

decrease the AVN delay and increase the strength of the ventricular wall contractions. The noradrenaline binding to the beta 1 receptors on the nodes increases the cells permeability to calcium and so there is a greater calcium ion influx at the action potential plateau. The greater the calcium influx the greater the release of calcium ions from the sarcoplasmic reticulum and so more actin myosin crossbridges formation

- The parasympathetic branch of the vagus nerve releases acetyl choline onto muscarinic receptors on the SAN and AVN to reduce the heart rate (bradycardia).

The many blood vessels within the body all have their own properties and their own pressures within the body.

- **Aorta** has the greatest elastin and collagen content of any blood vessels to cope with the huge pressure of blood it contains and some smooth muscle
- **Arteries** have slightly less elastin and collagen and slightly more smooth muscle but just because they are smaller as they still have roughly the same pressure as the aorta
- **Arterioles** have less elastin and collagen again but the most smooth muscle as this is important in heat regulation to allow vasodilation and vasoconstriction
- **Capillaries** are only one cell thick and so have no elastin collagen or smooth muscle
- **Venules** have the same elastin and collagen as arterioles but less smooth muscle
- **Veins** have more of everything to cope allow its capacitance and for it to function as a reservoir
- **Vena cava** has more again as it must contain all of the blood returning to the heart

- Blood clotting

Blood clotting is an important equilibrium between Haemostasis, keeping the blood volume at a stable level, and thrombosis, unwanted blood clotting.

Haemostasis:

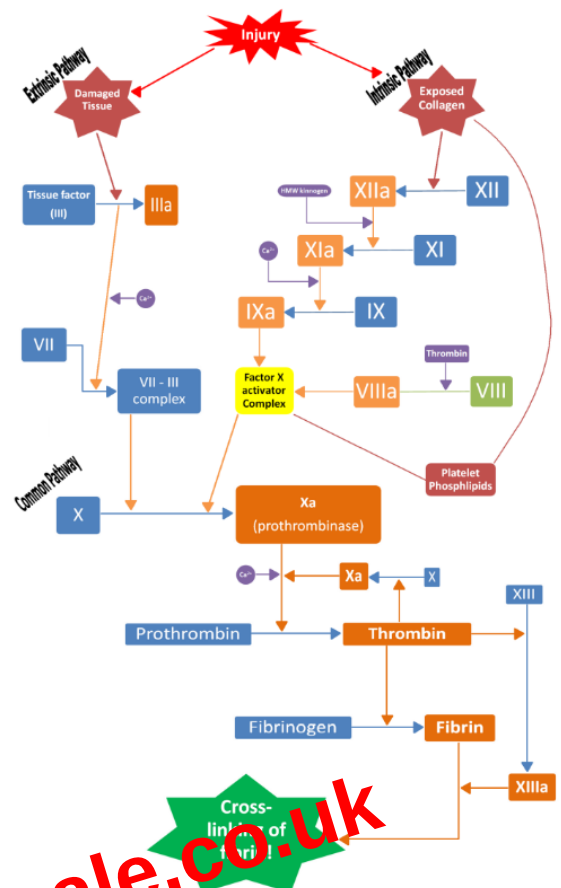
- Local vasoconstriction, reducing the blood flow to the damaged area slightly so less blood is lost
- Platelet adhesion and activation, platelets adhere to the collagen in the wall of damaged vessels as well as to other platelets which they activate and signal them to elongate.
- Initiation of the coagulation cascade forming the fibrin protein mesh

Platelet action:

1. Immediately after there is damage to the vessel wall platelets passively undergo capture to move along exposed collagen
2. Once activated the platelets use their contractile apparatus to alter their shape and release mediators to carry out positive feedback to increase activation as well as constricting vessels.
3. The platelet spreads out along the collagen strand and proteins on its surface bind to the collagen, adhering it in place. GPIIb/IIIa binds to the collagen strand and GPIIb/IIIa binds to von Willebrand factor on the surface of the collagen, both GP proteins are integrins.
4. As more platelets arrive they adhere to one another by forming cross bridges with GPIIb/IIIa and fibrinogen, creating a platelet aggregate
5. In addition to adhesion to other platelets, platelets also express phosphatidylserine (a positively charged phospholipid that is usually internalised) on the outer membrane leaflet.

Coagulation cascade:

1. When the blood vessel is damaged **tissue factor** is exposed
2. Tissue factor activates a series of proteases which cleaves **coagulation factor** enzymes and activates them, it is important to have the series of proteases to implement control in the **coagulation cascade**.
3. Eventually the series of coagulation factors amplifies the generation of **thrombin**
4. Thrombin lyses **fibrinogen** which converts it into its active form of **fibrin**
5. The fibrin filaments polymerise and form a protein mesh which, together with the platelet aggregate creates the clot.



The cascade has several promoters that increase the rate of clotting:

- **Cofactors** – factors VIII and V
Promote proteolysis and activation of coagulation factors on the phospholipids of platelets
- **Vitamin K**
is required to produce the active forms of the coagulation factors which bind to the phospholipids

Tissue factor activates factor VII

Factor V activates prothrombin to form thrombin

It is important to localise and control the clotting so that blood vessels are not blocked off entirely, to do this the body has a series of safety features to restrict the extent of the clotting:

- The factors are only activated on the cell surfaces and so the coagulation cannot occur within the plasma, only on the vessel wall. As well as this there are inhibitors of the proteases and of thrombin within the plasma which further prevents activation.
- There is also negative feedback of the coagulation cascade which is carried out by activated protein C which is activated by thrombin. APC binds to endothelial cells along with protein S in order to inactivate factor V and VII

Fibrin is broken down during **fibrinolysis**, this is carried out by plasmin. Plasmin is converted from plasminogen by tissue plasminogen activator to allow for the degradation of the clot, without tissue plasminogen activator large clots form within the body.

There are also substances that are capable of preventing the coagulation of fibrin to occur:

- **Heparin** – increases the action of antithrombin III which is a protein that inactivates proteases
- **Warfarin** – inhibits the action of Vitamin K, and so the active form of coagulation factors cannot be formed
- **Ca chelation (EDTA, citrate)** – these are substances that make calcium ions unreactive which prevents them from being used in activating thrombin so active fibrin cannot be made.

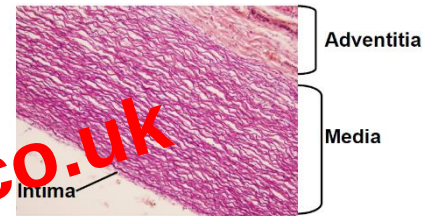
- Increases or decreases in blood volume
- Gravity causing venous pooling so more blood remains in the veins and is not returned to the heart
- The effects of the skeletal muscle pump can help return blood to the heart
- Ventilation can draw blood up into the thorax
- Venous tone can aid in increasing the CVP and helping more blood to return to the heart

Sterling's laws are important in our bodies as they ensure that the end diastolic volume is representative of the stroke volume to ensure equal quantities of blood are being pumped around the body as are being returned. Similarly it is important for the left side of the heart to have the same stroke volume as the right side.

We can change the end systolic volume by having different levels of sympathetic activity which alternates the circulating adrenaline as well as the release of noradrenaline from the Vagus nerve which stimulates the beta 1 adrenoceptors on the heart. These both in turn stimulate calcium influx which then leads to calcium induced calcium release. This increases contractility of the ventricular wall and means that more blood can be ejected.

- Elastic arteries

These are the first blood vessels that blood enters upon being ejected from the ventricles. They have a large media layer which is composed of multiple layers of elastin and some smooth muscle, only a small amount as the aorta has limited capacity to dilate and constrict.



The elastic arteries determine the body's blood pressure, the higher the pressure within these arteries the greater the extent of perfusion of blood through the systemic circulation. It is also the elastic arteries job to convert the intermittent flow of blood from the ventricles into a continuous flow that reaches the tissues.

The pressure within the aorta is at the lowest at the end of diastole, this is where the ventricular pressure exceeds that of the aorta, allowing the aortic valve to open. After this the pressure climbs and then drops slightly until the aortic valve closes once again, where the pressure slowly decreases once again.

Arteries are composed of the intima which is a single cell thick layer of endothelial cells that lines the lumen of the blood vessel, under this is the media which is comprised of smooth muscle and elastic tissues with the latter being more dominant in the elastic arteries, to allow the elastic arteries to recoil and resist the high pressure of the blood. The adventitia is the outermost layer of the elastic artery and is highly collagenous and provides support to arteries to prevent excessive stretching so the aorta doesn't burst. As we age the media loses elasticity and becomes more rigid, this means that the aorta cannot stretch as much through systole so does not distend as much so the pressure is greater. However as it is not distended as much it does not have as much elastic energy so the pressure of the aorta drops faster. This results in a pressure curve that is higher in systole and lower in diastole.

- When the pressure within the left ventricle exceeds that of the aorta, the aortic valve opens and allows blood into the aorta.
- The pressure of the blood distends the wall of the aorta until the adventitia eventually stops the expansion