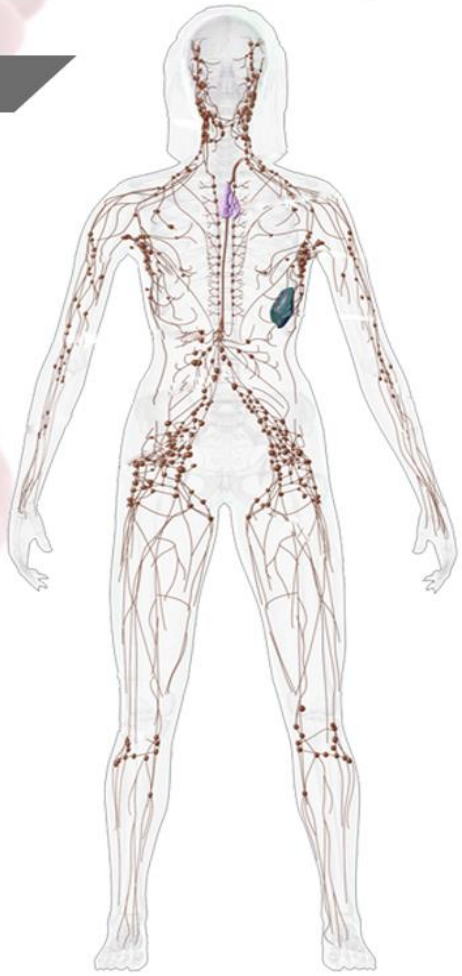
Sheet 10

Hematology and Lymphatic system

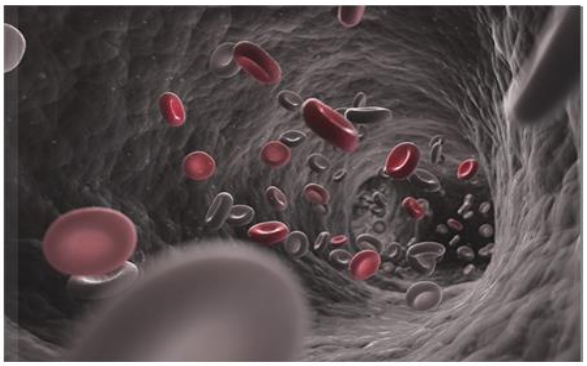


Subject | Physiology

Done by | Razan Al-zoubi

Corrected by | ...

Doctor | Saleem Khreisha



THROMBOEMBOLIC CONDITIONS

Last lecture, we said that even in healthy people minor clottings occur, but these clottings are **few** and **dissolve** immediately.

- NOW what if the clotting was **too much**?
  This leads to consumption of platelets leading to **thrombocytopenia**.

- What if the clots **did not dissolve**??
  It causes **thrombosis**. **(thrombus: lodged clot)**
- Sometimes the clot(thrombus) is pushed and removed from its attachment and start circulating in the blood, forming emboli. **(embolus: circulating clot).**
- Embolus may be a **bubble of air**, **fat** or even **debris.**

The emboli may lodge inside narrow blood vessels obstructing blood supply, and this may lead to serious conditions, especially if it forms thrombus in the heart or in the coronary arteries.

- So Embolus in arteries are more dangerous than in veins, especially if these arteries supply vital organs such as the brain or the heart.

Two conditions are related to embolism and thrombosis

Mainly causing HEART ATTACKS.

1) **Atherosclerosis**: the accumulation of lipids inside the blood vessels, so they become relatively narrow. So it causes 2 problems: 1) loss of flexibility.
   2) forming a rough layer, stimulating platelets.

2) Arteriosclerosis: the loss of blood vessels flexibility, due to aging for example. So vasoconstriction and vasodilatation would be much harder, thus causing rupture of the blood vessels, **leading to platelets stimulation**.

In vivo: the main cause of coagulation is the extrinsic pathway, although there is no tissue damage, so they say either the infection causes the release of tissue thromboplastin, or from lymphocytes.

In vitro (in the tube): the main cause of coagulation is the intrinsic pathway, because it is a foreign surface.

Causes of Thromboembolic Conditions:

1) **Injury to a blood vessel**: as may be caused by trauma or infection, the endothelium becomes rough resulting in platelet adhesion then activation and aggregation, in this case both extrinsic and intrinsic pathway are activated, Infections, however, mediate the inflammatory response which could cause injury of endothelium.

2) **Infections:** an infection in the inner surface of the blood vessel stimulate platelets, thus the platelets adhere then aggregate.

3) **Slowing of the blood flow**: this causes platelets to aggregate and adhere, especially if the **platelet count is high** such as, during **operation or childbirth,** so we advise patients to walk in the room to increase the blood flow, otherwise we give them anticoagulants (heparin).

   Also, when blood flow is very slow, the **composition of blood changes**, **high amount of plasma protein like fibrinogen is produced** with slow elimination of them from liver (because of slow circulation), this usually occur also in operations, childbirth or any other cause of dehydration.

- **Conditions that causes extensive bleeding in humans (Defects in homeostasis):**

  1. Increased fragility of vessels.
  2. Platelet deficiency or dysfunction.
  3. Defect of coagulation factors.
  4. Excessive fibrinolysis.

  → the MOST COMMON cause is **platelet number deficiency**, then **coagulation factors defects.**

1. Increased fragility of vessels (Vascular disorder)

The problem is either in the **blood vessel itself** or the **connective tissue around it**.

And this disorder is either **inherited** or **acquired**, characterized by bruising and spontaneous bleeding in small blood vessels.

• **Genetic**: usually **appears mild during childhood** and then becomes **moderate or severe (more vessels affected) during adulthood.**

• **Acquired** (latent): examples:

1- Senile purpura: easily bruised blood vessels because of advancing age.
2- Purpura associated with chronic infection: especially viral infection, due to microbial damage of the vessels.
3- Scurvy: vitamin C deficiency, it causes purpura.
4- Steroid purpura: a result of prolonged steroid therapy.

Purpura → it's a condition that occurs when skin or mucous membrane of such a person displays many small, purplish blotches.

2. Platelet count abnormality (thrombocytopenia)

Characterized by spontaneous skin purpura, mucosal hemorrhage and severe bleeding after trauma.

Remember: platelets are especially important for the repair of minute breaks in capillaries and other small vessels. (maintain the integrity of blood vessels)

Thrombocytopenia causes **easily bruised blood vessels (purpura**) characterized by skin and mucous hemorrhage.

Causes of thrombocytopenia:

1- Failure of platelets production due to some **toxins, drugs, chemicals, or viral infections**.
2- Depression of bone marrow due to **Leukemia, Aplastic anemia, and megaloblastic anemia.**
3- **Increased destruction of platelets** because of **high concentration of heparin**, or a condition called **Disseminated Intravascular Coagulation**; characterized by excessive clots formation; thus causing a depletion in platelets, which will eventually lead to unhealed bruises → Purpura Formation.
4- **Sequestration (abnormal distribution of platelets)**: The spleen normally sequesters little amount of the body's platelets, but this amount can rise **when the spleen is enlarged**, producing moderate degrees of thrombocytopenia.
5- **Platelets loss after massive blood transfusion**: because of the short half-life of WBC's and platelets, we can't donate them frequently, but we can for RBC's.

Thrombocytopenic purpura: It is a purpura due to **low platelets count**, when platelets' count is low, clot retraction is deficient, so there is poor repair of the injured blood vessels. This leads to higher susceptibility to bruising and multiple subcutaneous hemorrhages.

3) **Platelets function abnormalities**: Thrombocyto**pathies**: characterized by abnormal platelet function and normal platelet count.

It's either:

- Genetic: **problem in adhesion** (deficiency in glycoprotein-1 on the platelet) or **defect in production of substances like thromboxane**.
- Acquired: **Aspirin therapy**; aspirin is an inhibitor of the enzyme cyclooxygenase, which is required for the synthesis of thromboxane A2 and prostaglandins. These mediators play important roles in platelet aggregation and subsequent release reactions.

SO **Thrombasthenic purpura**; due to defect in platelets function.

here, the thrombocyte **count is normal**.

4) **Coagulation factors disorders:**

- Most of coagulation factor deficiencies are **inherited problems** with factor VIII or factor IX, which are known as Hemophilia A and B, respectively.
- Coagulation factor Diseases **all are uncommon**, but deficiencies in other factors are rare.

1. Hemophilia A (factor 8 deficiency):
-The most common inherited disorder of blood coagulation among the uncommon.
-It's a **sex- linked defect** with 33% of patients having NO family history of the defect.
- Incident rate is 1:10 000
- Appears in **males only** (because it's sex-linked). Females are only **CARRIERS. ***
-female patients usually do **NOT survive**, even newborns usually die IMMEDIATELY after birth.
- 2 abnormal genes are needed to consider the individual diseased
-Factor VIII (8)-c is deficient, but Factor8-related Antigen is normal, leading to **coagulation defect only**.

2. Hemophilia B (factor 9 deficiency):

-less common that Hemophilia A.
-Sex-linked with similar symptoms to Hemophilia A. (appears only in males).
-Deficiency in coagulation factor IX (9), SO no coagulation.

3. Von Willebrand's disease:

-No problem in the X chromosome of the factor 8-c, but there is a problem in the **Factor8-related Antigen**, and this results in rapid destruction of Factor8-c.
-Meaning, **NO ADHESION, NO ACTIVATION of platelets and NO AGGREGATION and COAGULSTION.**
-Somatic (autosomal) **dominant** inheritance. not sex-linked like Hemophilia A and B.
-Occurrence is equal in both males and females.

Table 13.2 Main clinical and laboratory findings in haemophilia A, factor IX deficiency (haemophilia B, Christmas disease) and von Willebrand's disease.

	Haemophilia A	Factor IX deficiency	Von Willebrand's disease
Inheritance	Sex-linked		Dominant
Platelet count	Normal	Normal	Normal
Bleeding time	Normal	Normal	Prolonged
Factor VIII:C	Low	Normal	Low
Factor VIII:AG	Normal	Normal	Low
aggregation	Normal	Normal	Impaired

*The doctor used this table to compare between the diseases, it's useful. DO NOT SKIP IT. Notice how everything in the middle column (Hemophilia B) is normal because the problem is related to factor 9, not 8.

-Hereditary disorders of other coagulation factors are extremely **rare**, and their mode of inheritance is **autosomal** (somatic).

-There's a good correlation -usually- between **facial symptoms and severity of the coagulation factor deficiency.**

- **Factor XII (12)** deficiency is not associated with abnormal bleeding (the deficiency of factor XII (12) does not cause severe bleeding, because platelets can directly activate Factor XI (11)).
- **Factor XI (11)** deficiency: not that serious problem, mild symptoms (stimulated directly by platelet).
- **Factor 13 deficiency** causes severe bleeding because the coagulation isn't "stable".
****Factor 13 (fibrin stabilizer)** is activated under the effect of thrombin and Ca++, it stabilizes fibrin.

Vitamin K-dependent factor: Factor 2, 7, 9, 10, Protein C and S. **these factors aren't synthesized properly in case of vitamin K deficiency.

Anticoagulants

Anticoagulants are used in medication (in vivo) and in lab experiments (in vitro) **to prevent blood clotting and coagulation.**

They are grouped into three groups:

A. Coumarin- like anticoagulants:
They are called in vivo **Warfarin-like** anticoagulant

- They interfere with the **production of vitamin K dependent coagulation factors** (2,7,9,10) by blocking the synthesis of vitamin K.
  SO mainly used in vivo, since there is no VITAMIN K synthesis in vitro.

Those were not mentioned by the doctor (from 2016 sheet):
They also prevent coagulation by:
1: Preventing the formation of prothrombin.
2: Delay the conversion of prothrombin into thrombin
3: Limiting the activity of thrombokinase.

B. Non Wettable surfaces:
We put the blood in a tube covered by wax, silicon or polystyrene. Taking the blood "nicely and smoothly" in a tube covered by silicon or wax, by this way we inhibit the formation of Thrombokinase.

C. Substances that capture the Ca++:
- **Oxalate, citrate, EDTA**; they block the action of Ca++
- **Ca++ (Coagulation factor 4)** is present in the whole intrinsic pathway, EXCEPT the first two steps.

****We also have** Heparin, Hirudin and the stirring method.

(1) Heparin:

It **inhibits the whole intrinsic pathway** by binding to anti-coagulant 3.

(2) Hirudin:

It's a chemical found in **leeches *العلق *** and it **inhibits the action of thrombin**. Pharaohs and Chinese used these leeches and put it on the vein or the blood vessel, leeches absorb about 50ml of the blood, they use it to deal with patients who have hypertension but mainly they dry it and use it as fibers.

(3) Stirring:

By stirring, **fibrin is removed** and thus coagulation is inhibited.

In medications we mostly use **Heparin and **Warfarin**:

The following table compares between the two:

Warfarin	Heparin
Of plant origin.	Of animal source (already present in our bodies). Secreted by basophils.
Slow acting (takes up to one day for it to start its action)	Acts rapidly.
Its effect lasts for days, longer duration (duration of action)	Shorter duration in comparison
It inhibit the formation of vitamin k dependent factors therefore its used only in vivo (mechanism of action)	Disturb the formation of thrombokinase and it may inhibit the reaction between thrombin and fibrinogen. It's used in vivo and in vitro. (Mechanism of action).