Hemostasis and Bleeding Disorders
(Part 1)

Lecture: 5

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Hemostasis is the normal response of the body to stop bleeding and loss of blood, keeping the blood within a damaged blood vessel.

Normal hemostasis

Hemostasis depends upon interactions between four elements:

1. Vessel wall
2. Platelets
3. Coagulation system (Clotting system)
4. Fibrinolytic system (Fibrinolysis)

Mechanism

During hemostasis four steps occur in a rapid sequence:

1. **Vascular spasm:** is the first response as the blood vessels constrict to allow less blood to be lost. This response is ***triggered by*** direct injury to vascular smooth muscle and chemicals released by endothelial cells and platelets. The spasm response becomes more effective in case of small blood vessels injury and in cases of large amount of damage.

2. **Platelet plug formation**: platelets stick together and to the damaged endothelium to form a temporary seal to cover the break in the vessel wall forming a platelet plug in ***15 seconds*** (primary hemostasis) and then degranulate. As more chemicals are released more platelets stick and release their chemicals; in a positive feedback loop.

3. **Blood coagulation or blood clotting:** the sequential process by which the multiple coagulation factors of the blood interact in the coagulation cascade resulting in the formation of insoluble fibrin clot. This response will reinforce the platelet plug by the formation of a thrombus, or clot which forces blood cells and platelets to stay trapped in the wounded area.

Though this is often a good step for wound healing, it has the ability to cause severe health problems ***if the thrombus becomes detached*** from the vessel wall and travels through the circulatory system; If it reaches the brain, heart or lungs it could lead to stroke, heart attack, or pulmonary embolism respectively. However, without this process, the healing of a wound would not be possible. This step of coagulation is referred to as secondary hemostasis.

4. **Fibrinolytic system (Fibrinolysis):** it is initiated at the same time of clotting, to stop its progression. The blood clots are reorganized and resorbed maintaining the patency of blood vessels. The main enzyme responsible for this process is the plasmin. This step of fibrinolysis is referred to as tertiary hemostasis.

Primary hemostasis (platelet plug): The factors associated with successful primary hemostasis are:

1. Adequate vascular response.
2. Adequate platelet number.
3. Adequate platelet function.
4. Adequate level of the Von Willebrand's Factor (vWF).

The **vWF** is a glycoprotein made by bone marrow and endothelial cells, it circulates in a low concentration in the plasma, it enhances the adhesion of the platelets.

Secondary hemostasis (fibrin clot): is the formation of fibrin through the coagulation cascade. The coagulation cascade is traditionally separated into three pathways intrinsic, extrinsic and common. Most of the clotting Factors are manufactured in the liver. ***Factors II, VII, IX, and X are vitamin K–dependent.***

The clotting factors present in the circulation in inactive form; which require activation. Once the platelet plug has been formed, the clotting factors activated and begin to create the fibrin clot which act as a mesh all around the platelet plug, holding the plug in its place. Red and white blood cells become caught up in the fibrin mesh which causes the clot to become even stronger.

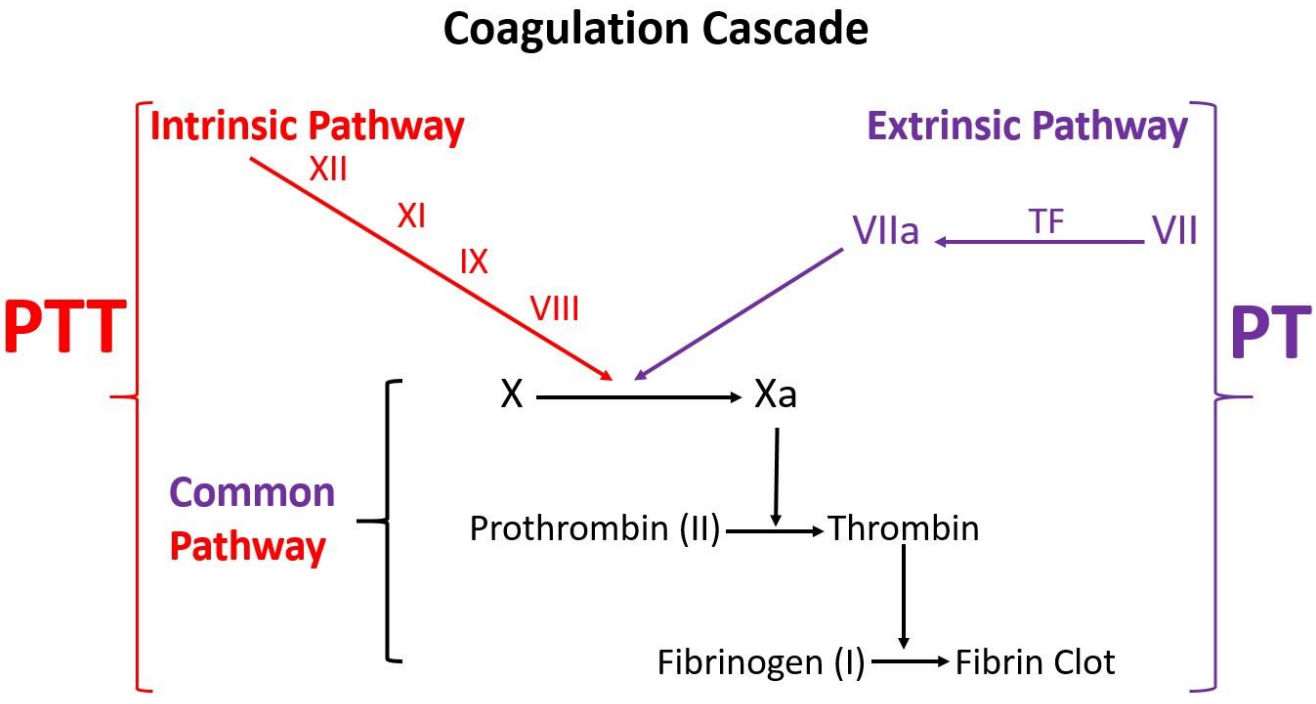
The **extrinsic pathway** (the main pathway to initiate coagulation) is initiated by exposure to tissue factor (factor III) released from endothelial cells and monocytes → activation of factor VII →VIIa → common pathway.

The **intrinsic pathway** (which amplifies coagulation) involves the activation of factors XII, XI, IX, and factor VIII → common pathway.

The **common pathway** involves the activation of factors X → Xa → prothrombin (factor II) → Thrombin which forms clot by cleaving fibrinogen (factor I) → ***soluble*** fibrin, thrombin also activates factor XIII, which, together with calcium, stabilize the soluble fibrin, forming cross-linked ***(insoluble)*** fibrin.

- Defects in the coagulation cascade cause more serious bleeding than do defects of primary hemostasis. They include bleeding into cavities (chest, joints and cranium) and subcutaneous hematomas. Petechial hemorrhages are not seen. The main inhibitor of secondary hemostasis is antithrombin which inhibits thrombin and many activated coagulation proteins.

- The ***immediate*** type of bleeding occurs when there are problems associated with the elements involved with primary hemostasis. The ***delayed*** type of bleeding occurs when there are problems associated with the elements involved with secondary hemostasis.



Factor	Name	Pathway
I	Fibrinogen	Both
II	Prothrombin	Both
III	Tissue Factor	Extrinsic
IV	Calcium	Both
V	Proaccelerin	Both
VI	Accelerin	Both
VII	Proconvertin	Extrinsic
VIII	Antihemophiliac	Intrinsic
IX	Christmas Factor	Intrinsic
X	Stuart-Prower Factor	Both
XI	Plasmathromboplastin antecedent (PTA)	Intrinsic
XII	Hageman Factor	Intrinsic
XIII	Protransglutaminase	Both

Tertiary hemostasis: Is the formation of plasminogen and then plasmin which is the main enzyme responsible for fibrinolysis. Activation of fibrinolysis is triggered by the presence of fibrin, and tissue-type plasminogen activators (t-PA) at the site of fibrin formation. Drugs that inhibit fibrinolysis (anti-fibrinolytic) include aminocaproic acid and tranexamic acid.

- Hemostasis can be achieved in various other ways if the body cannot do it naturally during surgery or medical treatment. When the body is under shock and stress, hemostasis is harder to achieve. Though natural hemostasis is most desired, having other means of achieving this is vital for survival in many emergency settings. During surgical procedures hemostasis can be achieved by a direct pressure, ligation or a hemostatic agent (chemical and/or mechanical).

Clinical assessment

Family history and duration of bleeding may indicate whether the disorder is congenital or acquired. Coexisting illness or drug therapy predisposing to bleeding should be sought.

During the examination, check for:
● Bruising. ● Purpura. ● Telangiectasia on lips (indicates hereditary hemorrhagic telangiectasia). ● Swollen joints/hemarthrosis. ● Hepatomegaly. ● Splenomegaly.

Muscle and joint bleeds indicate a coagulation defect. Purpura, prolonged bleeding from cuts, epistaxis, GI hemorrhage, excessive post-surgical bleeding and menorrhagia suggest a platelet disorder, thrombocytopenia or von Willebrand disease.

Investigations for bleeding disorders

Initial screening tests:

- Platelet count
- Bleeding time (BT)
- Prothrombin time (PT)
- Partial thromboplastin time (PTT)
- Thrombin time (TT)

The platelet count provides a quantitative evaluation of platelet. A normal platelet count should be 150000 - 400000 cells/mm^3. A platelet count of < 150000 cells/mm^3 (thrombocytopenia) can be associated with major postoperative bleeding. The average lifespan of a platelet ranges from 7 to 10 days.

The bleeding time (BT) is used to assess adequacy of platelet function. The test measures how long it takes a standardized skin incision to stop bleeding by the formation of a temporary hemostatic plug. The normal range of bleeding time depends on the way the test is performed but is usually between 1 and 6 minutes. The bleeding time is prolonged in patients with platelet abnormalities or taking medications that affect platelet function.

The prothrombin time (PT) is used to assess the extrinsic pathway (factor VII) and the common pathway (factors V, X, prothrombin (II), and fibrinogen).
It is prolonged by deficiencies of these factors and by liver disease. PT is most often used to monitor oral anticoagulant therapy such as warfarin. A normal PT is usually between 10 and 15 seconds.

The partial thromboplastin time (PTT) is used to assess the intrinsic and the common pathway. It tests for all factors except for factor VII. PTT is most often used to monitor heparin therapy. A normal PTT is usually 25-35 seconds. It is the best single screening test for coagulation disorders.

The international normalized ratio (INR) is the PT ratio (patient's PT/control PT). In a person with a PT within the normal range, the INR is approximately 1. An INR above 1 indicates that clotting will take longer than normal.

Thrombin time (TT): Thrombin converts fibrinogen in the blood to insoluble fibrin, which makes up the essential portion of a blood clot. This test bypasses the intrinsic, extrinsic, and most of the common pathway. For example, patients with hemophilia A have a normal TT. The normal range for the TT test is 9 to 13 seconds. Abnormal test results usually are caused by excessive plasmin or fibrin split products.

The end

Terms:

hemo=blood, stasis=stop

Endothelium: a membrane of special cells which lines the heart, the lymph vessels, the blood vessels and various body cavities

Hematomas is a localized collection of blood outside the blood vessels. It can be subdivided by size:

Petechia (<2 mm)

Purpura (2-10 mm)

Ecchymosis are > 1 cm

Telangiectasia: red, blue, or purple linear marks measuring less than 3 mm in width and several millimeters to centimeters in length