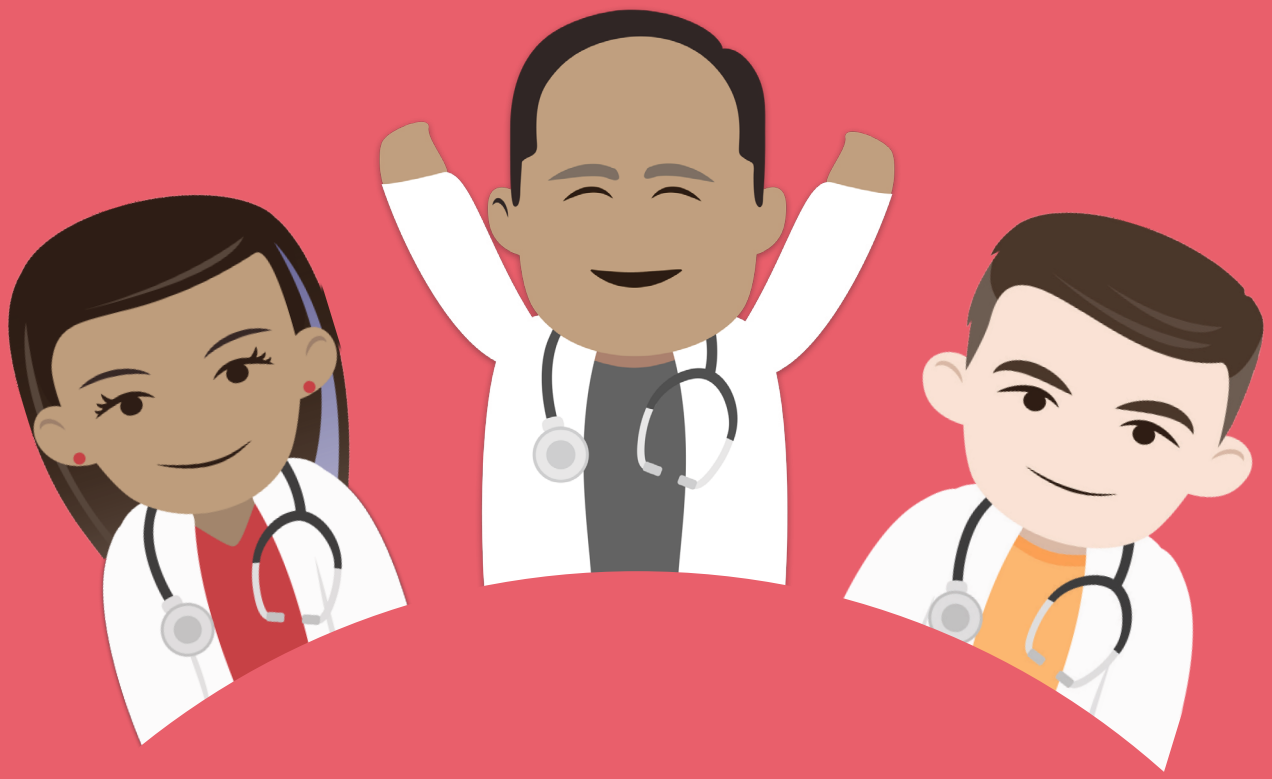
Hematology and Coagulation Essentials
Chapter 6

COAGULATION AND ASSESSMENT OF HEMOSTASIS



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Coagulation and assessment of hemostasis

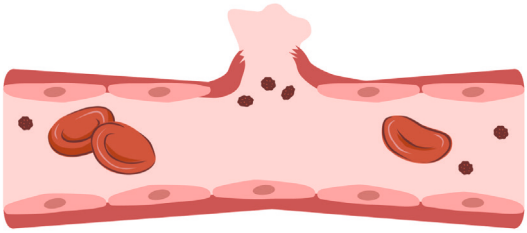
REVIEWING NORMAL HEMOSTASIS

There are four stages of hemostasis

1. Vasoconstriction
2. Primary hemostasis (platelet plug)
3. Secondary hemostasis (due to formation of fibrin meshwork)
4. Fibrinolysis (clot dissolution)

1. Vasoconstriction

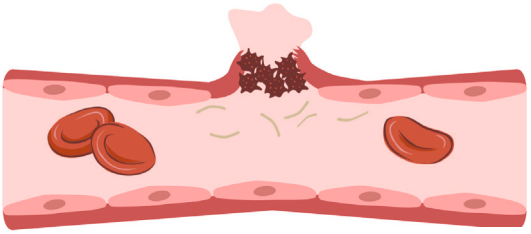
Vasoconstriction is a neurogenic mechanism, enhanced by endothelin (produced from damaged endothelial cells), serotonin, and TxA2 (both from activated platelets and endothelium).



Vasoconstriction

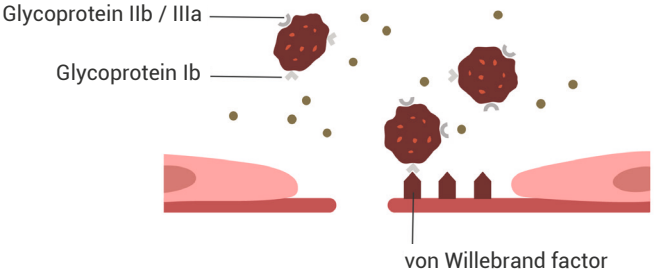
2. Primary hemostasis

Platelet events
- Platelet adhesion
- Platelet activation
- Platelet aggregation



Primary hemostasis

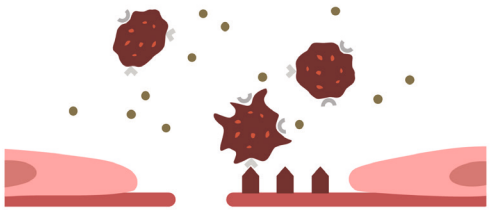
Platelet adhesion
Platelets adhere to exposed collagen. Platelets have collagen receptors (e.g., glycoprotein VI and glycoprotein I / II—they adhere to other platelets via a cohesion factor, glycoprotein IIb / IIIa). Platelets also adhere to collagen via VWF, mediated by glycoprotein Ib / IX.



Platelet adhesion

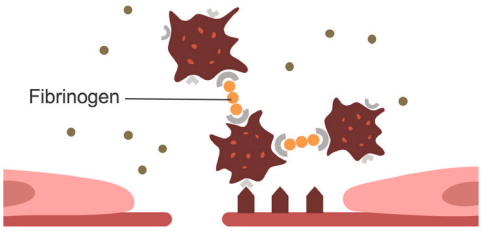
Platelet activation
Platelets change their shape from disc to sphere, release granule contents, and increase the number of cell-surface receptors for various chemicals.

Release of these chemicals enhances vasoconstriction, recruits more platelets for the platelet plug, and helps initiate the coagulation cascade.



Platelet activation

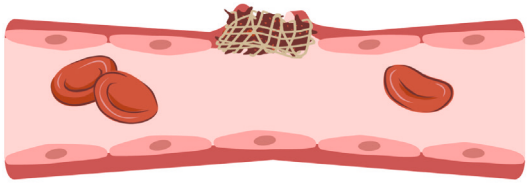
Platelet aggregation
Mediated by fibrinogen through glycoprotein IIb / IIIa receptors.



Platelet aggregation

3. Secondary hemostasis

Secondary hemostasis culminates in the formation of fibrin meshwork. The fibrin meshwork ensures that the platelet plug is stable and the flow of blood does not dislodge the plug.



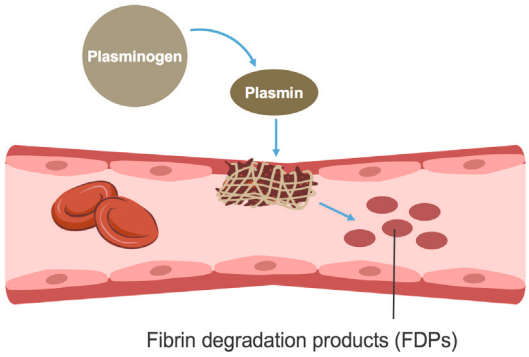
Secondary hemostasis

4. Fibrinolysis

Once the fibrin clot has formed, the clot needs to be lysed. A balance between fibrin deposition and lysis must be maintained.

The liver produces plasminogen, which is activated to form plasmin by plasminogen activators. Common plasminogen activators include tissue type plasminogen activator (tPA; found in endothelium and most tissues) and urokinase-like plasminogen activator (found in urine, tears, and saliva).

Plasmin proteolyzes fibrin to soluble fibrin degradation products.



Fibrinolysis

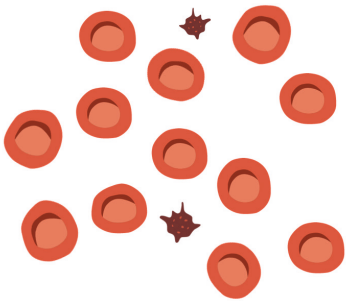
Fibrinolysis is controlled by
- Plasminogen activator inhibitor (e.g., PAI-1)
- Plasmin inhibitors (e.g., alpha-2-antiplasmin)

Coagulation and assessment of hemostasis

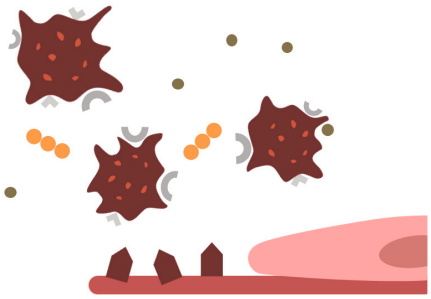
ASSESSING PLATELETS

Assessing platelet function

Defects in primary hemostasis almost always involve thrombocytopenia or thrombocytopathia.



Thrombocytopenia

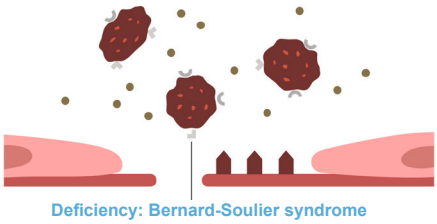


Thrombocytopathia

Common causes of congenital thrombocytopenia include

Disorders of platelet adhesion

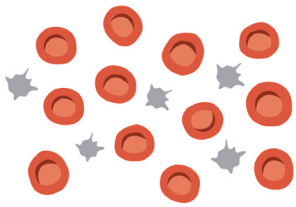
- Von Willebrand disease (VWD), Bernard-Soulier syndrome (lack of glycoprotein Ib)



Disorder of platelet adhesion

Disorders of platelet activation

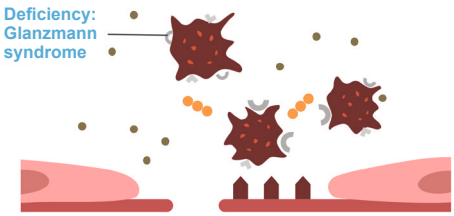
- Storage pool disorders, Chediak-Higashi syndrome, Hermansky-Pudlak syndrome, grey platelet syndrome



Disorder of platelet activation

Disorders of platelet aggregation

- Glanzmann syndrome (lack of glycoprotein IIb / IIIa)



Disorder of platelet aggregation

Common causes of acquired thrombocytopathia include

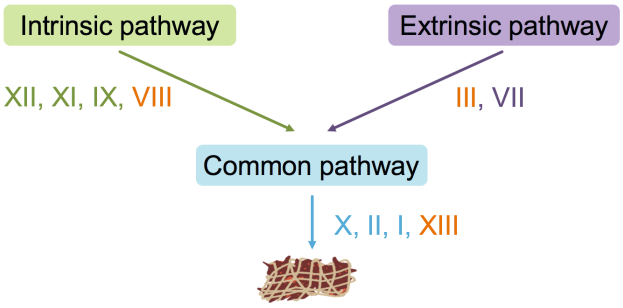
- Aspirin
- P2Y12 receptor blockers (e.g., clopidogrel, prasugrel)
- Uremia
- Antiplatelet antibodies
- Hypofibrinogenemia
- Acquired VWD

Tests for thrombocytopathia

- Platelet count
- Peripheral smear examination
- Bone marrow examination
- Bleeding time
- PFA-100
- Thromboelastography (test for global hemostasis)
- Platelet aggregation studies

Coagulation and assessment of hemostasis

MASTERING THE COAGULATION PATHWAY



NOTES ABOUT CLOTTING FACTORS

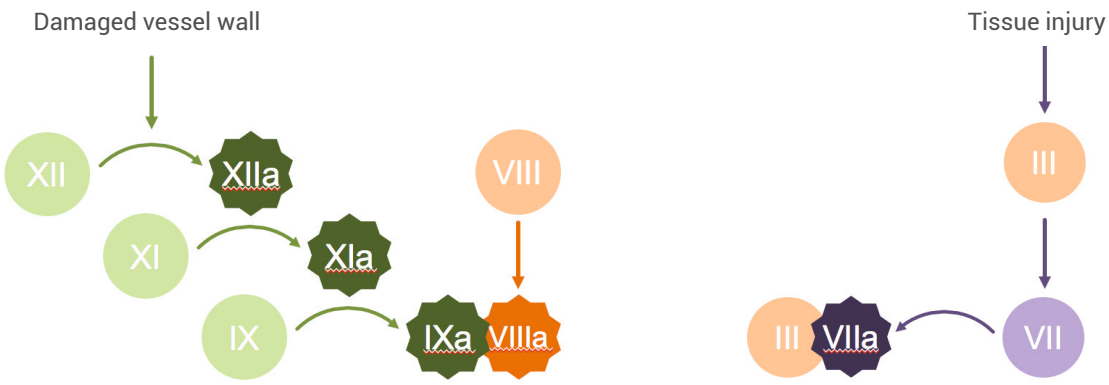
- *Roman numerals are used for the various clotting factors; factor VI is discontinued*
- *Activated forms are denoted by 'a'*
- *Most are synthesized in the liver (except factor VIII, which is produced primarily in the endothelium)*
- *Most are serine protease enzyme precursors*
- *Some are cofactors (e.g., factors V and VIII)*

Secondary hemostasis

Secondary hemostasis involves a series of enzymatic reactions culminating in conversion of fibrinogen to a fibrin clot. The coagulation or clotting pathway is traditionally divided into extrinsic and intrinsic pathways. This concept is antiquated but useful for understanding prothrombin time (PT) and partial thromboplastin time (PTT) tests.

The **intrinsic pathway** is triggered by activation of factor XII. Kallikrein and high molecular weight kininogen (HMWK) are also involved in this initial step. Once factor XII is activated, factor XI and then factors IX and VIII are activated. This results in activation of factor X.

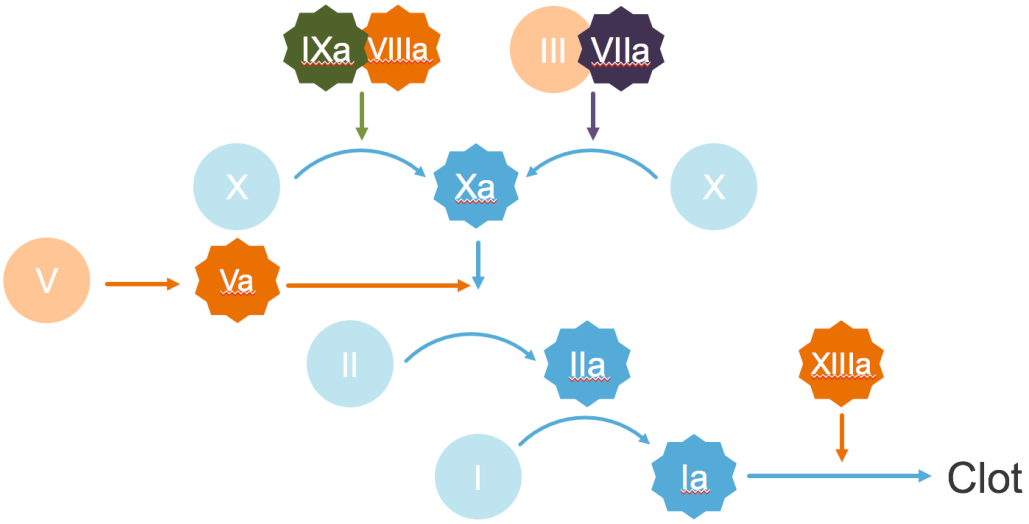
Activation of the **extrinsic pathway** involves tissue factor interacting with activated factor VII and ultimately activating factor X, which is the start of the common pathway.



Once factor X is activated, either by the extrinsic or intrinsic pathway, it converts prothrombin to thrombin. Factor V acts as a cofactor in this reaction. Thrombin converts fibrinogen to fibrin and the fibrin is further stabilized by factor XIII.

Calcium is required in multiple steps.

The fibrin meshwork stabilizes the platelet plug and ensures that the plug is permanent and is not washed away.



PLEASE NOTE

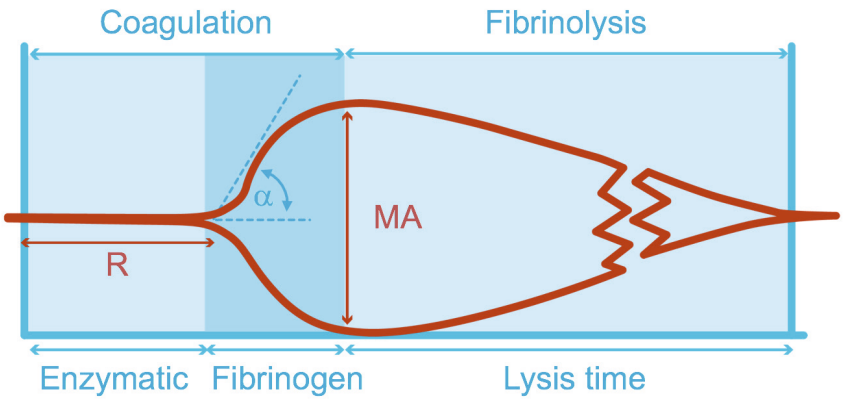
- *The integrity of the extrinsic and common pathways is assessed by the test PT.*
- *The integrity of the intrinsic and common pathways is assessed by the test PTT.*
- *Individuals with factor XII, prekallikrein, and HMWK deficiency do not bleed.*
- *Individuals with deficiency of factor XIII will bleed but have normal PT and PTT.*
- *Only a small amount (about 20%) of clotting factor is required to arrest bleeding.*
- *Factor VII has the shortest half-life (T1/2): 4–6 hrs.*
- *In patients with liver disease, the liver may not be able to produce enough factor VII to maintain the required minimum levels. Since factor VII is part of the extrinsic pathway, the PT will become prolonged.*

Coagulation and assessment of hemostasis

INTERPRETATION OF THROMBOELASTOGRAPH (TEG)

Interpretation of TEG

Thromboelastograph (TEG) is a test for global hemostasis that takes into account both primary and secondary hemostasis. In addition, TEG assesses fibrinolytic function. TEG is commonly ordered for bleeding patients, in order to assess which aspect of the hemostatic process is defective. This test has been available for over 60 years, but is now gaining popularity thanks to recent technical improvements.



Performing TEG

Whole blood collected in a citrate tube is placed in a cup. The cup rotates gently to mimic sluggish venous flow. Calcium and a clot activator, kaolin, are added to initiate the clotting process. A sensor shaft is inserted into the sample to monitor clotting. A clot will form between the cup and the sensor.

R time
The time required for a 2 mm clot to form is called the R time. R time is typically 5–10 minutes, and is dependent on clotting factors. Therefore, prolonged R time indicates clotting factor deficiency or the presence of an anticoagulant effect (e.g., heparin). In contrast, a short R time has no clinical significance.

If the TEG result shows a long R time, we can repeat the test by adding the enzyme heparinase to the blood. If the R time shortens significantly, this indicates the presence of heparin in the blood.

Angle alpha
The angle alpha is a measure of the rapidity of fibrin build up and cross linking. Normal values of angle alpha are approximately 50–70 degrees. Low angle alpha can be seen with low levels of fibrinogen, thrombocytopenia or thrombocytopathia.

Maximum amplitude (MA)
The maximum amplitude (MA) is a measure of clot strength. Normal values are between 50 and 70 mm. Low MA is seen with thrombocytopenia or thrombocytopathia. High MA is not clinically significant.

Ly30
Ly30 denotes the percentage of the clot that has lysed during the first 30 minutes after MA has been reached. Normal values are 0–8 %. High values of MA denote excessive fibrinolysis.

Clotting index (CI)
The clotting index (CI) is a numerical value derived from a mathematical equation that takes into account other TEG parameters. Normal values are from -3 to +3. Low CI means that the individual is hypocoagulable.

Fibrinolysis
In the condition known as primary fibrinolysis, circulating fibrinogen is lysed due to a pathologic state. This results in poor clot formation and patients with this condition have a tendency to bleed.

In patients with primary fibrinolysis, the TEG will demonstrate high Ly30, low MA, and low CI.

Secondary fibrinolysis occurs when adequate clot formation occurs, but it is followed by excessive fibrinolysis. An example of this is disseminated intravascular coagulation (DIC).

In patients with secondary fibrinolysis, the TEG will demonstrate high Ly30, but normal or high MA and CI values.

Limitations of TEG

Individuals on aspirin and adenosine diphosphate (ADP) receptor blockers will have a normal TEG. If a patient is on heparin, then naturally the R time is prolonged. Heparin can also artifactually lower values of angle alpha and MA. This can be resolved by repeating the TEG in the presence of heparinase. If values of alpha and MA are artifactually low these would normalize with TEG heparinase.