# HEMOSTATIC DISORDERS

## Overview of Hemostasis

Hemostasis refers to the physiologic mechanisms that control bleeding. Normal hemostasis may be viewed as occurring in three overlapping stages. Primary hemostasis involves blood vessels (particularly the endothelial layer) and cellular blood elements (particularly platelets) and culminates in the formation of the platelet plug. Secondary hemostasis involves plasma procoagulant proteins (clotting or coagulation factors) and the formation of a stable fibrin clot. The third stage involves repair of vascular damage that results in a return to the normal state. Two control processes, the fibrinolytic system and an anticoagulant system (consisting of inhibitor proteins and endothelial-cell-based mechanisms), are important in limiting clot formation to areas of vascular injury. Pathologic bleeding or thrombosis may result from derangement in any of these processes.[1]

### Blood Vessels and Endothelium

Under normal circumstances, the vascular endothelium maintains a thromboresistant surface by a variety of mechanisms, including secretion of the platelet inhibitory substances (such as prostacyclin and nitric oxide), expression of molecules involved in the inhibition of coagulation (eg, heparan and thrombomodulin), and provision of a barrier between intravascular elements and the tissue factor (TF)-rich extravascular structures. After injury, the blood vessel constricts, which limits blood flow. The interaction of blood elements with subendothelial structures allows adhesion and activation of platelets, and activation of procoagulant mechanisms.

Hereditary blood vessel disorders associated with a bleeding diathesis include connective tissue disorders (eg, Ehlers-Danlos and Marfan syndromes) and vascular malformations (eg, hereditary hemorrhagic telangiectasia syndrome and giant hemangioma).[2]

Acquired blood vessel disorders include medical conditions such as scurvy and vasculitis, vascular anomalies such as angiodysplasia, and physical disruptions such as those that occur with trauma or surgery. If available, treatment is directed to the underlying vascular abnormality. Postoperative anatomic bleeding caused by inadequate surgical hemostasis may be difficult to diagnose, particularly in patients with concomitant abnormalities of platelets or coagulation factors. In general, bleeding from one site suggests an anatomical lesion, whereas small-vessel bleeding from multiple sites (eg, wound edges, intravenous access sites, and the endotracheal tube) suggests abnormal hemostatic mechanisms.

### Platelets

Platelets are anuclear cell fragments produced by megakaryocytes under the influence of cytokines such as thrombopoietin, and they function to form a cohesive plug at the site of vessel injury. Endothelial disruption results in exposure of blood elements to extravascular collagen and TF. Platelet interaction with collagen [either directly via platelet glycoprotein VI (GPVI) or indirectly through adhesion to immobilized von Willebrand factor (vWF) via platelet GPIb/IX] leads to platelet adhesion. Platelet adhesion drives multiple secondary processes, including activation of the platelet fibrinogen receptor (GPIIb/IIIa) and release of platelet granular contents, leading to aggregation of more platelets to the growing hemostatic plug. Platelets play an important role in the coagulation system as well. Coagulation proteins and $Ca^{++}$ are stored within platelet granules, and coagulation factors assemble on the phospholipid surface of activated platelets, localizing thrombin generation.[3] In addition, platelets can influence leukocyte trafficking, inflammation, response to sepsis, tissue regeneration, and angiogenesis.[4]

### Coagulation Proteins

The initial platelet plug that forms at a site of vascular injury is stabilized by fibrin generated by the coagulation mechanism, which consists of a closely regulated series of reactions. The coagulation mechanism consists of procoagulant serine proteases that circulate as zymogens (ie, Factors II, VII, IX, X, XI, and XII), nonenzymatic cofactors (ie, Factors V and VIII), the substrate for fibrin gel formation (fibrinogen), and fibrin-stabilizing enzymes [Factor XIII and thrombin-activatable fibrinolysis inhibitor (TAFI)]. Coagulation can be divided into three phases: initiation, amplification/propagation, and clot formation.[3]

In vivo, the exposure of TF to blood is the key step in the initiation of coagulation.[5] TF is abundantly present in the subendothelium, may be expressed on activated endothelial cells (and possibly synthesized by activated platelets), and may also be transported to sites of vascular injury in the form of circulating microparticles. TF triggers the coagulation system at the site of injury by capturing circulating Factor VIIa. The Factor VIIa-TF complex converts Factor X to its active form either directly or indirectly via activation of Factor IX. Phospholipid membrane-bound Factor Xa then forms a complex with Factor Va, which in turn converts the zymogen prothrombin to the active enzyme thrombin. Thrombin functions in the amplification/propagation phase by feedback activation of Factors XI, VIII, and V. This positive feedback sustains further thrombin generation after the Factor VIIa-TF process is inhibited by TF pathway inhibitor (TFPI). Inadequate amplification of the initial hemostatic signal is thought to explain why those with hemophilia bleed despite normal levels of Factor VII. The thrombin generated via the amplification/propagation mechanism performs multiple functions, including conversion of fibrinogen to fibrin clot, further activation of platelets through protease-activated receptors (PARs), and activation of Factor XIII. Factor XIIIa stabilizes the clot by covalent crosslinking of fibrin.

TF is regarded as the main initiator of coagulation, but the coagulation cascade can also be initiated by another protease/cofactor system, the so-called contact factor system. Contact factors interact with negatively charged surfaces and, in turn, activate Factor XI. Although deficiencies of the contact factors (ie, Factor XII, prekallikrein, and kininogen) will prolong the activated partial thromboplastin time (aPTT) screening test (see below), they are not associated with a clinical bleeding diathesis, and there is increasing evidence that contact pathway activation is important in thrombotic complications associated with medical devices (eg, catheters, extracorporeal circuits), as well as in other pathologic conditions.[1]

### Natural Anticoagulant Systems and Fibrinolysis

The processes by which procoagulant activities are limited to the site of injury are important in the regulation of normal hemostasis. Two main processes are involved: the natural anticoagulant systems, which consist primarily of circulating and endothelial-based protease inhibitors, and the fibrinolytic system, which is primarily responsible for the proteolytic dissolution of the fibrin clot. Blood fluidity depends largely on the integrity of the two anticoagulant proteins, antithrombin and protein C. Antithrombin inhibits activated coagulation serine proteases, primarily thrombin and Factor Xa. Heparin and heparan-like molecules markedly augment antithrombin activity. Protein C is activated by thrombin bound to thrombomodulin on endothelial cells. Activated protein C, in the presence of protein S, degrades Factors Va and VIIIa. The protein C system subserves both anticoagulant and anti-apoptotic/anti-inflammatory functions. A mutation in Factor V (Factor V Leiden) results in resistance to the anticoagulant action of activated protein C and increased risk of venous thrombosis.[6]