenosis and blockage of the vascular flow.



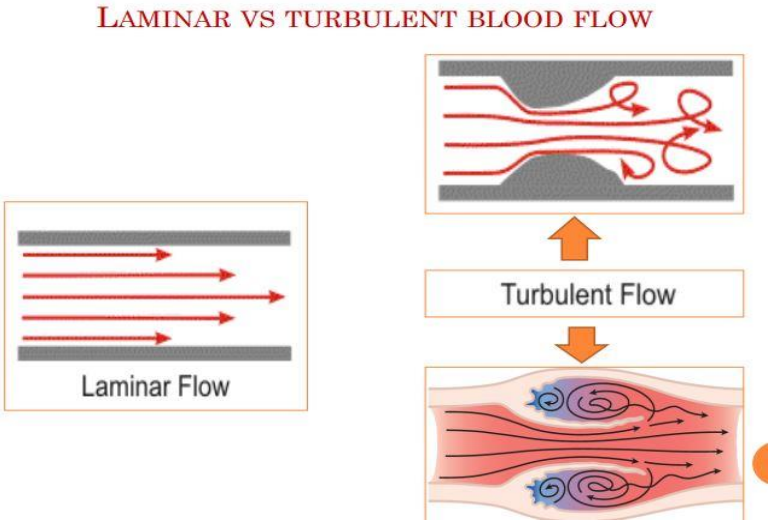
✓ The second factor in Virchow's Triad is abnormal blood flow.
We mean by abnormal blood flow is that the blood flow has either **stasis or turbulence.**
In order to understand what we mean by abnormal blood flow; we need to understand first what the normal blood flow is.



- Normal blood flow is said to be laminar meaning that it's laminated or it contains layers of constituents. So, the laminar blood flow means that the platelets will flow centrally in the vessel lumen and they will be separated from the surface of the endothelium by a **slower moving clear zone of plasma**. So, the fastest blood flow will be at the center of the blood vessel and the slowest blood flow would be just adjacent or very close to the endothelial surface of the wall.

Platelets are kept away from the endothelial cell surface under normal circumstances in order to inhibit unnecessary coagulation.
So, under normal circumstances, the laminar normal flow of the blood will prevent or help to prevent unnecessary coagulation. On the other hand, turbulent blood flow regardless of the cause, will lead to abnormal direction of the blood flow and sluggish movement of blood constituents, both of which might increase the risk to develop unnecessary coagulation.
What are the causes of turbulent blood flow? Anything that might lead to either stenosis or sudden narrowing of the lumen of the blood vessel OR, on the other hand, anything that leads to a dilation of the diameter of the blood vessel, both of which might lead to turbulence of the blood flow, sluggish movement of blood through the affected segment of the vessel, and consequently might lead to increased risk of blood clot formation.

Stasis is considered to be a major factor in Venus thrombi formation. stasis and turbulence in general, can lead to the following things:



- **They can lead to disruption of the normal blood flow**.
- **They can prevent the dilution of the activated clotting factors by fresh flowing blood**.
- **They retard the inflow of clotting factor inhibitors to the site of coagulation**, and <u>they will also promote endothelial cell injury</u>. All of these factors will contribute to the formation of the thrombus.

Causes of stasis:

i. **Atherosclerosis**, which will cause narrowing of the artery.
ii. **Aneurysms**, which will lead to abnormal dilation in the affected blood vessel.
iii. **Myocardial infarction** (non-contractile fibers in the heart), which might lead to blood stasis inside one of the heart chambers.
iv. **Mitral valve stenosis (atrial dilation):** Injury to the valve leading to chronic scarring and stenosis.
v. **Hyper viscosity syndrome**.
vi. Anything that leads to hypercoagulability of the blood might be a contributing factor.

Now the third and last factor in Virchow's Triad is blood hypercoagulability.
The word hypercoagulability means abnormally high tendency to develop blood clots.
This hypercoagulability has two major types, either genetic or acquired.

- <u>Genetic or primary hypercoagulability</u> usually results from mutations in genes that are involved in coagulation, like clotting factors or clotting factor inhibitors. These are rare in general, but the most common of which is probably mutations involving factor five and prothrombin gene.
- <u>Acquired or secondary hypercoagulability</u> is acquired during life. It's usually **multifactorial** and is more complicated. Many things might lead to acquired or secondary hypercoagulability, this hypercoagulability when it's secondary might be **local or systematic**. Many things might lead to it including immobilization, myocardial infarction, major surgeries, large or long bone fractures, burns, cancers, the use of prosthesis and etc.

Thrombi can develop in any location inside the cardiovascular system. So, inside the heart, inside arteries, inside veins and even inside capillaries.

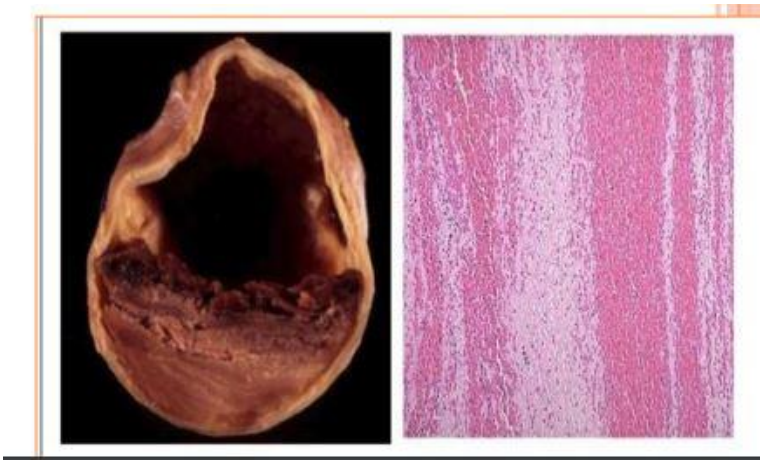
- ✓ Arterial or Cardiac thrombi usually begin at sites of endothelial injury. They are usually superimposed on atherosclerotic plaque.
- ✓ Venous thrombi are very common at sites of stasis or turbulence of blood flow. Most commonly affected veins are the lower extremity veins (90%).

Thrombi are focally attached to the underlying vascular surface. The other portion of the thrombus is called the propagating portion. This part is poorly attached, it is inside the lumen of the blood vessel and this portion is the one that is involved in fragmentation and in embolus formation.

Terms to Remember:

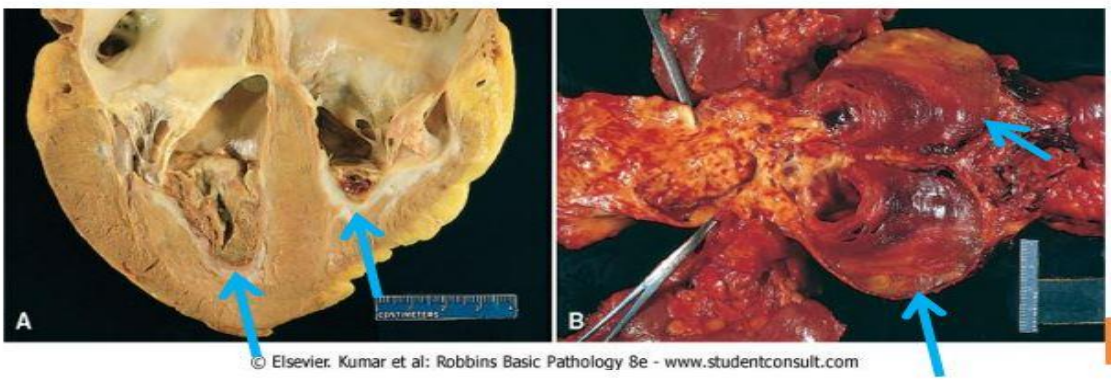
There are certain terms that we need to understand and remember, whenever we talk about cardiovascular thrombosis.

i. **Lines of ZAHN**. These are gross and microscopic evident laminations inside the lumen of the blood vessel, they represent a blood clot which contains pale platelets and fibrin layers alternating with darker erythrocyte rich layers. And this alteration in the layers will give the characteristic color differences in those lines. So, we have pale lines alternating with darker lines, and those lines can be seen both **grossly and microscopically**.



The significance of those lines is to distinguish between Antemortem versus postmortem blood clots. **Antemortem** means blood clots that form during life. Postmortem clots are blood clots that form after death. So, this is a forensic aspect of thrombosis. This can be sometimes very significant regarding determination the cause of death and whether the blood clots are formed during life or just some gravity effect that lead to blood clot formation after death.
Postmortem blood clots are non-laminated, and they do not contain lines of Zahn.

ii. **Mural Thrombi**. These are thrombi that develop inside the heart chambers or in the aortic lumen.



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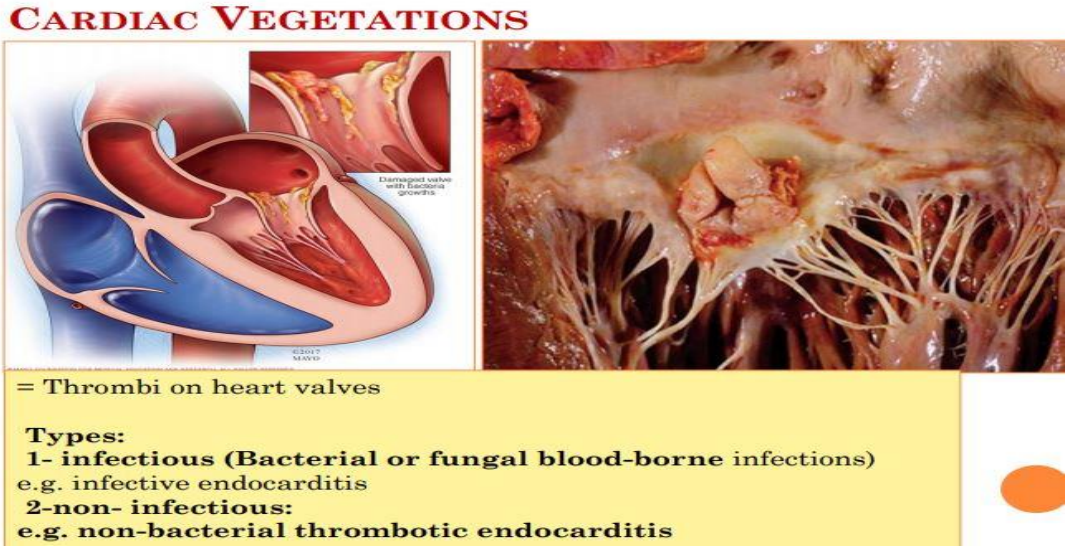
iii. Cardiac Vegetations.

Vegetations mean thrombi that are formed on or overlying the heart valves. These thrombi can be either infectious or noninfectious. And whenever we say infectious vegetations we mean by that there's certain bacterial or fungal blood borne infection that caused the formation of those vegetations. In this case, the vegetations or thrombi contain the infectious microorganisms.

Noninfectious cardiac vegetations can develop because of many things, for example, nonbacterial thrombogenic endocarditis.



Fates of a thrombus.

Whenever a thrombus is abnormally developing inside the cardiovascular system, what will happen to this thrombus? this depends on many things, including the location and the size of the affected blood vessel, the hemostasis status overall and the health status of the cardiovascular system.

- The first one of those fates is **resolution**, we mean by that removal of the formed thrombus, either alone or etiologically (with the use of certain medications). So, this is the perfect situation, and this is the fate of recently formed thrombi.

- The second fate is propagation of the thrombus. Which is the enlargement of the thrombus by accumulation of additional platelets, fibrin and red blood cells and this propagation might eventually lead to vessel obstruction.

- The third fate is thromboembolism, in which certain thrombi or fragments of the thrombi can dislodge or fragment, and the fragments are transported elsewhere in the vasculature. This will be the subject of our upcoming lecture.

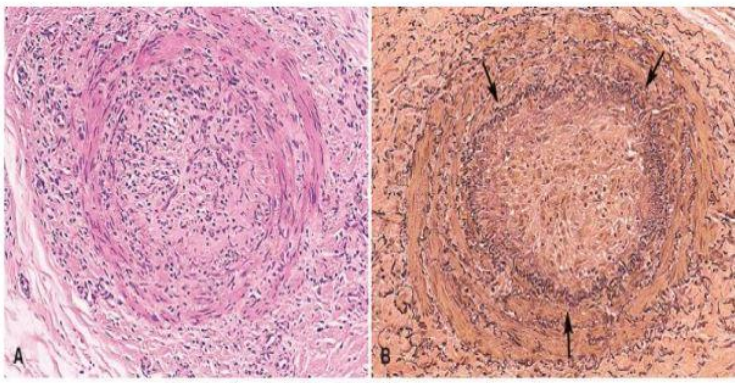
- The Fourth fate is organization and possibly recanalization. we mean by organization that the thrombus might induce inflammation and fibrosis. So, the process of coagulation is followed by inflammation and fibrosis, this might affect the vessel wall diameter, it might lead to complete occlusion of the affected blood vessel.

Organization is produced by ingrowth of cells including the endothelial cells, smooth cells and fibroblasts into the fibrin Rich thrombus and this needs a long time to happen. So, this affects chronic thrombi.
The word recanalization means that a new channel or a new lumen is developing inside or through the organized thrombus. This will lead to maintenance of certain amount of blood flow through the affected blood vessel.

- Finally, we have the Mycotic aneurysm or superimposed infection. This fate is rare, and it happens whenever there is a super imposed infection at the site of the thrombus formation. This subject will be discussed in a different lecture.

This picture shows us an example of an organized arterial thrombus

Picture A: H&E conventional staining.
Picture B: silver staining.
Can anyone tell me where is the lumen of this vessel?
No lumen is present. And this is what we mean by organization which is development or replacement of the lumen by tissue and sometimes it might lead to complete occlusion and loss of that blood vessel.



GOOD LUCK