HLS

MODIFIED NO. 7

PHYSIOLOGY

كتابة: إبراهيم الشوابكة و محمود الجرادات

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UNIT VI

Hemostasis and Blood Coagulation

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Color code

- Slides
- Doctor
- Additional info
- Important

We'll discuss several causes of excessive bleeding:
* Notice that any clotting factor deficiency can cause prolonged bleeding.

Most commonly:

- **Hepatocellular disease "Liver diseases"**
- **Vitamin K deficiency**
- **Hemophilia :**is a rare disorder in which the blood doesn't clot in the typical way because it doesn't have enough blood-clotting proteins (clotting factors).
- **Low platelet count as thrombocytopenia**

Vitamin K Deficiency

- **Vit K is essential to carboxylate glutamic acid in five important clotting factors:**
  - **prothrombin and factors VII, IX, X, and protein C,**
- **In this process vitamin K is oxidized and inactivated**
- **Vitamin K epoxide reductase complex 1 (VKOR c1) reduces vitamin K and reactivates it.**

During carboxylation process, Vit K is oxidized to an inactive form, known as Vit K epoxide.

Vitamin K production in the small intestine and VKOR c1 enzyme are important to have normal prothrombin production as well as other clotting factors (VII, IX, X).

Vitamin K

- **Produced in the intestine by bacteria so Vit K deficiency is very rare except for newborn whose intestines and normal flora are immature.**
- **Vit k is a fat-soluble vitamin (remember that vitamins are grouped into fat soluble vitamins as A,K,E and D and water soluble vitamins) so malabsorption of fats can lead to Vit Kdeficiency.**
- **Lack of bile production or delivery can cause fat malabsorption and vitamin K deficiency, because bile is essential for digesting fats.**
- **In patients with liver or biliary disease, vitamin K can be injected 4-8 hours before surgery to ensure proper blood clotting.**

Hemophilia

- **Hemophilia is a blood disorder that there is excessive bleeding.**

Hemophilia is subdivided into three types:
1) Hemophilia A : factor VIII deficiency.
2) Hemophilia B : factor IX deficiency.
3) Hemophilia C : factor XI deficiency.

- **Hemophilia A – Deficiency of factor VIII which is called anti-hemophilic factor.**
  - **85% of hemophilia cases**
  - **1 / 10,000 males**
- **Hemophilia B – Deficiency of factor IX**
  - **15% of cases**
  - **About 1 / 60,000 males**
- **Both types impair Intrinsic Pathway activation**
- **Both genes are on the X chromosome so it spreads among males more than females (males only get one copy).**
- **Clinically: Bleeding after minor trauma**

Factor VIII Deficiency

- **Recently found that factor VIII has a partener which is "Von willbrand factor ", work together.**
- **Deficiency of factor VIII causes hemophilia A**

  → treat bleeding with factor VIII replacement
- **Deficiency of vWB causes von Willebrand disease (resembles decreased platelet function)**

Thrombocytopenia

- **Thrombocytopenia is a condition in which you have a low blood platelet count.**
- **Bleeding from small venules or capillaries unlike hemophilia where bleeding happens in large vessels.**
- **Causes petechaiae, thrombocytopenic purpura.**

> - Petechiae: small, red or purple spots on the skin caused by minor bleeding from capillaries.
> - Thrombocytopenic Purpura: Larger patches of bleeding under the skin due to excessive bleeding from capillaries.

- **Often idiopathic arising spontaneously or from an unknown cause.**

  < 50,000 platelets / µL – usually modest bleeding.
  < 10,000 platelets / µL – life-threatening.

  important

  So the severity of the disease depends on the numbers of platelets that are available.

- **Treated with platelet infusions**

  → effective for 1 – 4 days each time

Thrombi and Emboli

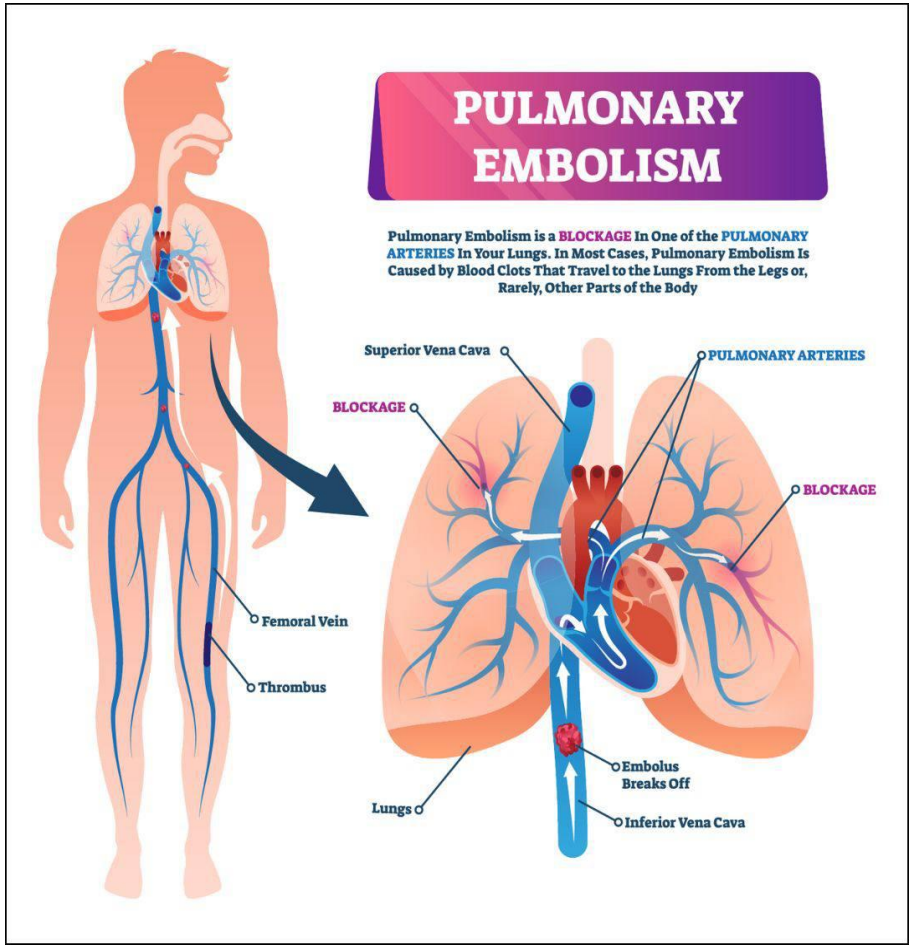
Unwanted clotting

Thrombus this is an abnormal clot that forms within a blood vessel or heart chamber. It remains attached to the site where it initially formed, which can obstruct blood flow and lead to conditions like deep vein thrombosis (DVT) or coronary artery thrombosis.
When a thrombus dislodges (تتفصل) from its original site and begins to float freely in the bloodstream, it becomes an emboli and it can travel through the circulation and lodge in other sites, causing blockages.

- **Caused by…**
  - **Endothelial roughening "damage" (e.g. atherosclerosis)**
  - **Slow flow (e.g. prolonged air travel)**
- **Treatment…**
  - **TPA " Tissue plasminogen activator factor "**
  - **Embolectomy**

Pulmonary Embolus

- Usually from deep leg veins
- Around 10% of the thrombus dislodges and begins to float (now called an embolus) so it is a part of thrombus disengages
- Pulmonary embolus usually occludes " blocks " pulmonary arteries which is potentially fatal
- Applying tPA via catheter within one hour of thrombosis can be live-saving by dissolving the clots.



Disseminated Intravascular Coagulation (DIC)

- Disseminated intravascular coagulation (DIC) is a rare blood clotting disorder that can cause organ damage and uncontrollable bleeding.
- DIC is a serious condition usually companies with septic shock due to massive tissue damage or sepsis.
- Result in wide-spread coagulation in small vessels and blockage of tissues which will cause circulatory shock
- Manifested as bleeding from multiple sites because of depletion of clotting factors.

Clinically Useful Anticoagulants

- Some of the clinically used anticoagulants that directed to the pathways that we learned in the previous lecture:
- Heparin
  - Binds, potentiates antithrombin III (inhibit the activity of thrombin)
  - Works rapidly, generally used acutely
- Coumarins (oral medication)
  - Inhibit VKOR c1(remember VKORc1 activates vitamin k)
  - Deplete active vitamin K → deplete active prothrombin, factors VII, IX, X which slowes the clotting formation and increases the bleeding tendency , that used therapeutically for certain conditions.
  - Slower acting (days) until the already present factors and active prothrombin depleted; used chronically and the action stays for longer time so after 1-3 days of leaving this treatment, bleeding can return to normal level
  - Over-anticoagulation due to more than required therapeutic dose– Treat with FFP (Fresh Frozen Plasma) and vitamin K supplementation.

In vitro Anti-coagulation

- **Siliconized containers prevent activation of factor XII and platelets thereby prevent the activation of intrinsic pathway. Unlike the glass tube ,Siliconized tubes prevent intrinsic coagulation for a long time).**
- **Heparin – used in blood collection, heart-lung and kidney machines that use blood transfer.**
- **Calcium chelators (citrate, EDTA) used in blood collection, blood storage.**
- **Oxalate can also be used, but citrate is safer when it is transferred to the patient's plasma; because it can be removed or eliminated by the liver, making it less toxic.**
- **EDTA is not used in the patient's plasma it's only used in the tubes.**

Blood Coagulation Tests

- There are two main times that can we record in lab testing:

- **Bleeding Time (from small cut)**
  - **normally 1 - 6 minutes to stop the bleeding normally.**
  - **Largely reflects platelet function so if the platelet number or function is defecient then this time will be prolonged.**

- **Clotting time**
  - **Invert tube every 30 seconds**
  - **Normally 6 – 10 minutes**
  - **Not reproducible there is a high variability in the clotting time using different methods , generally not used (it’s not used nowadays to measure clotting)**

Bleeding time

• A **bleeding time** is used to evaluate the second phase of hemostasis, which involves a adherence of the platelets to the injured vessel, platelet activation and aggregation (formation of a plug).

• The time measures how long it takes for a platelet plug to form.

• The time of bleeding It increases when the platelets count is low (thrombocytopenia),platelet function is abnormal or with the use of aspirin . (Which inhibits the production of the prostaglandins as well as Thrompoxane A2).

• Disadvantages: Insensitive, Invasive & operator dependent.
• Advantages: good test to evaluate the platelet's function and structural abnormalities

The Duke method

The doctor didn't discuss this slide, but we will cover it in the physiology lab

1. Clean the tip of the finger or the ear lobe with alcohol.
2. Puncture the skin with a special lancet. The wound should be 3–4 mm deep.
3. Wipe the blood drop by a filter paper every 30 seconds.
4. Repeat until no more blood is absorbed by the filter paper. Which indicates a platelet plug has formed.
5. Multiply the number of blood drops by 30 seconds.

•Or divide the number of spots of blood by 2 and that will give you the bleeding time in minutes.

•Normal value: is less than 5 minutes.

Clotting time

- It measures the time required for a blood sample to coagulate in vitro. Clotting time depends on the **availability of coagulation factors.**

- Many techniques are used the one we use in our lab depends on using non-hepranized capillary tubes.

- Clotting time is prolonged in conditions like hemophilia, vitamin K deficiency, liver diseases, and warfarin (anticoagulant treatment) overdose.

Prothrombin Time

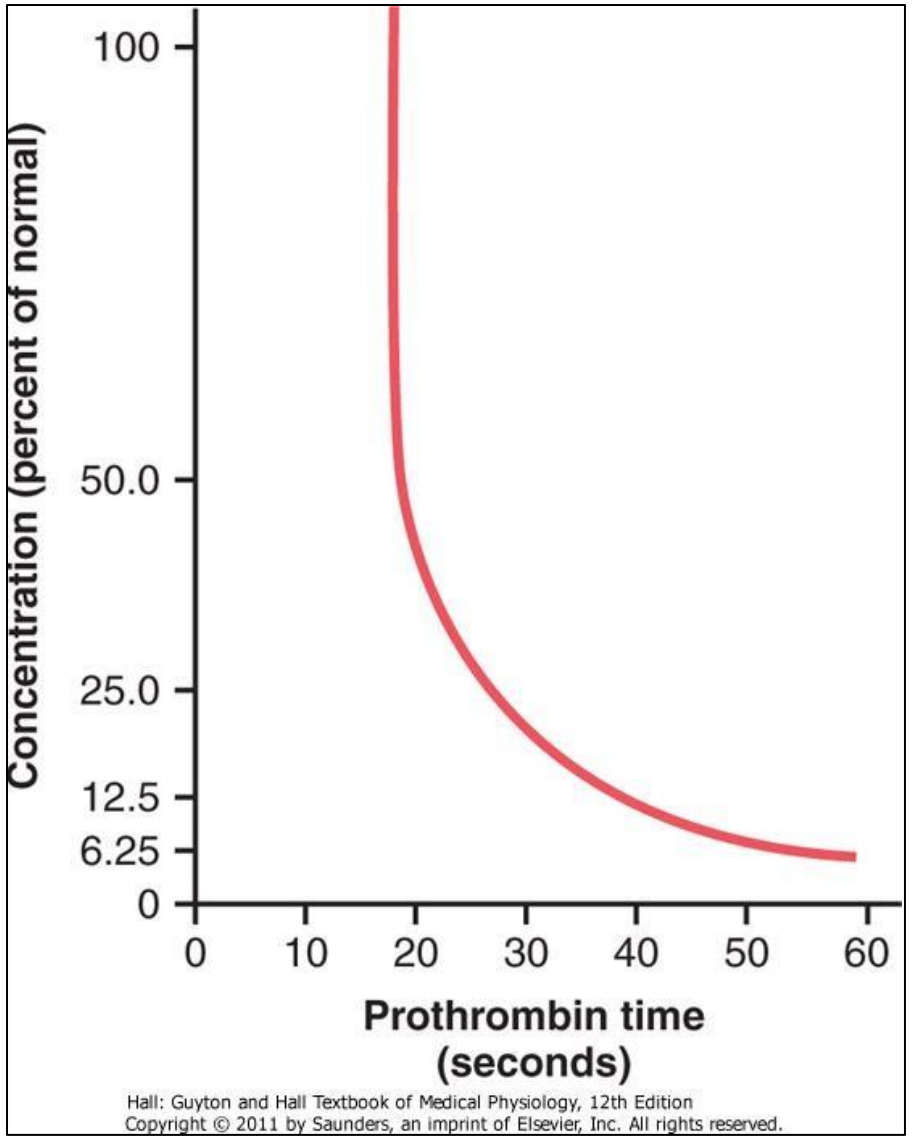
- **Add excess calcium to already citrated blood and also by adding tissue factor to oxylated blood, measure time to clot.**
- **That will induce Assesses Extrinsic and Common Pathways.**
- **Usually about 12 seconds but if it is prolonged, then there is a problem in prothrombin activity, especially the extrinsic pathway.**
- **Tissue factor batches have to be standardized (activity expressed as "International Sensitivity Index (ISI)")**

ISI accounts for the sensitivity of the tissue factor that was used for the measurement of prothrombin time .

Prothrombin Concentration and Function

Prothrombin time correlates with the concentration (which is a percentage of normal).

So,if we measure the prothrombin time in second we can detect the estimation of the concentration of prothrombin during that time.



International Normalized Ratio (INR)

$$INR = \left(\frac{PT_{test}}{PT_{normal}} \right)^{ISI}$$

- The normal INR is obtained from this formula: the patient's prothrombin time divided by the normal prothrombin time, raised to the power of standardized ISI.

- Thus, it depends on the sensitivity of the tissue factor that has been used.

- **Normal INR:0.9 – 1.3.** **if it is less than that, there is more tendency for clotting ,and if it is higher than normal, it reflects a tendency for bleeding .**

- **Therapeutic range of drugs that used as anticoagulant : 2.0 – 3.0.**

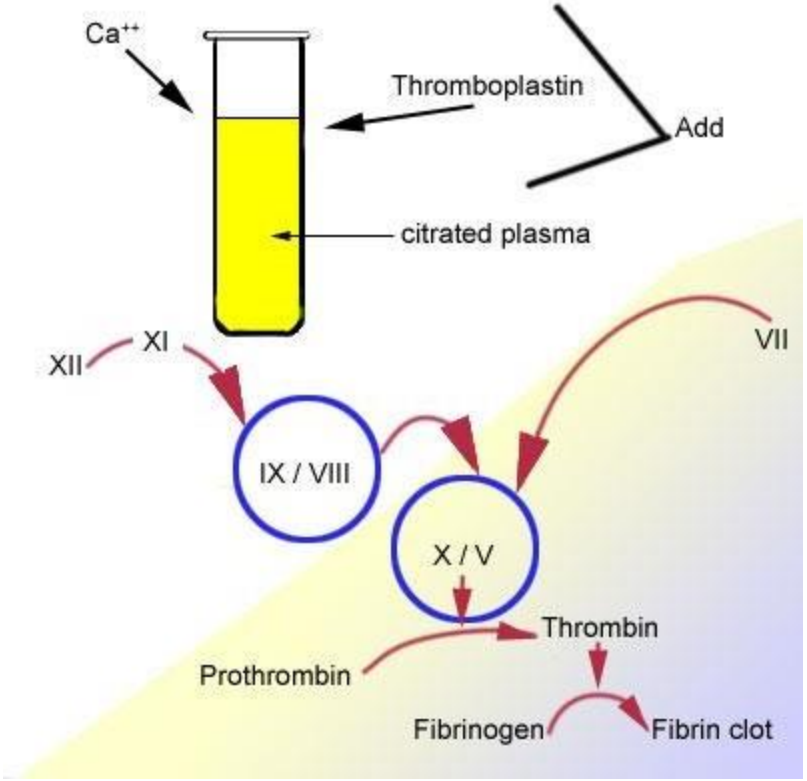
- **So, INR is always measured before surgeries, especially for people with bleeding problems or those receiving anticoagulant treatment.**

Tests of Other Clotting Factors

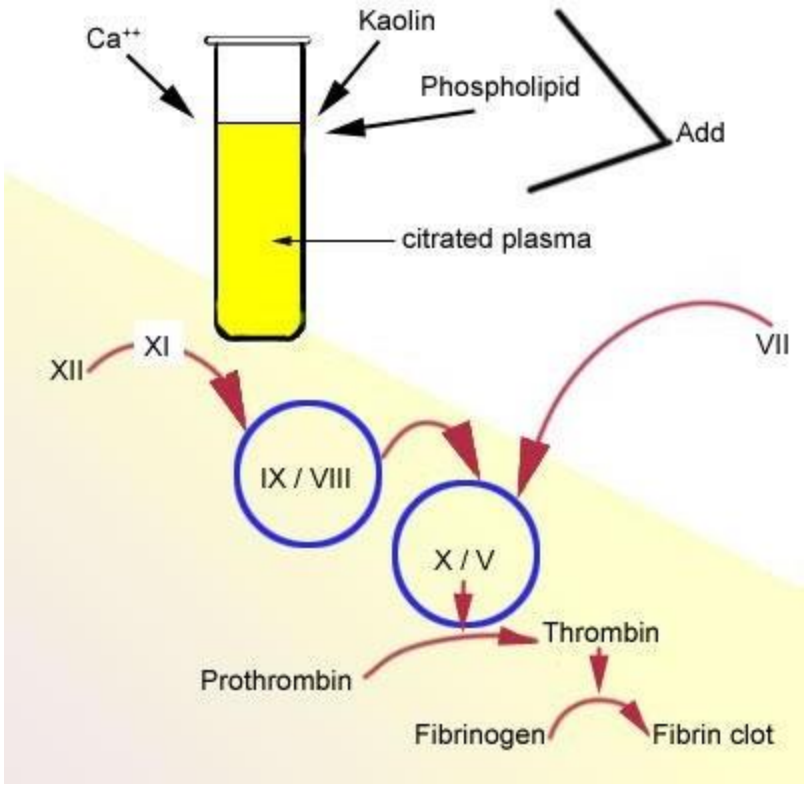
- **Mix the patient's plasma with a large excess of all needed components except the factor being tested.**
- **Therefore, if the clotting time is higher than normal, there is deficiency in that factor .**
- **Compare time to coagulation with that for pooled plasma of healthy volunteers.**

The doctor didn't discuss this slide.

PT



aPT



The doctor didn't discuss this slide.

aPTT

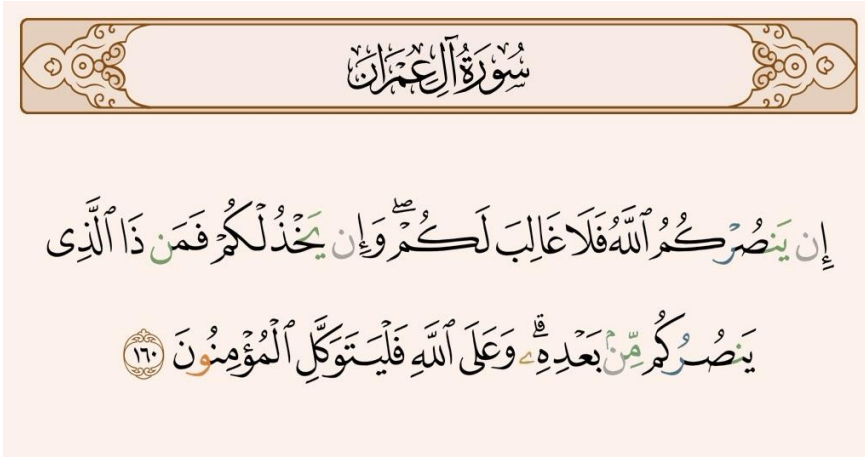
- The activated partial thromboplastin time (aPTT) is a test performed to investigate bleeding disorders and to monitor patients taking an anticlotting drug such as heparin which inhibits factors X and thrombin, while activating anti-thrombin.

The aPTT test uses blood which is decalcified to prevent clotting before the test begins. The plasma is separated by centrifugation. (Ionized) Calcium and activating substances are added to the plasma to start the intrinsic pathway of the coagulation cascade. The substances are: kaolin (hydrated aluminum silicate) and cephalin. Kaolin serves to activate the contact-dependent Factor XII, and cephalin substitutes for platelet phospholipids.

- The partial thromboplastin time is the time it takes for a clot to form, measured in seconds. Normally, the sample will clot in 35 seconds.

PTT measures the integrity of the intrinsic system (Factors XII, XI, VIII, IX) and common clotting pathways.

Increased levels in a person with a bleeding disorder indicate a clotting factor may be missing or defective. At this point, further investigation is needed and warrants the use of sensitive assays for specific coagulation factors. Liver disease decreases production of factors, increasing the PTT.



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V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!