17 HEMATOLOGY: BLOOD COAGULATION TESTS

Lea E. Dela Peña

OBJECTIVES

After completing this chapter, the reader should be able to

- **Describe the role of platelets, the coagulation cascade, and fibrinolytic system in normal hemostasis**
- **List the laboratory tests used to assess platelets and discuss factors that may influence their results**
- **List the laboratory tests used to assess coagulation and explain their use in evaluating anticoagulant therapy**
- **List the laboratory tests used to assess clot degradation and disseminated intravascular coagulation and discuss their limitations**
- **Interpret results and suggest follow-up action given results of laboratory tests used for evaluating coagulation and anticoagulant therapy in a case description**
- **Discuss the availability and use of point-of-care testing devices specifically for platelet and coagulation tests**

Normal hemostasis involves a complex interaction among the vascular subendothelium, platelets, coagulation factors, and proteins that promote clot formation, clot degradation and inhibitors of these substances. Disruption in normal hemostasis can result in bleeding or excessive clotting. Bleeding can be caused by trauma or damage to vessels, acquired or inherited deficiencies of coagulation factors, or physiological disorders of platelets, whereas excessive clotting can result from abnormalities of the vascular endothelium, alterations in blood flow, or deficiencies in clotting inhibitors.

Clinicians must monitor the hemostasis process in individual patients to ensure their safety from an imbalance in this complex system. For example, practitioners routinely order platelet tests in patients on certain antineoplastic medications to assess for thrombocytopenia. Likewise, clinicians closely monitor coagulation tests for patients receiving anticoagulants to prevent thromboembolic or hemorrhagic complications. Overall, the hemostatic process is intricate and requires a clinician knowledgeable in its dynamics for quality assessment.

This chapter reviews normal coagulation physiology, common tests used to assess coagulation and hypercoagulable states, and factors that alter coagulation tests.

PHYSIOLOGICAL PROCESS OF HEMOSTASIS

Normal *hemostasis* involves the complex relationship among participants that promote clot formation (platelets and the coagulation cascade), inhibit coagulation, and dissolve the formed clot. Each phase of the process is briefly reviewed.

Clot Formation

Numerous mechanisms promote and limit coagulation. Factors that promote coagulation include malignancy, estrogen therapy, pregnancy, obesity, immobilization, damage to the blood vessel wall, and causes of low blood flow or venous stasis. Normal blood flow dilutes activated clotting factors and results in their degradation in various tissues (e.g., liver) and by proteases. However, when low flow or venous stasis is present, activated clotting factors may not be readily cleared.

Platelets

Platelets are non-nucleated, disk-shaped structures, 1–5 microns in diameter, which are formed in the extravascular spaces of bone marrow from megakaryocytes. Megakaryocyte production and maturation are promoted by the hormone thrombopoietin, which is synthesized in the bone marrow and liver. Two thirds of the platelets are found in the circulation and one third in the spleen; however, in splenectomized patients nearly 100% are in the circulation.

The average human adult makes approximately 100 billion platelets per day, with the average platelet circulating for 7–10 days. On aging, platelets are destroyed by the spleen, liver, and bone marrow. Throughout their lifespan, platelet function is affected by numerous factors such as medications, vitamins, foods, spices,

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and systemic conditions, including chronic renal disease and hematological disorders (e.g., myeloproliferative and lymphoproliferative diseases, dysproteinemias, and the presence of antiplatelet antibodies).

The primary function of platelets is to regulate hemostasis, but platelets also play a prominent role in the pathological formation of arterial thrombi. Three processes (platelet adhesion, activation, and aggregation) are essential for arterial thrombus formation. The surface of normal blood vessels inhibits platelet function, thereby preventing thrombosis; however, endothelial injury to the vasculature, caused by flow abnormalities, trauma, or the rupture of atherosclerotic plaque in the vessel wall, starts the process of platelet plug formation. Subendothelial structures—such as collagen, basement membrane, and fibronectin—then become exposed (**Figure 17-1**), which can result in platelet adhesion. Platelet adhesion is enhanced by substances such as epinephrine, thrombin, adenosine diphosphate (ADP), serotonin, collagen, and von Willebrand factor (vWF).[1] Circulating vWF acts as a binding ligand between the subendothelium and glycoprotein Ib receptors on the platelet surface.

Once adhesion occurs, platelets change shape and activation occurs. Activated platelets release their contents—including nucleotides, adhesive proteins, growth factors, and procoagulants—which promotes platelet aggregation and completes the formation of the hemostatic plug.[2] This process is mediated by glycoprotein IIb/IIIa receptors on the platelet surface with fibrinogen acting as the primary binding ligand bridging between platelets. Platelets have numerous Gp IIb/IIIa binding sites, which are an attractive option for antiplatelet drug therapy.[1] However, the platelet plug is not stable and can be dislodged. To form a more permanent hemostatic plug, the clotting system must be stimulated. By releasing PF3, platelets initiate the clotting cascade and concentrate activated clotting factors at the site of vascular (endothelial) injury.

Prostaglandins (PGs) play an important role in platelet function. **Figure 17-2** displays a simplified version of the complex arachidonic acid pathways that occur in platelets and on the vascular endothelium. Thromboxane A_2, a potent stimulator of platelet aggregation and vasoconstriction, is formed in platelets. In contrast, prostacyclin (PG2), produced by endothelial cells lining the vessel luminal surface, is a potent inhibitor of platelet aggregation and a potent vasodilator that limits excessive platelet aggregation.

Cyclooxygenase and PG2 are clinically important. An aspirin dose of 50–81 mg/day acetylates and irreversibly inhibits cyclooxygenase in the platelet. Platelets are rendered incapable of converting arachidonic acid to PGs. This effect of low-dose aspirin lasts for the lifespan of the exposed platelets (up to 12 days). Vascular endothelial cells also contain cyclooxygenase, which converts arachidonic acid to PG2. Aspirin in high doses (3000–5000 mg) inhibits the production of PG2.[3] However, because the vascular endothelium can regenerate PG2, aspirin's effect is much shorter here than on platelets. Thus, aspirin's effect at high doses may both inhibit platelet aggregation and block the aggregation inhibitor PG2. This phenomenon is the rationale for using low doses of aspirin 75–162 mg/day to help prevent myocardial infarction.[4]

In summary, a complex interaction between the platelet and blood vessel wall maintains hemostasis. Once platelet adhesion occurs, the clotting cascade may become activated. After thrombin and fibrin are generated, the platelet plug becomes stabilized with insoluble fibrin at the site of vascular injury.

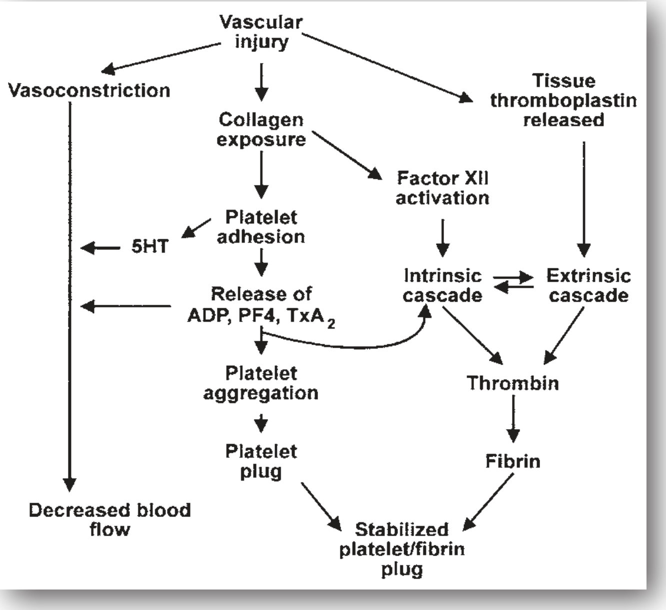

FIGURE 17-1. Relationship between platelets and the clotting cascade in the generation of a stabilized fibrin clot. 5HT = serotonin; ADP = adenosine diphosphate; PF4 = platelet factor 4; TxA_2 = thromboxane A_2.

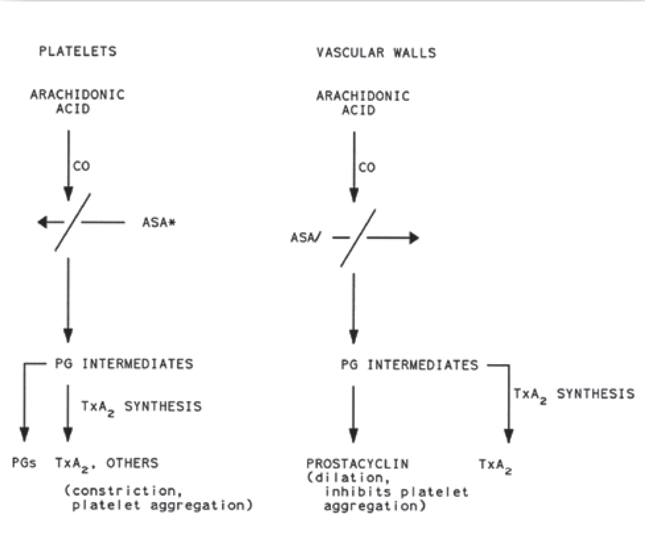

FIGURE 17-2. Formation of thromboxane A_2 (TxA_2), prostaglandins (PGs), and prostacyclin in platelets and vascular endothelial cells. CO = cyclooxygenase; ASA* = low-dose, irreversible, inactivation of platelet cyclooxygenase; ASA/ = high-dose inactivation of platelet cyclooxygenase.