Hemostasis comprises cellular and biochemical processes that limit blood loss resulting from injury, maintain intravascular blood fluidity, and promote revascularization of thrombosed vessels after injury. Normal physiologic hemostasis necessitates a delicate balance between procoagulant pathways responsible for generation of a stable localized hemostatic “plug” and counterregulatory mechanisms inhibiting thrombus formation beyond the injury site. Vascular endothelium, platelets, and plasma coagulation proteins play equally important roles in this process. Failure to maintain balance commonly leads to excessive bleeding or pathologic thrombus formation.

Vascular endothelial injury—mechanical or biochemical—leads to platelet deposition at the injury site, a process often referred to as primary hemostasis. Although primary hemostasis may prove adequate for a minor injury, control of more significant bleeding necessitates stable clot formation incorporating crosslinked fibrin—a process mediated by activation of plasma clotting factors and often referred to as secondary hemostasis. Although the terms primary and secondary hemostasis remain relevant for descriptive and diagnostic purposes, advances in understanding cellular and molecular processes underlying hemostasis suggest a far more complex interplay between vascular endothelium, platelets, and plasma-mediated hemostasis than is reflected in this model.

**Vascular Endothelial Role in Hemostasis**

Under normal conditions, vascular endothelium provides a nonthrombogenic surface to promote blood fluidity. Healthy endothelial cells possess antiplatelet, anticoagulant, and profibrinolytic effects to inhibit clot formation. Negatively charged vascular endothelium repels platelets and produces prostacyclin and nitric oxide (NO), which are potent platelet inhibitors. Adenosine diphosphate, synthesized by vascular endothelial cells degrades adenosine diphosphate (ADP), another potent platelet activator. Given these endogenous antiplatelet effects, nonactivated platelets do not adhere to healthy vascular endothelial cells. Vascular endothelium further expresses several inhibitors of plasma-mediated hemostasis, including thrombomodulin (an indirect thrombin inhibitor), heparin-like glycosaminoglycans, and tissue factor pathway inhibitor (TFPI). Finally, vascular endothelium synthesizes tissue plasminogen activator (t-PA), which is responsible for activating fibrinolysis—a primary counterregulatory mechanism limiting clot propagation.
Despite these natural defense mechanisms to inhibit thrombus generation, a variety of mechanical and chemical stimuli may shift the balance such that the endothelium promotes clot formation. Damage to vascular endothelial cells exposes the underlying extracellular matrix (ECM), including collagen, von Willebrand factor (vWF), and other platelet-adhesive glycoproteins. Platelets bind to and are activated by exposure to ECM components. Exposure of tissue factor, constitutively expressed by fibroblasts in the ECM, activates plasma-mediated coagulation pathways to generate thrombin and, ultimately, fibrin clot. Certain cytokines (i.e., interleukin-1, tumor necrosis factor, and γ-interferon) and hormones (i.e., desmopressin acetate or endotoxin) induce prothrombotic changes in vascular endothelial cells, including synthesis and expression of vWF, tissue factor, plasminogen activator inhibitor–1 (PAI-1, an inhibitor of fibrinolysis), and down-regulate normal antithrombotic cellular and biochemical pathways. Thrombin, hypoxia, and high fluid shear stress induce prothrombotic vascular endothelial changes. Increased vascular endothelial synthesis of PAI-1 and associated inhibition of fibrinolysis have been implicated in the prothrombotic state and high incidence of venous thrombosis after surgery.

**PLATELETS AND HEMOSTASIS**

Platelets contribute a critical role in hemostasis. Derived from bone marrow megakaryocytes, nonactivated platelets circulate as discoid anuclear cells. The platelet membrane is characterized by numerous receptors and a surface-connected open canalicular system serving to increase platelet membrane surface area and provide rapid communication between the platelet interior and external environment. Under normal circumstances, platelets do not bind vascular endothelium; however, when injury exposes ECM, platelets undergo a series of biochemical and physical alterations characterized by three major phases: adhesion, activation, and aggregation.

Exposure of subendothelial matrix proteins (i.e., collagen, vWF, fibronectin) allows for platelet adhesion to the vascular wall. vWF proves particularly important as a bridging molecule between ECM and platelet glycoprotein Ib/factor IX/factor V receptor complexes. Absence of either vWF (von Willebrand disease) or glycoprotein Ib/factor IX/factor V receptors (Bernard-Soulier syndrome) results in a clinically significant bleeding disorder.

As platelets adhere along the ECM, a series of physical and biochemical changes occur termed platelet activation. Platelets contain two specific types of storage granules: α granules and dense bodies. Alpha granules contain numerous proteins essential to hemostasis and wound repair, including fibrinogen, coagulation factors V and VIII, vWF, platelet-derived growth factor, and others. Dense bodies contain the adenine nucleotides ADP and adenosine triphosphate, as well as calcium, serotonin, histamine, and epinephrine. During the activation phase, platelets release granular contents, resulting in recruitment and activation of additional platelets and propagation of plasma-mediated coagulation. During activation, platelets undergo structural changes to develop pseudopod-like membrane extensions and to release physiologically active microparticles, with both mechanisms serving to increase dramatically platelet membrane surface area. Redistribution of platelet membrane phospholipids during activation exposes newly activated glycoprotein platelet surface receptors and phospholipid binding sites for calcium and coagulation factor activation complexes, which is critical to propagation of plasma-mediated hemostasis.

During the final phase of platelet aggregation, activators released during the activation phase serve to recruit additional platelets to the site of injury. Newly active glycoprotein Ib/IIIa receptors on the platelet surface bind fibrinogen to provide for cross-linking with adjacent platelets (platelet aggregation). The importance of these receptors is reflected by the bleeding disorder associated with their hereditary deficiency, Glanzmann thrombasthenia.

**PLASMA-MEDIATED HEMOSTASIS**

Plasma-mediated hemostasis, the coagulation cascade, might best be summarized as an amplification system to accelerate thrombin generation from an inactive precursor (i.e., prothrombin). Trace plasma proteins, activated by exposure to tissue factor or foreign surfaces, initiate a cascading series of reactions culminating in conversion of soluble fibrinogen to insoluble fibrin clot. Thrombin generation, the “thrombin burst,” represents the key regulatory step in this hemostatic process. Thrombin not only generates fibrin but also activates platelets and mediates a host of additional processes affecting inflammation, mitogenesis, and even down-regulation of hemostasis.

Traditionally, the coagulation cascade describing plasma-mediated hemostasis has been depicted as intrinsic and extrinsic pathways, both of which culminate in a common pathway in which fibrin generation occurs. Although this cascade model has proved an oversimplification, it remains a useful descriptive tool for organizing discussions of plasma-mediated hemostasis (Fig. 62-1). Coagulation factors are, for the most part, synthesized hepatically and circulate as inactive proteins termed zymogens. The somewhat confusing nomenclature of the classic coagulation cascade derives from the fact that inactive zymogens were identified using Roman numerals assigned in order of discovery. As the zymogen is converted to an active enzyme, a lower-case letter “a” is added to the Roman numeral identifier. For example, inactive prothrombin is referred to as factor II and active thrombin is identified as factor IIa. Some numerals were subsequently withdrawn or renamed as our understanding of the biochemistry underlying hemostasis evolved.

The coagulation cascade characterizes a series of enzymatic reactions in which inactive precursors—zymogens—undergo activation to amplify the overall reaction. Each stage of the cascade requires assembly of membrane-bound activation complexes, each composed of an enzyme (activated coagulation factor), substrate (inactive precursor zymogen), cofactor (accelerator or catalyst), and calcium. Assembly of these activation complexes occurs on phospholipid membranes (most often platelet or microparticle membranes) that localize and concentrate reactants. In the absence of phospholipid membrane anchoring sites,
activation of coagulation factors slows dramatically, further localizing clot generation to injury sites.

**EXTRINSIC PATHWAY OF COAGULATION**

The extrinsic pathway of coagulation, widely recognized as the initiating step in plasma-mediated hemostasis, begins with exposure of blood plasma to tissue factor. Tissue factor is prevalent in subendothelial tissues surrounding vasculature; however, under normal conditions the vascular endothelium minimizes contact between tissue factor and plasma coagulation factors. After vascular injury, small concentrations of factor VIIa circulating in plasma form phospholipid-bound activation complexes with tissue factor, factor X, and calcium to promote conversion of factor X to Xa. Recently, the tissue factor/factor VIIa complex has been demonstrated to activate factor IX of the intrinsic pathway, further demonstrating the key role of tissue factor in initiating hemostasis.

**INTRINSIC PATHWAY OF COAGULATION**

Classically, the intrinsic or contact activation system was described as a parallel pathway for thrombin generation by way of factor XII. However, the rarity of bleeding disorders resulting from contact activation factor deficiencies led to our current understanding of the intrinsic pathway as an amplification system to propagate thrombin generation initiated by the extrinsic pathway. Recent cell-based models of coagulation suggest that thrombin generation by way of the extrinsic pathway is limited by a natural inhibitor, TFPI. However, small quantities of thrombin generated before neutralization of the extrinsic pathway activate factor XI and the intrinsic pathway. The intrinsic pathway subsequently amplifies and propagates the hemostatic response to maximize thrombin generation. Proteins of the intrinsic pathway may, however, contribute to inflammatory processes, complement activation, fibrinolysis, kinin generation, and angiogenesis.

**Common Pathway of Coagulation**

The final pathway, common to both extrinsic and intrinsic coagulation cascades, depicts thrombin generation and subsequent fibrin formation. Signal amplification through both extrinsic and intrinsic pathways culminates in formation of prothrombinase complexes (phospholipid membrane–bound activation complexes) comprising factor Xa, factor II (prothrombin), factor Va (cofactor), and calcium ions. Prothrombinase complexes mediate the thrombin burst—a surge in thrombin generation from the
inactive precursor prothrombin. Thrombin proteolytically cleaves fibrinopeptides A and B from fibrinogen molecules to generate fibrin monomers, which polymerize into fibrin strands (i.e., fibrin clot). Finally, factor XIIIa, a transglutaminase activated by thrombin, covalently crosslinks fibrin strands to produce an insoluble fibrin clot resistant to fibrinolytic degradation. Both fibrinogen and factor XIII have been implicated in acquired bleeding disorders. Reduced concentrations of either protein may promote excess postoperative hemorrhage and transfusion requirements. Recent availability of plasma concentrates for both fibrinogen and factor XIII suggest potential for randomized controlled trials to determine efficacy of these biologics in treatment of acquired coagulopathies. Regardless, thrombin generation remains the key enzymatic step regulating hemostasis. Not only does thrombin activity mediate conversion of fibrinogen to fibrin, it also activates platelets and factor XIII, converts inactive cofactors V and VIII to active conformations, activates factor XI and the intrinsic pathway of coagulation, up-regulates cellular expression of tissue factor, and stimulates vascular endothelial expression of PAI-1 to down-regulate fibrinolytic activity.

**Intrinsic Anticoagulant Mechanisms**

Once activated, regulation of hemostasis proves essential to limit clot propagation beyond the injury site. One simple, yet important, anticoagulant mechanism derives from flowing blood and hemodilution. The early platelet and fibrin clot proves highly susceptible to disruption by shear forces within flowing blood. Blood flow further limits localization and concentration of both platelets and coagulation factors such that a critical mass of hemostatic components may fail to coalesce. However, later in the clotting process more robust counterregulatory mechanisms are necessary to limit clot propagation. Four major counterregulatory pathways have been identified that appear particularly crucial for down-regulating hemostasis: fibrinolysis, TFPI, the protein C system, and serine protease inhibitors.

The fibrinolytic system comprises a cascade of amplifying reactions culminating in plasmin generation and proteolytic degradation of fibrin and fibrinogen. As with the plasma-mediated coagulation cascade, inactive precursor proteins are converted to active enzymes, necessitating a balanced system of regulatory controls to prevent excessive bleeding or thrombosis (Fig. 62-3). The principal enzymatic mediator of fibrinolysis, plasmin, is generated from an inactive precursor, plasminogen. In vivo, plasmin generation most often is initiated by release of t-PA or urokinase from vascular endothelium. Thrombin provides a potent stimulus for t-PA synthesis. Factor XIIa and kallikrein of the intrinsic pathway activate fibrinolysis after exposure to foreign surfaces. The presence of fibrin accelerates plasmin generation. Rapid inhibition of free plasmin also limits spread of fibrinolytic activity. In addition to enzymatic degradation of fibrin and fibrinogen, plasmin inhibits hemostasis by degrading essential cofactors V and VIII and reducing platelet glycoprotein surface receptors essential to adhesion and aggregation. Fibrin degradation products also possess mild anticoagulant properties. TFPI inhibits the tissue factor/factor VIIa complex and thereby the extrinsic coagulation pathway, which is responsible for initiation of hemostasis. TFPI and factor Xa form phospholipid membrane–bound complexes that incorporate and inhibit tissue factor/factor VIIa complexes. Most TFPI is bound to vascular endothelium but may be released into circulation by heparin administration. Heparin further catalyzes TFPI inhibitory activity. As TFPI rapidly extinguishes tissue factor/VIIa activity, the critical role of the intrinsic pathway to continued thrombin and fibrin generation becomes apparent.

The protein C system proves particularly important in down-regulating hemostasis because it inhibits thrombin and the essential cofactors Va and VIIIa. Thrombin initiates this inhibitory pathway by binding a membrane-associated protein, thrombomodulin, to activate protein C. Protein C, complexed with the cofactor protein S degrades both cofactors Va and VIIIa. Loss of these critical cofactors limits formation of tenase and prothrombinase activation complexes essential to formation of factor X and thrombin, respectively. Thrombin, once bound to thrombomodulin, is inactivated and removed from circulation, providing another mechanism by which protein C down-regulates hemostasis.

The most significant serine protease inhibitors regulating hemostasis include antithrombin and heparin cofactor II. Antithrombin binds to and inhibits thrombin and factors IXa, Xa, XIa, and XIIa. Heparin cofactor II inhibits thrombin alone. Although the precise physiologic role for heparin cofactor II remains unclear, antithrombin plays a major role in down-regulating hemostasis. Heparin, a catalyst accelerator, binds antithrombin to promote inhibition of targeted enzymes. Heparin-like glycosaminoglycans, located on vascular endothelial cells, provide inhibitory sites for thrombin and factor Xa in vivo.

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**DISORDERS OF HEMOSTASIS**

**EVALUATION OF BLEEDING DISORDERS**

Few would argue the importance of assessing bleeding risk preoperatively; however, appropriate methods for ascertaining this risk remain subject to debate. Although...
routine coagulation testing of all surgical patients preoperatively intuitively may be appealing, this approach lacks predictive value for bleeding disorders and certainly lacks cost effectiveness. A carefully performed history of bleeding remains the single most effective predictor for perioperative bleeding.

A thorough history should focus on prior bleeding episodes. Does the patient have a history of excessive bleeding in association with trauma or prior surgery? Were blood transfusions or reoperation required to control the bleeding? A history suggestive of a bleeding disorder might include frequent epistaxis of a severity necessitating packing the nasal passage or surgical intervention. Oral surgery and dental extractions prove a particularly good test of hemostasis because of high concentrations of fibrinolytic activity in the oral cavity. Von Willebrand disease does not infrequently manifest as menorrhagia, and postpartum hemorrhage commonly occurs in women with underlying disorders of hemostasis. A history of spontaneous hemorrhage (nontraumatic) proves particularly concerning when associated with joints (hemarthroses) or deep muscles. Identification of a bleeding disorder at an early age or in family members suggests an inherited, as opposed to acquired, condition. A careful medication history including direct questions relating to consumption of aspirin-containing nonprescription drugs, herbs, and fish oil may prove noteworthy. Finally, inquiries regarding coexisting diseases should be included (i.e., renal, hepatic, thyroid, and bone marrow disorders and malignancy).

For most patients, a thoughtfully conducted bleeding history will eliminate need for preoperative laboratory-based coagulation testing. Regardless, several valid reasons remain for preoperative coagulation testing. Should the preoperative history or physical examination reveal signs or symptoms suggestive of a bleeding disorder, further laboratory-based assessment of coagulation would be indicated. Preoperative screening tests of coagulation may be indicated, despite a negative history, in cases in which major surgery commonly associated with significant bleeding is planned (i.e., cardiopulmonary bypass). Finally, preoperative testing may prove justified in settings in which the patient is unable to provide a bleeding history preoperatively. Should evidence of a bleeding disorder be detected preoperatively, underlying mechanisms must be ascertained if possible before proceeding with surgery.

INHERITED BLEEDING DISORDERS

Although inherited disorders of hemostasis may involve platelet function, plasma-mediated hemostasis, or fibrinolytic pathways, von Willebrand disease characterized by quantitative or qualitative deficiencies of vWF proves the most common of inherited bleeding disorders. Variants include types I and III with varying quantitative vWF deficiencies and type II comprising a collection of qualitative defects affecting vWF function. Under normal conditions, vWF plays a critical role in platelet adhesion to ECM. vWF further acts as a carrier molecule preventing proteolytic degradation of factor VIII in free plasma. Classically, patients with von Willebrand disease describe a history of easy bruising, recurrent epistaxis, and menorrhagia, all characteristic of defects in primary (i.e., platelet mediated) hemostasis. In more severe cases (i.e., type III vWD), concomitant reductions in factor VIII may lead to serious spontaneous hemorrhage, including hemarthroses, which is common in hemophilia. Laboratory testing often demonstrates mild-to-moderate prolongation of the activated partial thromboplastin time (aPTT), prolonged bleeding time, decreased immunoreactive VWF concentrations, and reduced platelet aggregation in response to ristocetin. Increasingly, the PFA-100 and similar ex-vivo platelet function tests have replaced bleeding times in assessing for vWD. Measurable reductions in factor VIII activity may occur in severe cases. Mild cases of vWD often respond to desmopressin acetate (DDAVP); however, given a significant bleeding history, specific replacement of vWF and factor VIII with select factor VIII concentrates (i.e., Humate-P [CSL Behring, King of Prussia, Pa.]) may be indicated.

Although relatively uncommon, the hemophilias merit consideration given their diverse clinical presentation. Hemophilia A, characterized by variable degrees of factor VIII deficiency, is an X-linked inherited bleeding disorder most frequently presenting in childhood as spontaneous hemorrhage involving joints, deep muscles, or both. Hemophilia A occurs with an incidence of 1:5000 males; however, nearly one third of cases represent new mutations with no family history. In mild cases, patients with hemophilia may not be identified until later in life, often after unexplained bleeding with surgery or trauma. Classically, laboratory testing in patients with hemophilia reveals prolongation of the aPTT, whereas the prothrombin time (PT) and bleeding time remain within normal limits. Specific measurement of factor VIII:C is required to confirm the diagnosis and to clarify the severity of factor VIII deficiency. Mild cases of hemophilia A may be treated with desmopressin; however, in most cases, perioperative management of these patients necessitates consultation with a hematologist and administration of recombinant or purified factor VIII concentrates. An increasingly common complication of hemophilia, particularly in the case of hemophilia A, has been development of alloantibodies directed against the factor VIII protein. In cases of high-titer antibodies, administration of factor VIII concentrates may fail to control bleeding. Several approaches have reduced bleeding in these patients, including substitution of porcine factor VIII, administration of activated or nonactivated prothrombin complex concentrates, or treatment with recombinant factor VIIa (NovoSeven, Novo Nordisk Inc., Bagsvaerd, Denmark) (see also Chapter 63). Also inherited as an X-linked disorder, hemophilia B (i.e., Christmas disease) occurs in approximately 1:40,000 and necessitates blood component replacement with factor IX concentrates.

ACQUIRED BLEEDING DISORDERS

A detailed account of acquired hemostatic disorders is beyond the scope of this discussion; however, given that a limited number of drugs and coexisting medical conditions account for the majority of acquired bleeding disorders, these conditions merit consideration. Heparin,
warfarin, and fibrinolytic drugs historically accounted for most serious drug-induced bleeding complications (Table 62-1).48,49 More recently, antiplatelet drug therapy further has complicated perioperative management (Table 62-2).49-52 Unfractionated heparin comprises a heterogeneous mixture of membrane-associated glycosaminoglycans derived from either bovine or porcine mucosal tissues. Specificity and potency of unfractionated heparin varies by molecular weight, which ranges between 5000 and 30,000 daltons.35 Heparin derives its anticoagulant effect by interacting with plasma antithrombin, which in turn inhibits serine proteases participating in plasma-mediated hemostasis.34 The half-life of heparin is 1 to 2 hours and varies directly with total dose. Heparin is cleared from the circulation both renally and hepatically. Most often, heparin's anticoagulant effect is monitored using the aPTT with a target prolongation of 1.5 to 2 times control, commonly used for treatment of venous thrombosis.53 At heparin concentrations exceeding measurement limits of the aPTT, such as during cardiopulmonary bypass or interventional cardiovascular procedures, the activated clotting time (ACT) provides an alternative, albeit less sensitive, measure of heparin anticoagulation.54 Heparin's anticoagulant effect is rapidly reversible by protamine administration.55 More recently, low-molecular-weight heparins (LMWHs) have gained favor as a result of reduced dosing frequency and the lack of need for monitoring. Owing to shorter saccharide chain lengths, LMWHs exhibit reduced inhibitory activity toward thrombin while retaining factor Xa inhibitory activity.56 Theoretically, LMWHs may be associated with reduced bleeding tendencies. Regardless, LMWHs have a more predictable pharmacokinetic response, fewer effects on platelet function, and a reduced risk for heparin-induced thrombocytopenia (HIT). Although monitoring of LMWHs is not performed routinely, the PT and aPTT most often are unaffected, necessitating measurement of anti-factor Xa activity. Furthermore, should rapid

<table>
<thead>
<tr>
<th>Drug</th>
<th>Site of Action</th>
<th>Route</th>
<th>Plasma Half-life</th>
<th>Excretion</th>
<th>Antidote</th>
<th>Stop Before Procedure</th>
<th>Prolongation of PT/aPTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unfractionated heparin</td>
<td>IIa/Xa</td>
<td>IV/subcutaneous</td>
<td>1.5 hr</td>
<td>Hepatic</td>
<td>Protamine</td>
<td>6 hr</td>
<td>No/Yes</td>
</tr>
<tr>
<td>LMWH</td>
<td>Xa</td>
<td>Subcutaneous</td>
<td>4.5 hr</td>
<td>Renal</td>
<td>Protamine (partial reversal)</td>
<td>12-24 hr</td>
<td>No/No</td>
</tr>
<tr>
<td>Streptokinase t-PA</td>
<td>Plg</td>
<td>IV</td>
<td>23 min</td>
<td>Hepatic</td>
<td>Antifibrinolytics</td>
<td>3 hr</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Coumarin</td>
<td>Vitamin K-dependent factors</td>
<td>Oral</td>
<td>2-4 days</td>
<td>Hepatic</td>
<td>Vitamin K</td>
<td>2-4 days</td>
<td>Yes/No</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Xa</td>
<td>SC</td>
<td>14-17 hr</td>
<td>Renal</td>
<td>None</td>
<td>3 days*</td>
<td>No/No</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Ila</td>
<td>IV</td>
<td>25 min</td>
<td>Hepatic</td>
<td>None</td>
<td>3 hr</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Ila</td>
<td>IV</td>
<td>45 min</td>
<td>Hepatic</td>
<td>None</td>
<td>4-6 hr</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Lepirudin/Desirudin</td>
<td>Ila</td>
<td>IV</td>
<td>1.5 hr</td>
<td>Renal</td>
<td>PMMA, dialysis</td>
<td>8-10 hr*</td>
<td>Yes/Yes</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Xa</td>
<td>Oral</td>
<td>9-13 hr</td>
<td>Renal</td>
<td>None</td>
<td>24-48 hr*</td>
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</tr>
<tr>
<td>Apixaban</td>
<td>Xa</td>
<td>Oral</td>
<td>9-14 hr</td>
<td>Hepatic</td>
<td>None</td>
<td>26-30+ hr*</td>
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<tr>
<td>Dabigatran</td>
<td>Ila</td>
<td>Oral</td>
<td>14-17 hr</td>
<td>Vitamin K</td>
<td>None</td>
<td>±5 days</td>
<td>Yes/Yes</td>
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</tbody>
</table>

Data from Roberts HR, Monroe DM, Escobar MA: Current concepts of hemostasis: implications for therapy, Anesthesiology 100:722-730, 2004, with permission. HIT, Heparin-induced thrombocytopenia; Ila, thrombin; IV, intravenous; LMWH, low-molecular-weight heparin; PCCs, prothrombin complex concentrates; Plg, plasminogen; PMMA, polymethyl methacrylate; rFVIIa, recombinant factor VIIa; t-PA, tissue plasminogen activator.

*Limited data regarding safe interval (assumes prophylactic dosage regimen).
†Argatroban and hirudins may increase the prothrombin time by several seconds.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Site of Action</th>
<th>Route</th>
<th>Plasma Half-life</th>
<th>Metabolism</th>
<th>Antidote</th>
<th>Stop Before Procedure</th>
<th>Prolongation of PT/aPTT</th>
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</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>COX 1-2</td>
<td>Oral</td>
<td>20 min</td>
<td>Hepatic</td>
<td>None</td>
<td>7 days</td>
<td>No/No</td>
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<td>Dipyridamole</td>
<td>Adenosine</td>
<td>Oral</td>
<td>40 min</td>
<td>Hepatic</td>
<td>None</td>
<td>24 hr</td>
<td>No/No</td>
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<tr>
<td>Clopidogrel</td>
<td>ADP</td>
<td>Oral</td>
<td>7 hr</td>
<td>Hepatic</td>
<td>None</td>
<td>7 days</td>
<td>No/No</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>ADP</td>
<td>Oral</td>
<td>7 hr</td>
<td>Serum/hepatic</td>
<td>None</td>
<td>7-10 days</td>
<td>No/No</td>
</tr>
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<td>Ticlopidine</td>
<td>ADP</td>
<td>Oral</td>
<td>4 days</td>
<td>Hepatic</td>
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<td>12-14 days</td>
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<td>Abciximab</td>
<td>GPIIb-IIIa</td>
<td>IV</td>
<td>30 min</td>
<td>Renal</td>
<td>None</td>
<td>48-72 hr</td>
<td>No/No</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>GPIIb-IIIa</td>
<td>IV</td>
<td>2.5 hr</td>
<td>Renal</td>
<td>None</td>
<td>24 hr</td>
<td>No/No</td>
</tr>
<tr>
<td>Tiroliban</td>
<td>GPIIb-IIIa</td>
<td>IV</td>
<td>2 hr</td>
<td>Renal</td>
<td>Hemodilus</td>
<td>24 hr</td>
<td>No/No</td>
</tr>
</tbody>
</table>

Data from Roberts HR, Monroe DM, Escobar MA: Current concepts of hemostasis: implications for therapy, Anesthesiology 100:722-730, 2004, with permission. ADP, Adenosine diphosphate; COX, cyclooxygenase diphosphate; IV, intravenous; GP, glycoprotein.
reversal of LMWH prove necessary, protamine is only partially effective.57

Oral anticoagulant therapy in the form of coumarin derivatives, interferes with hepatic synthesis of vitamin K–dependent coagulation factors—factors II, VII, IX, X, protein C, and protein S.58 Specifically, coumarin inhibits carboxylation of glutamic acid residues essential for anchoring coagulation factor activation complexes to phospholipid membranes. Coumarin therapy is monitored using the international normalized ratio (INR) system derived from the PT. Generally, an INR of 2 to 3 is considered reflective of adequate anticoagulation.53 In most cases, excessive coumarin anticoagulation is managed by withholding drug administration. However, given a half-life of 2 to 4 days, more rapid reversal in perioperative settings may be needed. Vitamin K administered orally or parentally in doses of 1 to 2 mg reverses coumarin anticoagulation.58 More rapid reversal may be achieved by administration of plasma or prothrombin complex concentrates.59 Recombinant factor VIIa also has proved effective at reversing coumarin-associated bleeding.

Despite relatively short half-lives and increasing fibrin specificity, fibrinolytic drug administration continues to be associated with significant bleeding potential. Bleeding after fibrinolytic drugs proves multifactorial resulting from proteolytic degradation of fibrin and fibrinogen, proteolysis of cofactors V and VIII, and digestion of platelet glycoprotein surface receptors.39 In addition, both fibrin and fibrinogen degradation fragments impair platelet function and inhibit assembly of fibrin monomers into strands. Once the fibrinolytic agent is cleared from plasma, antifibrinolytic drugs prove of limited benefit. Therapy must rely on selective repletion of platelet and plasma protein constituents. In many cases, cryoprecipitate or fibrinogen concentrate will be administered to replace fibrinogen and platelet infusions will be needed to compensate for qualitative platelet dysfunction. Plasma infusions may be required to replete plasma coagulation factors, particularly cofactors V and VIII.

Liver Disease

Hemostatic defects associated with hepatic failure prove complex and multifactorial. Severe liver disease impairs synthesis of coagulation factors, impedes clearance of activated clotting and fibrinolytic proteins, and produces quantitative and qualitative platelet dysfunction. Laboratory findings commonly associated with liver disease include a prolonged PT, possible prolongation of the aPTT, and thrombocytopenia.60 Prolongation of bleeding time reflects qualitative defects in platelet adhesion and aggregation. Treatment of bleeding in the setting of liver disease most often is based on laboratory abnormalities. Plasma and platelets frequently are administered for acute bleeding. Low fibrinogen concentrations may necessitate administration of cryoprecipitate or fibrinogen concentrate. In addition, low-grade fibrinolysis may benefit from antifibrinolytic drug administration in select settings.

Renal Disease

Platelet dysfunction commonly occurs in association with chronic renal failure, as reflected by a prolonged bleeding time and propensity for bleeding associated with surgery or trauma. Underlying mechanisms appear multifactorial and may include accumulation of guanidinosuccinic acid and NO in uremic plasma.61 In addition, red blood cell (RBC) concentration has been speculated to play a role as correction of anemia results in shortened bleeding times, presumably related to the role of RBCs in causing platelet margination along the vessel wall under laminar flow conditions.28 Both dialysis and correction of anemia have been reported to shorten bleeding times in patients with chronic renal failure. Traditionally, cryoprecipitate administration occurs in this setting; however, desmopressin 0.3 μg/kg and conjugated estrogens similarly may shorten bleeding times.43 Risks associated with these therapies, and the predictive value of bleeding time for subsequent hemorrhage, remain unclear.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) comprises a pathophysiologic hemostatic response to tissue factor/factor VIIa complex exposure and activation of the extrinsic pathway of coagulation. Numerous underlying disorders may precipitate DIC, including trauma, amniotic fluid embolus, malignancy, sepsis, or incompatible blood transfusions.52 Most often, DIC presents clinically as a diffuse bleeding disorder associated with consumption of coagulation factors and platelets during widespread microvascular thrombotic activity. Underlying fibrinolysis, providing a counterregulatory mechanism to maintain vascular integrity, proves common as well. Laboratory findings typical of DIC include reductions in platelet count; prolongation of the PT, aPTT, and thrombin time (TT); and elevated concentrations of soluble fibrin and fibrinogen degradation products. Chronic DIC states have been identified with relatively normal screening tests of coagulation accompanied by elevated concentrations of soluble fibrin and fibrinogen degradation products.53 Management of DIC requires alleviating the underlying condition precipitating hemostatic activation. Otherwise, treatment includes selective blood component transfusions to replete coagulation factors and platelets consumed in the process. Antifibrinolytic therapy generally is contraindicated in DIC owing to potential for catastrophic thrombotic complications.

**PROTHROMBOTIC STATES**

Thrombophilia, a propensity for thrombotic events, most often manifests clinically in the form of venous thrombosis (frequently deep venous thrombosis of the lower extremity).64 As with bleeding disorders, thrombophilia may result from inherited or acquired conditions (Box 62-1). In the majority of cases, a precipitating event may be identified.65 For example, thrombotic complications often occur after surgery, during pregnancy, and in association with obesity or underlying malignancy.66 Random screening of asymptomatic patients for thrombotic risk has not proved cost effective or clinically efficacious.67,68 As with bleeding disorders, a careful history focusing on prior thrombotic events, family history of thrombosis, and concurrent drug therapy offers greater predictive value than random screening.
Common Inherited Thrombotic Disorders

Although understanding of thrombotic disorders from a biochemical and molecular level remains limited at present, careful testing may identify an underlying heritable thrombotic predisposition in as many as 50% of patients with venous thromboembolism.69 Relatively common inherited conditions underlying prothrombotic tendencies include single point mutations in genes for factor V (factor V Leiden) or prothrombin (prothrombin G20210A). In the case of the factor V Leiden mutation, the essential cofactor Va acquires resistance to degradation by protein C.70 This simple alteration in balance to 75%).74,75

Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Antiphospholipid antibody syndrome

Moderate Risk
Factor V Leiden genetic polymorphism
Prothrombin G20210A genetic polymorphism
Hyperhomocysteinemia
Dysfibrinogenemia
Postoperative prothrombotic state
Malignancy
Immobilization

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia describes an autoimmune-mediated drug reaction occurring in as many as 5% of patients receiving heparin therapy. As opposed to other drug-induced thrombocytopenias, HIT results in platelet activation and potential for venous and arterial thromboses.74,75 Evidence suggests that HIT is mediated by immune complexes (composed of immunoglobulin G [IgG] antibody, platelet factor 4 [PF4], and heparin) that bind platelet Fcγ receptors to activate platelets. Anti-PF4/heparin antibodies may “activate” vascular endothelium, monocytes, and macrophages by up-regulating tissue factor expression (Fig. 62-4). Patients developing HIT during heparin therapy experience substantially increased risk for thrombosis (odds ratio 20:40, absolute risk 30% to 75%).74,75

In most cases, HIT manifests clinically as thrombocytopenia occurring 5 to 14 days after initiating heparin therapy. However, with prior heparin exposure, thrombocytopenia or thrombosis may occur within 1 day. In some reported cases, thrombosis occurred simultaneously with thrombocytopenia, providing no warning. Although HIT remains a clinical diagnosis, laboratory testing provides confirmatory evidence. Both functional (i.e., serotonin platelet release assays or heparin-induced platelet aggregation) and quantitative (i.e., solid-phase enzyme-linked immunosorbent assays [ELISA]) tests for PF4/heparin immune complexes prove beneficial.72 Recent evidence suggests that PF4/heparin antibodies alone, in the absence of thrombocytopenia or thrombosis, may predict adverse outcomes.76,77

A diagnosis of HIT should be entertained for any patient experiencing thrombocytopenia or thrombocytopenia (absolute or relative ≥50% reduction in platelet count) during or after heparin administration. In cases in which HIT is suspected, heparin must be discontinued immediately (i.e., including unfractionated heparin, heparin-bonded catheters, heparin flushes, LMWH). Alternative nonheparin anticoagulation must be administered concurrently. In most cases, a direct thrombin inhibitor (i.e., bivalirudin, lepirudin, argatroban) is substituted for heparin until adequate prolongation of the INR can be achieved with warfarin.78,79 Typically, PF4/heparin immune complexes clear from the circulation within 3 months. If possible, patients experiencing HIT should avoid future exposure to unfractionated heparin; however, several reports describe subsequent limited perioperative reexposure to antiphospholipid syndrome results in mild prolongation of the aPTT and positive testing for lupus anticoagulant or anticardiolipin antibodies.72 Despite the prolonged aPTT, antiphospholipid syndrome poses no increased bleeding risk but rather increases the potential for thrombosis. Antibodies associated with antiphospholipid syndrome interfere with phospholipids common to many laboratory-based tests of coagulation. Isolated prolongation of an aPTT in a preoperative patient merits consideration of the diagnosis of antiphospholipid syndrome. Patients with this syndrome who have experienced a thrombotic complication are at increased risk for recurrent thrombosis and most often are managed by life-long anticoagulation.73

COMMON ACQUIRED THROMBOTIC DISORDERS

Antiphospholipid Syndrome

Antiphospholipid syndrome describes an acquired autoimmune disorder characterized by venous or arterial thromboses, or both, and recurrent pregnancy loss. This syndrome may occur secondarily to autoimmune disorders such as systemic lupus erythematosus or rheumatoid arthritis, or it may occur in isolation. Characteristically,
unfractionated heparin after laboratory testing to ensure absence of PF4/heparin immune complexes.

**MONITORING COAGULATION**

Traditionally, perioperative coagulation monitoring has focused on (1) preoperative testing to identify patients at increased risk for perioperative bleeding and (2) intraoperative monitoring of heparin therapy during cardiac and vascular surgery. As discussed previously, routine preoperative coagulation testing lacks either predictive value or cost efficacy. However, in patients with a history suggestive of a bleeding disorder or whose surgery may be associated with a high incidence of bleeding or coagulopathy, baseline preoperative coagulation testing may be advisable.

Given the widely acknowledged pharmacokinetic and pharmacodynamic response to heparin, monitoring anticoagulation during cardiac and vascular surgery remains necessary. Patient-specific factors affecting response to heparin include age, weight, intravascular volume, and plasma and membrane concentrations of antithrombin, heparin cofactor II, PF4, and other heparin-binding proteins. Therefore, patients experience widely divergent anticoagulant responses to identical weight-based doses of heparin. Regardless, monitoring of heparin anticoagulation must be performed if only to prevent the rare, but potentially lethal, complication resulting from inadvertent failure to administer heparin before cardiopulmonary bypass or vascular surgery.

The ideal test of perioperative coagulation would prove simple to perform, accurate, reproducible, diagnostically specific, and cost effective. No current coagulation monitor meets these expectations; however, integrating results from multiple forms of monitoring may provide valuable diagnostic insight into perioperative coagulopathies.

**COMMON LABORATORY-BASED MEASURES OF COAGULATION**

**Activated Partial Thromboplastin Time**

The aPTT assesses integrity of the intrinsic and common pathways of plasma-mediated hemostasis. It measures the time required in seconds for clot formation to occur after mixing a sample of patient plasma with phospholipid, calcium, and an activator of the intrinsic pathway of coagulation (i.e., celite, kaolin, silica, or ellagic acid). In most cases, coagulation factor deficiencies are detectable at factor concentrations below 30% to 40% of normal; however, aPTT reagents vary in sensitivity to factor concentrations, necessitating institutional specific determination of “normal” ranges. Prolongation of the aPTT is evaluated further with mixing studies to determine whether delayed clot formation is attributable to a coagulation factor deficiency or an inhibitor (i.e., heparin, antiphospholipid antibody, fibrin split products). The mixing study is performed by mixing the patient’s plasma sample with “normal” donor plasma. In the case of a coagulation factor deficiency, time to clot formation will correct and sequential assays for specific coagulation factor concentrations allow for identification of the deficiency. A common means of confirming heparin prolongation of the aPTT is to perform a thrombin clotting time (TCT) test. In this test, the patient’s citrate-containing plasma sample is mixed with thrombin and time to clot formation is measured in seconds. The most common mechanism underlying prolongation of the TCT is presence of heparin or a direct thrombin inhibitor anticoagulant; however, dysfibrinogenemia or fibrinogen degradation products also may impair clot formation in this setting.

**Prothrombin Time**

The PT assesses integrity of the extrinsic and common pathways of plasma-mediated hemostasis. It measures
time required in seconds for clot formation to occur after mixing a sample of patient plasma with tissue factor (thromboplastin) and calcium. As with the aPTT, thromboplastin test reagents vary in sensitivity, limiting the ability to compare results between laboratories. Given the importance of monitoring PT results for patients on long-term warfarin therapy, the INR was introduced as a means of normalizing PT results among different laboratories.\textsuperscript{81} Thromboplastin reagents are tested against an international recombinant standard and assigned an international sensitivity index (ISI) based on results. The INR subsequently is calculated as $\text{INR} = \frac{\text{patient PT}}{\text{standard PT} \times \text{ISI}}$, in which the standard PT represents the geometric mean of multiple normal samples from the testing laboratory. Institution of the INR substantially reduced interlaboratory variations in the PT. As with the aPTT, prolongation of the PT is assessed further with mixing studies.

**Platelet Count and Bleeding Time**

The platelet count remains a standard component in screening for coagulation abnormalities. Automated platelet counts are performed in bulk using either optical-based or impedance-based measurements. Recommendations regarding optimal platelet counts prove somewhat arbitrary; however, platelet counts exceeding 100,000/μL commonly are associated with normal hemostasis. Abnormally low platelet counts merit further assessment, including a visual platelet count using a blood smear. Sample hemodilution and platelet clumping are common causes for false low platelet counts. Ethylenediaminetetraacetic acid (EDTA)-induced platelet clumping, a common artifact underlying thrombocytopenia, may be identified by manually counting platelets or by substituting a citrate anticoagulant (as opposed to EDTA).

With growth in point-of-care platelet function monitors the bleeding time has declined in popularity; however, under controlled conditions the bleeding time may provide useful information regarding primary hemostasis. Employing a commercial template cutting device and a sphygmomanometer adjusted to 40 mm Hg venous pressure, bleeding times of 2 to 10 minutes on the anterior forearm are considered normal. Limitations of the bleeding time include poor reproducibility, time needed to perform the test, and potential for scarring. Furthermore, the bleeding time is affected by numerous confounding variables, including skin temperature, skin thickness, age, ethnicity, anatomic test location, and a host of other factors.\textsuperscript{82} In general, the bleeding time has not proved predictive of bleeding and for that reason its use as a preoperative screening test to assess bleeding risk is not recommended.

**COMMON POINT-OF-CARE MEASURES OF COAGULATION**

Although laboratory-based measures of coagulation remain the mainstay of preoperative coagulation testing, increasing availability of sensitive and specific point-of-care coagulation monitoring may soon offer opportunities to direct blood component and hemostatic drug therapy more specifically without delays inherent to standard laboratory testing. Commercially available point-of-care monitors applicable in the perioperative setting may be considered in four broad categories: (1) functional measures of coagulation or assays that measure the intrinsic ability of blood to generate clot, (2) heparin concentration monitors, (3) viscoelastic measures of coagulation, and (4) platelet function monitors.

**Functional Measures of Coagulation**

The ACT, described by Hattersley in 1966 as a variation of the Lee-White whole blood clotting time, employs a contact activation initiator, typically celite (diatomaceous earth) or kaolin, to accelerate clot formation and reduce time for assay completion. Kaolin is recommended for use in patients receiving the antifibrinolytic drug aprotinin because celite ACTs in this setting are subject to artifactual prolongation.\textsuperscript{83} Failure to appreciate this drug-mediated effect may result in inadequate heparin administration if using celite ACT measurements with aprotinin. Whether high plasma concentrations of aprotinin affect the kaolin ACT remains unclear.

Current commercial ACT monitors automate clot detection. One of the more widely available ACT monitors uses a glass test tube containing a small magnet (Hemochron Response Whole Blood Coagulation System, ITC, Edison, NJ). After adding sample blood, the tube is placed into the analyzer and the tube is rotated slowly at 37° C, allowing the magnet to maintain contact with a proximity detection switch. As fibrin clot forms, the magnet becomes entrapped and dislodged from the detection switch, thereby triggering an alarm to signal completion of the ACT. Another ACT device uses a “plumb bob” flag assembly that is raised and released repeatedly to settle in the sample vial containing blood and contact activator (Hepon H MS Plus, Medtronic, Minneapolis, Minn.). With clot formation, the descent rate of the flag through the blood sample slows, triggers an optical detector, and sets off an alarm to signal completion of the ACT.

The ACT in normal individuals is $107 \pm 13$ seconds (mean ± SD). However, the time at which a patient’s baseline ACT is measured influences the result.\textsuperscript{84} After surgical incision, baseline ACT may decrease. Because the ACT measures clot formation by way of intrinsic and common pathways, heparin and other anticoagulants prolong time to clot formation. The ACT proves somewhat resistant to platelet dysfunction and thrombocytopenia.

ACT testing remains a popular perioperative coagulation monitor because of its simplicity, low cost, and linear operating response at high heparin concentrations. Limitations of ACT monitoring include lack of sensitivity at low heparin concentrations and poor reproducibility.\textsuperscript{83} ACT testing performed with and without added heparinase improves sensitivity for detecting low heparin concentrations. Further limitations of the ACT include artifactual prolongation of results with hemodilution or hypothermia and the fact that ACT values beyond 600 seconds exceed the linear response range for the assay. Duplicate measurements improve results; however, newer electrochemically based ACT analyzers (i-STAT, Abbott, Princeton, NJ) improve reproducibility such that single ACT determinations may prove adequate.
The high-dose thrombin time (HiTT) (ITC) provides an alternative functional measure of heparin anticoagulation. Primarily employed in cardiac surgical settings, the HiTT assay contains high thrombin concentrations to cleave fibrinogen directly and generate fibrin clot. Given excess thrombin concentrations, clot formation occurs independently of plasma coagulation factors other than fibrinogen. As a result, HiTT is prolonged by heparin (or other thrombin inhibitors), extreme degrees of hypofibrinogenemia or dysfibrinogenemia, and high concentrations of fibrin split products (as occur with fibrinolysis). During most surgical procedures requiring heparin administration, HiTT prolongation will correlate with heparin anticoagulant effect.

**Heparin Concentration Measurement**

Protamine titration remains the most popular point-of-care method for determining heparin concentration in perioperative settings. Protamine, a strongly basic polycationic protein, directly inhibits heparin in a stoichiometric manner. In other words, 1 mg of protamine will inhibit 1 mg (~100 units) of heparin, thereby forming the basis for protamine titration as a measure of heparin concentration. As increasing concentrations of protamine are added to a sample of heparin-containing blood, time to clot formation decreases until the point at which the protamine concentration exceeds heparin concentration to delay clot formation. If a series of blood samples with incremental doses of protamine are analyzed, the sample in which the protamine and heparin concentrations are most closely matched will clot first. In this manner, protamine titration methodology allows for heparin concentration estimation. Assuming that the heparin-protamine titration curve for an individual patient remains constant throughout the operative period, protamine titration methods may estimate heparin doses required to achieve a desired plasma heparin concentration or the protamine dose needed to reverse a given heparin concentration in blood. Current point-of-care heparin concentration monitoring employs automated measurement techniques (Hepcon HMS Plus, Medtronic). Advantages of heparin concentration measurement include sensitivity for low heparin concentrations as well as relative insensitivity to hemodilution and hypothermia. In addition, heparin concentration measures are unaffected by aprotinin.

A major limitation of heparin concentration monitoring is failure to assess directly for an anticoagulant effect. To use an extreme example, consider a patient with a homozygous deficiency of antithrombin; in this setting, heparin administration, HiTT prolongation will correlate with heparin anticoagulant effect.

**Viscoelastic Measures of Coagulation**

Initially developed in the 1940s, viscoelastic measures of coagulation have undergone a resurgence in popularity. The unique aspect of viscoelastic monitors lies in their ability to measure in whole blood the entire spectrum of clot formation from early fibrin strand generation through clot retraction and eventual fibrinolysis. The early thromboelastograph (TEG) developed by Hartert in 1948 has evolved into two independent viscoelastic monitors: the modern TEG, or TEG 5000 Thromboelastograph Hemostasis Analyzer System (Haemoscope, Braintree, Mass.) and rotational thromboelastometry (ROTEM) (TEM Systems, Durham, NC). In the case of the thromboelastograph (TEG 5000), a small (0.35-mL) sample of whole blood is placed into a disposable cuvette within the instrument. The cuvette is maintained at a temperature of 37°C and continuously rotates around an axis of approximately 5 degrees. A sensor “piston” attached by a torsion wire to an electronic recorder is lowered into the blood within the cuvette. Addition of an activator, most often kaolin or celite, initiates clot formation. As the fibrin-platelet plug evolves, the piston becomes enmeshed within the clot, transferring rotation of the cuvette to the piston, torsion wire, and electronic recorder.

Although variables derived from the TEG tracing do not coincide directly with laboratory-based tests of coagulation, the TEG depicts characteristic abnormalities in clot formation and fibrinolysis. Various parameters describing clot formation and lysis are identified and measured by the TEG. For example, the R value (reaction time) measures time to initial clot formation (normal, 7.5 to 15 minutes). Comparable to the whole blood clotting time, addition of a contact activator (i.e., celite or kaolin) to the sample cuvette reduces time to results. The R value may be prolonged by a deficiency of one or more plasma coagulation factors or inhibitors such as heparin. Maximum amplitude (MA) provides a measure of clot strength and may be decreased by either qualitative or quantitative platelet dysfunction or decreased fibrinogen concentration. Normal MA is 50 to 60 mm. The α angle and K (Bikoagulierung or coagulation) values measure rate of clot formation and may be prolonged by any variable slowing clot generation such as a plasma coagulation factor deficiency or heparin anticoagulation. Modification of clotting activators may be incorporated to assess platelet or fibrin contributions to clot strength. In a somewhat analogous manner, ROTEM measures viscoelastic changes in a sample of whole blood subjected to activation of coagulation. Specific activators differ from that of the TEG 5000 with resulting quantitative measures termed (1) coagulation time (CT; seconds), (2) α angle (clot formation time; seconds), (3) maximal clot firmness (MCF; millimeter), and (4) lysis time (LT; second).

The Sonoclot Analyzer (Sienco, Arvada, Colo.) provides an alternative viscoelastic measure of coagulation. In contrast to thromboelastography and ROTEM, the Sonoclot Analyzer immerses a rapidly vibrating probe into a 0.4-mL sample of blood. As clot formation proceeds, impedance to probe movement through the blood increases to generate an electrical signal and characteristic clot signature. The analyzer signature may be used to derive the ACT and to provide information regarding clot strength and presence of fibrinolysis. Viscoelastic monitors generate characteristic diagrams by translating mechanical resistance to sensor movement within a sample of whole blood to an electronic waveform subject to quantitative analysis. One of the more common applications for viscoelastic monitoring has been real-time detection of excess fibrinolysis during liver transplantation or cardiac surgery. Evidence suggests that viscoelastic monitoring may prove beneficial in...
differentiating surgically related bleeding from that due to a coagulopathy. When used as one component of a diagnostic algorithm, both thromboelastography and ROTEM have been demonstrated to reduce blood administration. More widespread application of viscoelastic monitoring has been hindered by lack of specificity associated with abnormal findings and qualitative assay interpretation. Digital automation of these instruments has simplified interpretation and improved reproducibility.

**PLATELET FUNCTION MONITORS**

Assessment of platelet function has proved challenging for several reasons. Historically, tests of platelet function have proved costly, time consuming, and technically demanding. Platelet dysfunction may occur as a result of diverse inherited or acquired disorders affecting surface receptors involved in adhesion or aggregation, storage granules, internal activation pathways, phospholipid membranes, or other mechanisms. Lack of standardized quality controls necessitates use of local donor blood to establish normal control ranges. Furthermore, even established tests such as platelet aggregation lack performance standardization, resulting in widely varying results across laboratories. Complicating assessment further is the fact that platelets are highly susceptible to activation or desensitization during sample collection, transport, storage, and processing.

Although viscoelastic measures of coagulation (i.e., TEG 5000 or ROTEM) may detect platelet dysfunction, sensitivity and specificity prove limited. Incorporation of a platelet mapping assay into thromboelastography provides a method for viscoelastic measurement of drug-induced platelet inhibition with reasonable correlation to optical aggregometry. The standard laboratory-based method for identifying qualitative platelet dysfunction remains optical aggregometry performed using specific platelet agonists and samples of platelet-rich plasma. Flow cytometry employing fluorescent-labeled antibodies provides another sensitive method for quantitating platelet activation, responsiveness, and surface receptor availability. Despite representing standards of care, these measures remain technically challenging, costly, and time-consuming laboratory-based assays.

Fortunately, an increasing array of platelet function assays specifically designed as point-of-care instruments are available. As a measure of primary hemostasis, the PFA-100 (Platelet Function Analyzer, Siemens, Tarrytown, NY) increasingly has replaced the bleeding time in assessment of primary hemostasis. Unique among both laboratory-based and point-of-care platelet function monitors, the PFA-100 incorporates high-shear conditions to simulate small vessel injury in the presence of either ADP or epinephrine, both potent platelet activators. Time to clot–mediated aperture occlusion is reported as closure time. The PFA-100 has proved effective in detecting von Willebrand disease and aspirin-mediated platelet dysfunction. This instrument, as a component of a standardized screening protocol, reduces time to identify and classify platelet dysfunction. Limitations of the PFA-100 include interference by thrombocytopenia and hemodilution.

The HemoSTATUS (Medtronic) platelet function test exploits the ability of platelet activating factor (PAF) to accelerate clot formation of the kaolin-activated ACT. HemoSTATUS testing is performed on the Medtronic HMS Plus coagulation analyzer employing a six-channel kaolin ACT cartridge preloaded with serially increasing concentrations of PAF. A clot ratio is determined for each individual patient assay based on the ratio of the PAF-accelerated ACT to the standard ACT. An individual patient’s clot ratio is compared with a maximal clot ratio derived from normal volunteers to provide a relative measure of platelet function. In the presence of platelet dysfunction, higher concentrations of PAF are required to achieve a comparable PAF-activated ACT. In cardiac surgery, investigators demonstrated a relationship between platelet dysfunction and postoperative bleeding. Furthermore, the maximal clot ratio as determined by HemoSTATUS improved after desmopressin or platelet administration. Other investigators, however, failed to identify a relationship between platelet dysfunction as measured by HemoSTATUS and postoperative bleeding.

The VerifyNow System (formerly known as the Ultegra Rapid Platelet Function Analyzer, Accumetrics, San Diego, Calif.) is an automated turbidimetric whole blood platelet function assay that assesses ability of activated platelets to bind fibrinogen-coated polystyrene beads. On addition of the whole blood test sample, thrombin receptor activating peptide directly activates platelets within the sample to stimulate glycoprotein IIb/IIIa platelet surface receptor expression. As activated platelets bind and aggregate fibrinogen-coated beads, light transmission through the sample increases to generate a signal. Although the VerifyNow System is simple to operate and provides a rapid bedside measure of platelet function, a baseline reference measurement is suggested for each patient to calculate the extent of subsequent changes in platelet function. Potential applications for this methodology in the perioperative setting remain unclear.

Plateletworks (Helena Laboratories, Beaumont, Tex.) employs a hemocytometer to perform automated platelet counts on whole blood samples collected in the presence and absence of platelet-stimulating agonists such as collagen or ADP. The difference in platelet counts before and after agonist addition provides a direct measure of platelet aggregation (i.e., platelet responsiveness) and is reported as % aggregation. Preliminary investigations demonstrated reasonable correlations between platelet counts attained with the Plateletworks monitor and laboratory-based instruments. In addition, the Plateletworks assay proved effective in identifying platelet dysfunction in the setting of glycoprotein IIb/IIIa antagonists and appeared to correlate relatively well with laboratory-based measures of platelet aggregation.

Employing a sample of whole blood, the Hemostasis Analysis System (Hemodyne, Bethesda, Md.) measures platelet contractile force, the force produced by platelets during clot retraction, and clot elastic modulus, a measure of clot rigidity. In preliminary investigations, platelet contractile force was reduced after cardiopulmonary bypass and modestly correlated with perioperative blood loss.

Advances in our understanding of hemostasis and thrombosis at the molecular level have contributed directly to recent biotechnologic innovations in
point-of-care testing. Further advances in point-of-care coagulation monitoring offer the opportunity for clinicians to make informed decisions about transfusion therapy and hemostatic drug administration to minimize perioperative bleeding. In considering any point-of-care coagulation testing, it must be recognized that results will not necessarily mirror those reported from laboratory-based testing. Reagent sensitivities vary across manufacturers and even one lot of reagent to another. In addition, point-of-care testing typically relies on whole blood samples for testing as opposed to laboratory-based testing using plasma or processed platelets. A final consideration for which point-of-care platelet function testing provides a particularly relevant example is that monitors from different manufacturers measure differing aspects of platelet-mediated or plasma-mediated hemostasis. In the case of platelet function monitors, a dozen instruments purport to measure platelet function. However, using different instruments results may vary from “severe” platelet dysfunction to “no platelet dysfunction” in a single sample of blood. Before adopting any point-of-care monitoring, an understanding of the quality assurance requirements, test methodology, and concomitant strengths and weaknesses will prove essential to inform patient care.

Complete references available online at expertconsult.com.

REFERENCES
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