50 Patient Blood Management: Coagulation

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KEY POINTS

- Normal hemostasis is a balance between generation of a localized hemostatic clot and uncontrolled thrombus formation.
- The extrinsic pathway of coagulation begins with exposure of blood plasma to tissue factor and represents the initiation phase of plasma-mediated hemostasis.
- The intrinsic pathway amplifies and propagates the hemostatic response to maximize thrombin generation.
- The common pathway generates thrombin, forms fibrin, and crosslinks fibrin strands to produce an insoluble fibrin clot.
- Routine preoperative coagulation testing of all surgical patients is costly and lacks predictive value for detection of hemostatic abnormalities. Testing should be based on the preoperative history and physical examination and the planned surgery.
- Antiplatelet agents and anticoagulants are used to reduce the formation of blood clots in the setting of coronary or cerebral atherosclerosis or after vascular thrombosis.
- Thrombolytic therapy is used to break up or dissolve blood clots.
- Procoagulant drugs (antifibrinolytics, factor replacements, prothrombin complex concentrate) help control blood loss during surgery.
- Perioperative management of patients who require chronic anticoagulation or antiplatelet therapy involves balancing the risk of surgical bleeding against the risk of developing postoperative thromboembolism.

Introduction

Hemostasis is an ordered enzymatic process involving cellular and biochemical components that function to preserve the integrity of the circulatory system after injury. The ultimate goal of this process is to limit blood loss secondary to vascular injury, maintain intravascular blood flow, and promote revascularization after thrombosis. As such, normal physiologic hemostasis is a constant balance between procoagulant pathways responsible for generation of a stable localized hemostatic clot and counter-regulatory mechanisms inhibiting uncontrolled thrombus propagation or premature thrombus degradation. Vascular endothelium, platelets, and plasma coagulation proteins play equally important roles in this process. Derangements in this delicate system can lead to excessive bleeding or pathologic thrombus formation. This chapter will examine normal and abnormal hemostasis, mechanisms to monitor coagulation, medications to manipulate coagulation, and management options for the perioperative anticoagulated patient.

Normal Hemostasis

Vascular endothelial injury—mechanical or biochemical—leads to platelet deposition at the injury site, a process often referred to as primary hemostasis. Although this initial platelet plug 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.[1]

VASCULAR ENDOTHELIAL ROLE IN HEMOSTASIS

In order to maintain blood flow throughout the circulatory system, the vascular endothelium employs several strategies to inhibit unprovoked thrombus formation. Healthy endothelial cells possess antiplatelet, anticoagulant, and profibrinolytic effects to inhibit clot formation.[2] The negatively charged vascular endothelium repels platelets, and endothelial cells produce potent platelet inhibitors such as prostacyclin (prostaglandin I_2,) and nitric oxide (NO).[3,4] An adenosine diphosphatase (CD39) expressed on the surface of vascular endothelial cells also serves to block platelet activation via degradation of adenosine diphosphate (ADP), a potent platelet activator.[5] Given these endogenous antiplatelet effects, quiescent platelets normally do not adhere to healthy vascular endothelial cells.

The vascular endothelium also plays a pivotal anticoagulant role through expression of several inhibitors of plasma-mediated hemostasis. Endothelial cells increase activation of protein C, an anticoagulant, via surface glycoprotein thrombomodulin (TM), which acts as a cofactor for thrombin-mediated activation of protein C, making its activation 1000 times faster. Endothelial cells also increase endothelial cell protein C receptor, which further enhances protein C activation by an additional 20-fold.[6] Endothelial-bound glycosaminoglycans, such as heparan sulfate, function to accelerate the protease activity of antithrombin (AT), which degrades factors IXa, Xa, and thrombin.[7] Endothelial cells also produce tissue factor pathway inhibitor (TFPI), which inhibits the procoagulant activity of factor Xa as well as the TF-VIIa complex.[8] Finally, the vascular endothelium synthesizes tissue plasminogen activator (t-PA), which is responsible for activating fibrinolysis, a primary counter-regulatory 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 instead promotes clot formation. Damage to vascular endothelial cells exposes the underlying extracellular matrix (ECM), which contains collagen, von Willebrand factor (vWF), and other platelet-adhesive glycoproteins.[9,10] 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 fibrin clot.[11] Certain cytokines (i.e., interleukin-1, tumor necrosis factor, and γ-interferon) and hormones (i.e., desmopressin acetate [DDAVP] or endotoxin) induce prothrombotic changes in vascular endothelial cells by increasing synthesis and expression of vWF, tissue factor, and plasminogen activator inhibitor-1 (PAI-1), and down-regulating normal antithrombotic cellular and biochemical pathways.[12,13] Finally, thrombin, hypoxia, and high fluid shear stress can also induce prothrombotic vascular endothelial changes such as increased synthesis of PAI-1. This associated inhibition of fibrinolysis has been implicated in the prothrombotic state and high incidence of venous thrombosis after surgery.[14,15]

PLATELETS AND HEMOSTASIS

Platelets contribute a critical role in hemostasis. Derived from bone marrow megakaryocytes, nonactivated platelets circulate as discoid anuclear cells with a lifespan of 8 to 12 days.[16] Under normal conditions, approximately 10% of platelets are consumed to support vascular integrity with $1.2–1.5 \times 10^{11}$ new platelets formed daily.[17] 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 exterior environment.[18] Under normal circumstances, platelets do not bind the vascular endothelium. However, when injury occurs, platelets contribute to hemostasis by adhering to the damaged vasculature, aggregating with one another to form a platelet plug, and facilitating generation of fibrin crosslinks to stabilize and reinforce the plug. Initially, upon exposure of the 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 collagen and platelet glycoprotein Ib/factor IX/factor V receptor complexes.[19] Absence of either von Willebrand disease (vWF) or glycoprotein Ib/factor IX/factor V receptors (Bernard-Soulier syndrome) results in a clinically significant bleeding disorder.

In addition to promoting their adhesion to the vessel wall, the platelet interaction with collagen serves as a potent stimulus for the subsequent phase of thrombus formation, termed platelet activation. The generation of thrombin resulting from exposure of tissue factor, functions as a second pathway for platelet activation. Platelets contain two specific types of storage granules: α granules and dense bodies.[18] α 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.[20] During activation, platelets undergo structural changes to develop pseudopod-like membrane extensions and to release physiologically active microparticles, which serve to dramatically increase 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.[1]

During the final phase of platelet aggregation, activators released during the activation phase recruit additional platelets to the site of injury. Newly active glycoprotein IIb/IIIa receptors on the platelet surface bind fibrinogen, thereby promoting cross-linking and aggregation with adjacent platelets.[20] The importance of these receptors is reflected by the bleeding disorder associated with their hereditary deficiency, Glanzmann thrombasthenia.

PLASMA-MEDIATED HEMOSTASIS

Plasma-mediated hemostasis was originally described as a cascade or waterfall sequence of steps involving the serial activation of enzymes and cofactors to accelerate and amplify fibrin generation by thrombin.[21] Trace plasma proteins, activated by exposure to tissue factor or foreign surfaces, initiate this series of reactions culminating in conversion of soluble fibrinogen to insoluble fibrin clot.[22] Thrombin generation, the "thrombin burst," represents the key regulatory step in this 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.[23]

Traditionally, the coagulation cascade describing plasma-mediated hemostasis has been depicted as extrinsic and intrinsic pathways, both of which culminate in a common pathway in which fibrin generation occurs.[24] This cascade model has proven to be an oversimplification,

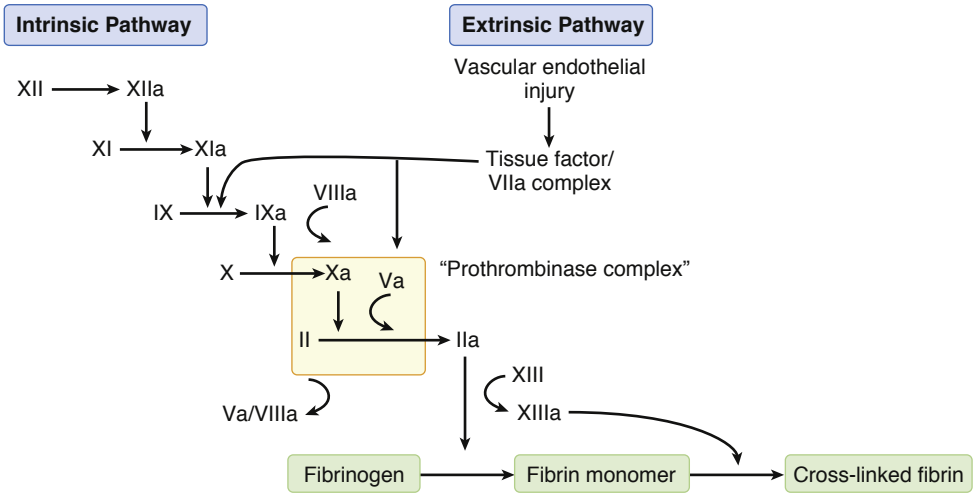

Fig. 50.1 Depiction of the Classic Coagulation Cascade Incorporating Extrinsic and Intrinsic Pathways of Coagulation. (From Slaughter TF. The coagulation system and cardiac surgery. In: Estafanous FG, Barasch PG, Reves JG, eds. *Cardiac Anesthesia: Principles and Clinical Practice*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001: 320, with permission.)

as it does not fully reflect in vivo hemostasis. For instance, individuals with deficiencies in the intrinsic pathway (factor XII, prekallikrein, or high molecular weight kininogen) exhibit prolongations of the activated partial thromboplastin time (aPTT), but do not actually experience an increased bleeding risk. Nevertheless, the cascade model remains a useful descriptive tool for organizing discussions of plasma-mediated hemostasis (Fig. 50.1). Coagulation factors are, for the most part, synthesized by the liver 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 coagulation pathway evolved.

The 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.[25] Assembly of these activation complexes occurs on platelet or microparticle phospholipid membranes that localize and concentrate reactants. Coagulation factor activation slows dramatically in the absence of these phospholipid membrane anchoring sites. This requirement functionally confines clot formation to sites of injury.

Extrinsic Pathway of Coagulation

The extrinsic pathway of coagulation is now understood to represent the initiation phase of plasma-mediated hemostasis and begins with exposure of blood plasma to tissue factor.[26] Tissue factor is prevalent in subendothelial tissues surrounding the vasculature. 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.[22] Additionally, the tissue factor/factor VIIa complex also activates factor IX of the intrinsic pathway, further demonstrating the key role of tissue factor in initiating hemostasis.[27]

Intrinsic Pathway of Coagulation

Classically, the intrinsic or contact activation system was described as a parallel pathway for thrombin generation initiated by factor XII activation after contact with negatively charged surfaces such as glass, dextran sulfate, or kaolin. 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.[28] Recent cell-based models of coagulation suggest that thrombin generation by way of the extrinsic pathway is limited by a natural inhibitor, TFPI,[29] but the small quantities of thrombin generated do activate factor XI and the intrinsic pathway. The intrinsic pathway then subsequently amplifies and propagates the hemostatic response to maximize thrombin generation (Fig. 50.2). Although factor XII may be activated by foreign surfaces (i.e., cardiopulmonary bypass [CPB] circuits or glass vials), the intrinsic pathway plays a minor role in the initiation of hemostasis. Proteins of the intrinsic pathway may, however, contribute to inflammatory processes, complement activation, fibrinolysis, kinin generation, and angiogenesis.[28]

Common Pathway of Coagulation

The final pathway, common to both extrinsic and intrinsic coagulation cascades, depicts thrombin generation and subsequent fibrin formation. Signal amplification results from activation of factor X by both intrinsic (FIXa, FVIIIa, Ca^{2+}) and extrinsic (tissue factor, FVIIa, Ca^{2+}) tenase complexes. The tenase complexes in turn facilitate formation of the

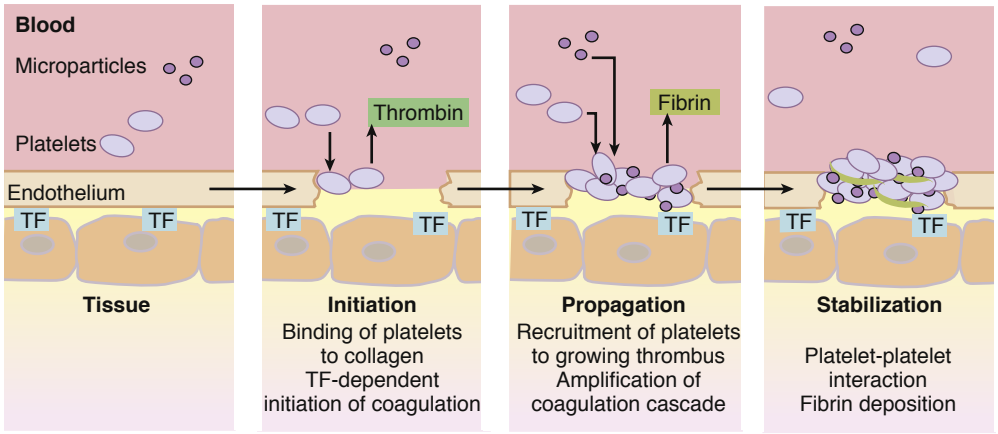

Fig. 50.2 Clot Formation at Vascular Injury Site. Vascular injury exposes subendothelial tissue factor *(TF)* initiating plasma-mediated hemostasis via the extrinsic pathway. The intrinsic pathway further amplifies thrombin and fibrin generation. Platelets adhere to exposed collagen to undergo activation, resulting in recruitment and aggregation of additional platelets. (From Mackman N, Tilley RE, Key NS. Role of extrinsic pathway of blood coagulation in hemostasis and thrombosis. *Arterioscleros Thromb Vasc Biol*. 2007;27:1687–1693, with permission.)

prothrombinase complex (FXa, FII [prothrombin], FVa [cofactor], and Ca^{2+}), which mediates a surge in thrombin generation from prothrombin.[30] Thrombin proteolytically cleaves fibrinopeptides A and B from fibrinogen molecules to generate fibrin monomers, which polymerize into fibrin strands to form clot.[30] Finally, factor XIIIa, a transglutaminase activated by thrombin, covalently crosslinks fibrin strands to produce an insoluble fibrin clot resistant to fibrinolytic degradation.[31]

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 the potential for randomized controlled trials to determine efficacy of these biologics in treatment of acquired coagulopathies.[32]

Thrombin generation remains the key enzymatic step regulating hemostasis. Not only does thrombin activity mediate conversion of fibrinogen to fibrin, but it also has a host of other actions. It activates platelets and factor XIII, converts inactive cofactors V and VIII to active conformations, activates factor XI and the intrinsic pathway, up-regulates expression of tissue factor, stimulates vascular endothelial expression of PAI-1 to down-regulate fibrinolytic activity, and suppresses uncontrolled thrombosis through activation of protein C.[33]

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 from 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.[30,34] However, later in the clotting process, more robust counter-regulatory mechanisms are necessary to limit clot propagation. Four major counter-regulatory pathways have been identified that appear particularly crucial for down-regulating hemostasis: fibrinolysis, TFPI, the protein C system, and serine protease inhibitors (SERPINs).

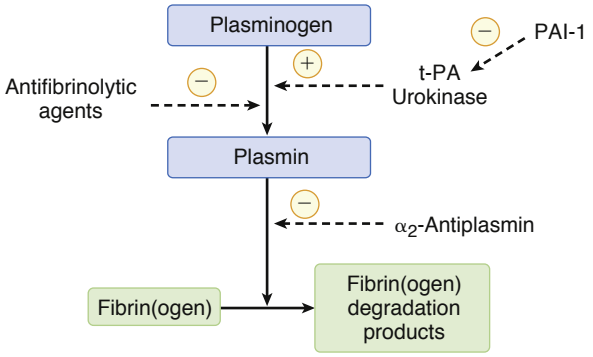

Fig. 50.3 Principal Mediators of Fibrinolysis. Dashed lines depict sites of action for promoters and inhibitors of fibrinolysis. *PAI,* Plasminogen activator inhibitor; *tPA,* tissue plasminogen activator. (From Slaughter TF. The coagulation system and cardiac surgery. In: Estafanous FG, Barasch PG, Reves JG, eds. *Cardiac Anesthesia: Principles and Clinical Practice*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2001:320, with permission.)

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. 50.3). The principal enzymatic mediator of fibrinolysis is the serine protease, plasmin, which is generated from plasminogen.[35] In vivo, plasmin generation is most often accomplished by release of t-PA or urokinase from the vascular endothelium. Activity of t-PA and urokinase is accelerated in the presence of fibrin, which limits fibrinolysis to areas of clot formation. Factor XIIa and kallikrein of the intrinsic pathway also contribute to fibrinolysis through activation of plasminogen after exposure to foreign surfaces.[36] Fortunately, fibrinolytic activity is limited by the rapid inhibition of free plasmin. 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.[37] Fibrin degradation products also possess mild anticoagulant properties.

TFPI and factor Xa form phospholipid membrane-bound complexes that incorporate and inhibit tissue factor/factor VIIa complexes.[38] This inhibition leads to downregulation of the extrinsic coagulation pathway.[39] As TFPI rapidly extinguishes tissue factor/VIIa activity, the critical role of the intrinsic pathway to continued thrombin and fibrin generation becomes apparent.[28]

The protein C system proves particularly important in down-regulating coagulation through inhibition of thrombin and the essential cofactors Va and VIIIa. After binding to TM, thrombin's procoagulant function decreases and instead its ability to activate protein C is augmented.[40] 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 Xa and thrombin, respectively. Additionally, once bound to TM, thrombin is rapidly inactivated and removed from circulation, providing another mechanism by which the protein C pathway down-regulates hemostasis.[40]

The most significant SERPINs regulating hemostasis include AT and heparin cofactor II. AT inhibits thrombin, as well as factors IXa, Xa, XIa, and XIIa. [41] Heparin binds AT causing a conformational change that accelerates AT-mediated inhibition of targeted enzymes. Heparin cofactor II is a more recently discovered SERPIN that inhibits thrombin alone.[42] Although the precise physiologic role for heparin cofactor II remains unclear, when bound by heparin, its inhibitory activity is dramatically increased.

Disorders of Hemostasis

EVALUATION OF BLEEDING DISORDERS

The perioperative period presents significant challenges to the hemostatic system; therefore, identification and correction of hemostatic disorders can be of vital importance. Unfortunately, assessment of bleeding risk continues to be a challenge and the optimal methods for preoperative evaluation remain controversial. Although routine preoperative coagulation testing of all surgical patients may seem prudent, such an approach is costly and lacks predictive value for detection of hemostatic abnormalities. Standard coagulation tests such as the prothrombin time (PT) and aPTT were designed as diagnostic tests to be used when a bleeding disorder is suspected based on clinical evaluation. As a result, when used as screening tests, these in vitro assays are limited in their ability to reflect the in vivo hemostatic response.[43] For example, because of the nature of establishing normal value ranges for these tests, 2.5% of healthy individuals will have abnormal PT or aPTT values. Meanwhile, those with mild hemophilia A, vWD, and factor XIII deficiency may experience clinically significant bleeding despite having normal values on standard testing.[44] Consequently, a carefully performed bleeding history remains the single most effective predictor of perioperative bleeding.

A thorough history should focus on prior bleeding episodes.[45] In particular, patients should be asked whether they have experienced excessive bleeding after hemostatic challenges such as dental extractions, surgery, trauma, or childbirth and whether blood transfusions or reoperation were required to control the bleeding. Common presentations suggestive of a bleeding disorder may include frequent epistaxis necessitating nasal packing or surgical intervention. Oral surgery and dental extractions prove particularly good tests of hemostasis because of increased fibrinolytic activity on the mucous membranes of the oral cavity. Women with platelet disorders or vWD may experience menorrhagia, and postpartum hemorrhage commonly occurs in those with underlying disorders of hemostasis.[46] A history of spontaneous nontraumatic hemorrhage proves particularly concerning when associated with hemarthroses or deep muscle bleeding. Identification of a bleeding disorder at an early age or in family members suggests an inherited condition. A careful medication history including direct questions relating to consumption of aspirin and nonsteroidal antiinflammatory drugs (NSAIDs), as well as supplements such as ginkgo and vitamin E.[47] 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 the need for preoperative laboratory-based coagulation testing. Should the preoperative history or physical examination reveal signs or symptoms suggestive of a bleeding disorder, further laboratory testing is indicated. Preoperative coagulation screening tests may be indicated, despite a negative history, in cases in which the planned surgery is commonly associated with significant bleeding (i.e., CPB). Finally, preoperative testing may prove justified in settings in which the patient is unable to provide an adequate preoperative bleeding history. Should evidence of a bleeding disorder be detected, underlying etiologies should be clarified if possible before proceeding with surgery.

INHERITED BLEEDING DISORDERS

Von Willebrand Disease

Inherited disorders of hemostasis include those involving platelet quantity and function, coagulation factor deficiencies, or disorders of fibrinolytic pathways. Among these inherited bleeding disorders, vWD is the most common and is characterized by quantitative or qualitative deficiencies of vWF resulting in defective platelet adhesion and aggregation.[48] Affecting up to 1% of the population, vWD is categorized into three main types (types 1, 2, and 3). with most cases demonstrating an autosomal dominant inheritance pattern.[49] Types 1 and 3 lead to varying quantitative vWF deficiencies, while type 2 encompasses four subtypes expressing qualitative defects that affect vWF function. Under normal conditions, vWF plays a critical role in platelet adhesion to the ECM and prevents degradation of factor VIII by serving as a carrier molecule.[50] Classically, patients with vWD describe a history of easy bruising, recurrent epistaxis, and menorrhagia, which are characteristic of defects in platelet-mediated hemostasis. In more severe cases (i.e., type 3 vWD), concomitant reductions in factor VIII may lead to serious spontaneous hemorrhage, including hemarthroses.

Routine coagulation studies are generally not helpful in the diagnosis of vWD, as the platelet count and PT will be normal in most patients and the aPTT may demonstrate

mild-to-moderate prolongation depending on the level of factor VIII reduction.[51] Instead, initial screening tests involve measurement of vWF levels (vWF antigen) and vWF platelet binding activity in the presence of the ristocetin cofactor, which leads to platelet agglutination. Measurable reductions in factor VIII activity may occur in severe cases.[52] Increasingly, platelet function tests have replaced bleeding times in assessing for vWD.[53,54] Mild cases of vWD often respond to DDAVP, which results in the release of vWF from endothelial cell. Use of vWF:factor VIII concentrates (Humate-P, CSL Behring, King of Prussia, PA) may be indicated in the perioperative period if there is a significant bleeding history.[55]

Hemophilias

Although less common than vWD, the hemophilias merit consideration given their diverse clinical presentation. Hemophilia A, factor VIII deficiency, and hemophilia B, factor IX deficiency, are both X-linked inherited bleeding disorders most frequently presenting in childhood as spontaneous hemorrhage involving joints, deep muscles, or both. Hemophilia A occurs with an incidence of 1:5000 males and hemophilia B in 1:30,000 males. While most cases are inherited, nearly one third of cases represent new mutations with no family history.[56] The severity of the disease depends on an individual's baseline factor activity level.[57] 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 PT, bleeding time, and platelet count remain within normal limits. However, a normal aPTT may also be seen in mild forms of hemophilia; therefore, specific factor analyses need to be performed to confirm the diagnosis and determine the severity of the factor deficiency. In most cases, perioperative management of patients with hemophilia A or B necessitates consultation with a hematologist and administration of recombinant or purified factor VIII or factor IX concentrates, respectively.[58] Mild cases of hemophilia A may be treated with desmopressin. An increasingly common complication of hemophilia, particularly in the case of hemophilia A, has been the development of alloantibodies directed against the factor VIII protein.[59] Administration of factor VIII concentrates will fail to control bleeding in patients with high-titer antibodies. Several approaches to reduce bleeding in these patients include: substitution of porcine factor VIII, administration of activated (FEIBA, Shire Inc., Lexington, MA) or non-activated prothrombin complex concentrates (PCCs), or treatment with recombinant factor VIIa (NovoSeven, Novo Nordisk Inc., Bagsvaerd, Denmark).[60]

ACQUIRED BLEEDING DISORDERS

Drug Induced

Medications represent the most significant cause of acquired coagulopathy in perioperative patients. In addition to anticoagulants such as heparin and warfarin, the increasing number of direct oral anticoagulants(DOACs) and antiplatelet drugs have further complicated perioperative management. An understanding of the effect of these agents and strategies for reversal can be critical to reduce bleeding complications during urgent and emergent procedures. Additionally, there are several classes of medications that may unintentionally increase bleeding risk due to side effects, primarily via platelet inhibition. β-Lactam antibiotics impair platelet aggregation that can result in clinically significant bleeding in patients with higher baseline risk.[61] Nitroprusside,[62] nitroglycerin,[63] and NO[64] also result in decreased platelet aggregation and secretion. Similarly, selective-serotonin reuptake inhibitors, such as paroxetine, decrease platelet serotonin storage, which inhibits platelet aggregation and may have clinical consequences in individuals with preexisting coagulopathies.[65] These medications should be considered in patients with an otherwise unexplained coagulopathy.

Liver Disease

Hemostatic defects associated with hepatic failure prove complex and multifactorial. Severe liver disease impairs synthesis of coagulation factors, produces quantitative and qualitative platelet dysfunction, and impedes clearance of activated clotting and fibrinolytic proteins. The liver is the primary site for the production of procoagulant factors including fibrinogen, prothrombin (factor II), factors V, VII, IX, X, XI, XII, as well as the anticoagulants protein C and S, and AT. Laboratory findings commonly associated with liver disease include a prolonged PT and possible prolongation of the aPTT, suggesting that these individuals are at increased risk of bleeding. However, the abnormal values only reflect the decrease in procoagulant factors and do not account for the concomitant decrease in anticoagulant factors.[66] As a result, patients with chronic liver disease are thought to have a rebalanced hemostasis and actually generate amounts of thrombin equivalent to healthy individuals.[67]

Similarly, thrombocytopenia from splenic sequestration is often observed in patients with liver disease and portal hypertension[68] and is accompanied by platelet dysfunction due to increased production of endothelial NO and prostacyclin resulting in platelet inhibition.[69] Despite these alterations, increases in vWF commonly observed in these patients may serve to restore platelet function. Also, levels of the plasma metalloprotease ADAMTS13, responsible for cleaving vWF multimers, are decreased in chronic liver disease and result in high circulating levels of large vWF multimers that promote platelet aggregation.[70] This increase in vWF may in part correct for thrombocytopenia and platelet dysfunction but also can result in a prothrombotic state and increased clotting risk.

Fibrinolysis of formed clot is also aberrant in patients with liver disease. Normally, fibrin clot is degraded by plasmin, which is converted to its active form by t-PA and urokinase plasminogen activator (u-PA). Excessive fibrinolysis is prevented by thrombin-activatable fibrinolysis inhibitor (TAFI), which blocks activation of plasmin from plasminogen. TAFI is synthesized by the liver and as levels are decreased in patients with chronic liver disease, it was believed that such individuals are at increased bleeding risk due to hyperfibrinolysis.[71] However, levels of PAI-1, a SERPIN of t-PA and u-PA, are also increased in liver disease, which may in actuality normalize fibrinolysis.[72]

In summary, procoagulant and anticoagulant hemostatic mechanisms are rebalanced in patients with chronic

liver disease, but this balance is easily disrupted and these patients are at risk for both bleeding and inappropriate clotting.[73] Traditional coagulation testing does not correlate with bleeding risk in these patients, which has led to studies looking at the use of viscoelastic coagulation testing using thromboelastography (TEG) or rotational thromboelastometry (ROTEM) as a means of assessing functional coagulation and guiding perioperative blood product transfusion and administration of antifibrinolytic agents.[73,74]

Renal Disease

Platelet dysfunction commonly occurs in association with chronic renal failure and uremia, as reflected by a prolonged bleeding time and propensity for bleeding associated with surgery or trauma. The underlying mechanisms are multifactorial but have mostly been attributed to decreased platelet aggregation and adhesion to injured vessel walls. Impaired adhesion is likely due to defects of the glycoprotein IIb/IIIa, which facilitates platelet binding of fibrinogen and vWF.[75,76] Additionally, accumulation of guanidinosuccinic acid and the resulting increase in endothelial NO synthesis further decreases platelet responsiveness.[77] Red blood cell (RBC) concentration has also been speculated to contribute to platelet dysfunction, 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.[78] Both dialysis and correction of anemia have been reported to shorten bleeding times in patients with chronic renal failure. Treatment of platelet dysfunction related to chronic renal disease includes transfusion of cryoprecipitate (rich in vWF) or administration of desmopressin (0.3 μg/kg), which stimulates release of vWF from endothelial cells.[79] Additionally, conjugated estrogens (0.6 mg/kg intravenously for 5 days) have been demonstrated to shorten bleeding times,[80] perhaps via decreased generation of NO.[81]

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) is a pathologic hemostatic response to tissue factor/factor VIIa complex that leads to excessive activation of the extrinsic pathway, which overwhelms natural anticoagulant mechanisms and generates intravascular thrombin. Numerous underlying disorders may precipitate DIC, including trauma, amniotic fluid embolus, malignancy, sepsis, or incompatible blood transfusions.[82] Most often, DIC presents clinically as a diffuse bleeding disorder associated with consumption of coagulation factors and platelets during widespread microvascular thrombotic activity, which results in multiorgan dysfunction. 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 fibrin degradation products. However, DIC is both a clinical and laboratory diagnosis; hence, laboratory data alone do not provide sufficient sensitivity or specificity to confirm a diagnosis.[83] For example, chronic DIC states have been identified with relatively normal screening coagulation tests accompanied by elevated concentrations of soluble fibrin and fibrin degradation products.[84] Management of DIC requires management of the underlying condition precipitating hemostatic activation. Otherwise, treatment is mostly supportive and includes selective blood component transfusions to replete coagulation factors and platelets consumed in the process. The use of anticoagulants such as heparin remains controversial with recommendations that its use be limited to conditions with the highest thrombotic risk.[85] Antifibrinolytic therapy generally is contraindicated in DIC, owing to the potential for catastrophic thrombotic complications.[86]

CARDIOPULMONARY BYPASS-ASSOCIATED COAGULOPATHY

Institution of CPB by directing blood flow through an extracorporeal circuit causes significant perturbations to the hemostatic system. Initial priming of the bypass circuit results in hemodilution and thrombocytopenia.[87] Adhesion of platelets to the synthetic surfaces of the bypass circuit further decreases platelet counts and contributes to platelet dysfunction.[88] During CPB, expression of platelet surface receptors important for adhesion and aggregation (GPIb, GPIIb/IIIa) are downregulated and the number of vWF-containing α granules are decreased, thereby impairing platelet function.[89] Furthermore, induced hypothermia during CPB results in reduced platelet aggregation and plasma-mediated coagulation by decreasing clotting factor production and enzymatic activity.[90] Hyperfibrinolysis may also occur as a result of CPB, supporting the use of antifibrinolytic drugs to decrease intraoperative blood loss.[91]

TRAUMA-INDUCED COAGULOPATHY

Uncontrolled hemorrhage is a frequent cause of trauma-related deaths. Coagulopathy in this setting may be due to acidosis, hypothermia, and hemodilution from resuscitation; however, an independent acute coagulopathy is also experienced by these individuals.[92] Termed trauma-induced coagulopathy (TIC) or acute traumatic coagulopathy, this process involves disordered hemostasis and increased fibrinolysis observed early after injury.[93] The anticoagulant effect of activated protein C (APC) is thought to play a primary role in TIC by decreasing thrombin generation via inhibition of factor Va and VIIIa and promoting fibrinolysis through inhibition of PAI-1. The relevance of APC in the development of TIC is supported by the association of hypoperfusion and increasing injury severity with increased levels of APC activity.[94] Hypoperfusion is thought to be the stimulus for APC activation.[95] Additionally, degradation of the endothelial glycocalyx (EG), a gel-like matrix lining the vascular endothelium, is linked to factors associated with trauma, including tissue damage, hypoperfusion, elevated catecholamines, and inflammation. The EG has anticoagulant properties and contains proteoglycans such as syndecan-1, hyaluronic acid, heparan sulfate, and chondroitin sulfate which are shed during endothelial injury. Shedding of proteoglycans results in an "autoheparinization" phenomenon that contributes to TIC. Markers of EG degradation have been found to be associated with inflammation, coagulopathy, and increased mortality in trauma patients.[96]

Although platelet counts appear to be normal, platelet dysfunction contributes to increased bleeding in TIC. Significant platelet hypofunction in response to various agonists, including ADP, arachidonic acid, and collagen, has

BOX 50.1 Hypercoagulable States and Risk for Perioperative Thrombosis

High Risk

Heparin-induced thrombocytopenia
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

been observed acutely in trauma patients prior to resuscitation.[97,98] It is hypothesized that trauma patients experience "platelet exhaustion" as a result of activation from widespread release of ADP from injured tissues. This diffuse activation renders platelets unresponsive to subsequent stimulation.[98] Platelet insensitivity to ADP is also associated with increased susceptibility of clots to tPA-mediated fibrinolysis.[99] The importance of early treatment to reduce hyperfibrinolysis in trauma is supported by the findings of the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2 (CRASH-2) trial, which demonstrated a mortality benefit from early administration of tranexamic acid (TXA).[100,101]

PROTHROMBOTIC STATES

Thrombophilia, a propensity for thrombotic events, commonly manifests clinically in the form of venous thrombosis (frequently deep venous thrombosis [DVT] of the lower extremity).[102] As with bleeding disorders, thrombophilia may result from inherited or acquired conditions (Box 50.1). The pathogenesis of thrombosis is thought to be due to Virchow's triad (blood stasis, endothelial injury, and hypercoagulability).[9] In the majority of cases, a risk factor or precipitating event is identified; however, a single factor generally does not result in clinically significant thrombosis.[103] Instead, multiple factors act synergistically to increase risk.[104] For example, thrombotic complications often occur after surgery or during pregnancy in association with obesity, underlying malignancy, or an inherited thrombophilia.[105] Random screening of asymptomatic patients for thrombotic risk has not proven cost effective or clinically efficacious.[106,107] As with bleeding disorders, a history focusing on prior thrombotic events, family history of thrombosis, and concurrent drug therapy offers greater predictive value than random screening.

INHERITED THROMBOTIC DISORDERS

Improvements in biochemical and molecular testing have dramatically improved our understanding of blood coagulation and the prevalence of prothrombotic disorders.[108] Because of more specific testing, an inheritable thrombotic predisposition is identified in as many as 50% of patients presenting with venous thromboembolism.[109] The most common inherited prothrombotic conditions include single point mutations in genes for factor V (factor V Leiden) or prothrombin (prothrombin G20210A). In the case of the factor V Leiden, the mutation results in APC resistance whereby the essential cofactor Va is no longer susceptible to APC-mediated degradation. This simple alteration in balance between hemostasis and the APC counter-regulatory system induces a prothrombotic condition present in approximately 5% of the Caucasian population.[110] In the case of the prothrombin gene mutation, increased prothrombin concentrations in plasma generate a hypercoagulable state. Less common inherited forms of thrombophilia include deficiencies of AT, protein C, or protein S.[108] Inherited forms of thrombophilia are characterized by highly variable penetrance affected by blood type, sex, and other confounding variables. Environmental factors such as oral contraceptive use, pregnancy, immobility, infection, surgery, or trauma greatly affect the incidence of thrombosis in those with an inherited predisposition.[111] In the absence of coexisting precipitating conditions, presence of a family history, test abnormality suggesting thrombophilia, or history of thrombosis, risks associated with long-term preventive anticoagulation may outweigh potential benefits.[106] After a thrombotic complication, however, these patients most often are managed with life-long anticoagulation.

ACQUIRED THROMBOTIC DISORDERS

Antiphospholipid Syndrome

Antiphospholipid syndrome (APS) describes an acquired autoimmune disorder characterized by venous or arterial thromboses, or both, and recurrent pregnancy loss. This syndrome may occur in association with autoimmune disorders such as systemic lupus erythematosus or rheumatoid arthritis, or it may occur in isolation. APS results from development of autoantibodies directed against phospholipid-binding proteins, which affect the coagulation system and is associated with up to 10% of cases of DVT and 6% of pregnancy-associated morbidity.[112] Characteristically, APS results in mild prolongation of the aPTT and positive testing for lupus anticoagulant, anticardiolipin or anti-β2-glycoprotein I antibodies.[113] Antibodies associated with APS interfere with phospholipids common to many laboratory-based tests of coagulation. Despite the prolonged aPTT, APS poses no increased bleeding risk but rather increases the potential for thrombosis. Isolated prolongation of an aPTT in a preoperative patient merits consideration of the diagnosis of APS. 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.[114]

HEPARIN-INDUCED THROMBOCYTOPENIA

Heparin-induced thrombocytopenia (HIT) describes an autoimmune-mediated drug reaction occurring in as many as 5% of patients receiving heparin therapy. Patients with HIT experience a mild-to-moderate thrombocytopenia. As opposed to other drug-induced thrombocytopenias, HIT

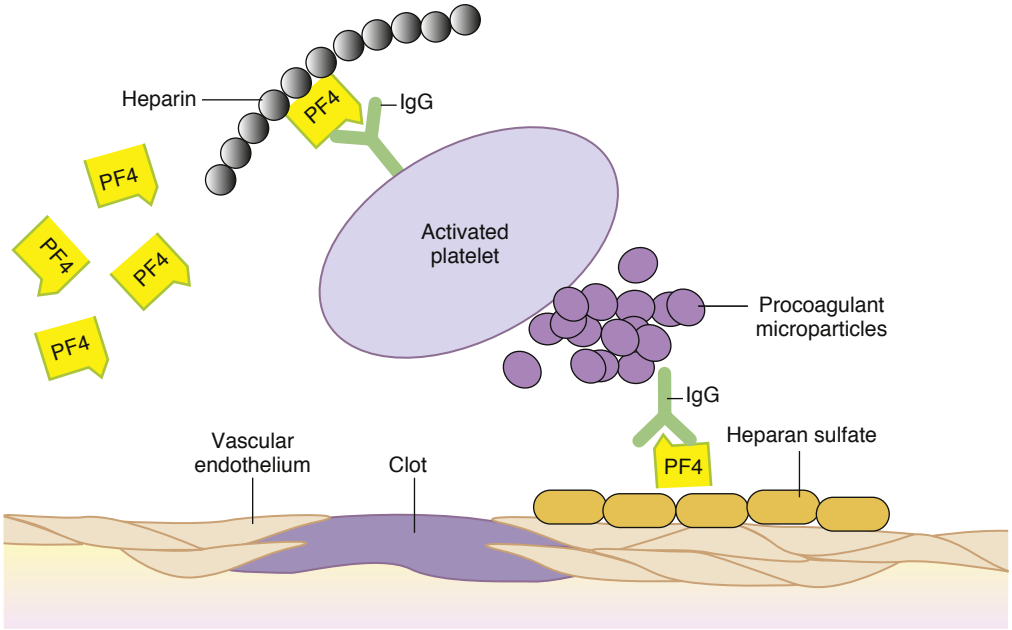

Fig. 50.4 Mechanisms Underlying Thrombosis in Heparin-Induced Thrombocytopenia. Immune complexes composed of heparin, platelet factor 4 *(PF4)*, and antibodies bind to platelet surface Fcγ receptors to activate platelets. PF4/heparin immune complexes further activate vascular endothelium, monocytes, and macrophages to increase tissue factor expression. *IgG,* Immunoglobulin G. (From Slaughter TF, Greenberg CS. Heparin-associated thrombocytopenia and thrombosis: Implications for perioperative management. *Anesthesiology*. 1997;87:669, with permission.)

results in platelet activation and potential for venous and arterial thromboses.[115] 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. 50.4). Risk factors for development of HIT include patient population, gender, and heparin formulation used. Women are at increased risk of HIT (odds ratio [OR] 2.37; 95% CI 1.37-4.09) as are surgical patients compared to medical patients (OR 3.25; 95% CI 1.98-5.35). [116] Given the high doses of heparin administered during cardiac surgery with CPB, these patients have a higher incidence of anti-PF4 antibody development (up to 50%); however, the incidence of HIT in this population appears to be similar to other surgical groups.[117] Use of unfractionated heparin (UFH) carries a greater risk of HIT development than low-molecular-weight heparin (LMWH) (absolute risk 2.6% vs. 0.2%).[118] Patients developing HIT during heparin therapy experience substantially increased risk for thrombosis (OR 20:40, absolute risk 30% to 75%).[115]

HIT manifests clinically as thrombocytopenia occurring 5 to 14 days after initiating heparin therapy. With prior heparin exposure, thrombocytopenia or thrombosis may occur within 1 day. A diagnosis of HIT should be entertained for any patient experiencing thrombosis or thrombocytopenia (absolute or relative ≥ 50% reduction in platelet count) during or after heparin administration. Although HIT remains a clinical diagnosis, HIT antibodies testing should be undertaken to confirm the diagnosis. The enzyme-linked immunosorbent assay (ELISA) is sensitive, but not as specific as the serotonin release assay (SRA), because the SRA indicates heparin-induced platelet activation. For many intensive care patients, a positive ELISA test does not lead to a positive SRA, which means these patients are unlikely to have HIT.[119]

In cases where HIT is suspected, heparin must be discontinued immediately (including UFH, LMWH, heparin-bonded catheters, heparin flushes). Alternative nonheparin anticoagulation must be administered concurrently. In most cases, a direct thrombin inhibitor (DTI, e.g., bivalirudin, lepirudin, or argatroban) is substituted for heparin until adequate prolongation of the international normalized ratio (INR) can be achieved with warfarin. Initiation of warfarin alone is contraindicated for HIT treatment because the initial decreased synthesis of proteins C and S enhances the patient's prothrombotic state. Platelet transfusions should be held unless the patient is severely thrombocytopenic ($<20 \times 10^9$/L) with signs of bleeding. Use of DOACs (e.g., rivaroxaban, apixaban, dabigatran, edoxaban) is being investigated.[120]

Typically, PF4/heparin immune complexes are cleared from the circulation within 3 months. If possible, patients experiencing HIT should avoid future exposure to UFH; however, several reports describe subsequent limited perioperative reexposure to UFH after laboratory testing to ensure absence of PF4/heparin immune complexes. If titers remain high, treatment with plasmapheresis for rapid antibody clearance is an alternative plan, but risks and benefits should be discussed with the hematologists.[121] Otherwise, bivalirudin, the shortest acting DTI, is the alternative agent for anticoagulation while on CPB.

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. The ideal test for perioperative coagulation should be 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

Prothrombin Time

The PT assesses the 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. It is sensitive to deficiencies in fibrinogen, and factors II, V, VII, or X. As three of these factors have vitamin K-dependent synthesis (factors II, VII, and X), the PT assay has been used to monitor anticoagulation with vitamin K antagonists (VKAs) such as warfarin. The thromboplastin reagent, derived from animal or recombinant sources, can vary in its ability to bind factor VII and initiate coagulation, which limits interlaboratory comparisons. 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.[122]

Thromboplastin reagents are tested against an international recombinant standard and assigned an international sensitivity index (ISI) based on the results. The INR subsequently is calculated as INR = (patient PT/standard PT)^{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. The PT is more sensitive at detecting decreases in factors VII and X than levels of fibrinogen and factors II and V; however, due to variations in thromboplastin reagents, factor levels as low as 40% to 50% may not prolong the PT.[123]

Any prolongation of the PT should be assessed further with mixing studies to determine whether delayed clot formation is attributable to a coagulation factor deficiency or an inhibitor (e.g., antiphospholipid antibody, fibrin degradation 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 whereas time to clot formation will not correct in the presence of an inhibitor.

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 (e.g., celite, kaolin, silica, or ellagic acid). The aPTT is more sensitive to deficiencies in factors VIII and IX than other factors in the intrinsic and common pathways. In most cases, coagulation factor levels below 30% to 40% of normal are detectable; however, aPTT reagents vary in their sensitivity to factor concentrations and may not be prolonged until levels drop below 15% for some factors.[124] Additionally, as there is no reference standard reagent for the aPTT analogous to the INR for PT, individual institutions must set their own normal ranges and aPTT values cannot be compared between laboratories.

Monitoring anticoagulation during cardiac and vascular surgery remains necessary given the widely acknowledged pharmacokinetic and pharmacodynamic response to heparin. Patient-specific factors affecting response to heparin include age, weight, intravascular volume, and concentrations of AT, heparin cofactor II, PF4, and other heparin-binding proteins. Therefore, patients experience widely divergent anticoagulant responses to identical weight-based doses of heparin. In situations where heparin therapy must be initiated in patients with a baseline aPTT prolongation (lupus anticoagulant or factor inhibitors), alternative tests such as anti-factor Xa activity or heparin level measurements must be used.

Anti-Factor Xa Activity

The anti-factor Xa activity assay or factor Xa inhibition test is being used with increasing frequency to monitor heparin anticoagulation instead of, or in addition to, the aPTT assay. The assay involves combining patient plasma with reagent factor Xa and an artificial substrate that releases a colorimetric signal after factor Xa cleavage, thereby providing a functional assessment of heparin anticoagulant effect.[125] While aPTT values can be affected by several patient factors such as coagulation factor deficiencies, factor inhibitors, or the presence of lupus anticoagulant, measurement of the heparin-bound AT inhibition of factor Xa activity is not influenced by these variables. Anti-factor Xa testing can also be used to measure the effect of other anticoagulants such as LMWH, fondaparinux, and factor Xa inhibitors. As with the aPTT assay, the anti-factor Xa test lacks adequate standardization, and activity levels vary based on the type of assay used, and patient population assayed.[126] Furthermore, significant discordance between aPTT and anti-factor Xa results can be observed in hospitalized patients receiving heparin therapy.[127] Data supporting the use of anti-factor Xa over aPTT is sparse; however, it may be helpful to use anti-factor Xa testing in combination with the aPTT to monitor both heparin effect and generalized coagulation status, respectively.

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, but platelet counts exceeding 100,000 μL commonly are associated with normal hemostasis. Abnormally low platelet counts merit further assessment, including a visual platelet count from a blood smear. Sample hemodilution and platelet clumping are common etiologies for falsely low platelet counts.

With the growth of point-of-care platelet function monitors, the bleeding time has declined in popularity. 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.[128] In general, the bleeding time is not predictive of bleeding and for that reason its use as a preoperative screening test to assess bleeding risk is not recommended.[129]

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 tests applicable in the perioperative setting may be considered in four broad categories: (1) functional measures of coagulation that measure the intrinsic ability of blood to generate clot, (2) heparin concentration monitors, (3) viscoelastic measures of coagulation, and (4) platelet function monitors.

Activated Clotting Time

The activated clotting time (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.[130] 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 (Hepcon HMS Plus, Medtronic, Minneapolis, MN). With clot formation, the flag descent slows, which triggers an optical detector and sets off an alarm to signal completion of the ACT.

The ACT in normal individuals is 107 ± 13 seconds. 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 response at high heparin concentrations. Limitations of ACT monitoring include lack of sensitivity at low heparin concentrations and poor reproducibility.[131] Further limitations of the ACT include artefactual prolongation of results with hemodilution or hypothermia, and values beyond 600 seconds exceed the linear response range for the assay. Although duplicate measurements improve results, newer electrochemically based ACT analyzers (i-STAT, Abbott, Princeton, NJ) improve reproducibility such that single ACT determinations may prove adequate.

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. This methodology allows for an estimate of heparin concentration. 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.[132] Current point-of-care heparin concentration monitoring employs automated measurement techniques (Hepcon HMS Plus, Medtronic, Minneapolis, MN). The advantages of measuring heparin concentration include sensitivity for low heparin concentrations as well as relative insensitivity to hemodilution and hypothermia. A major limitation of heparin concentration monitoring is failure to assess directly for an anticoagulant effect. For example, consider a patient with a homozygous deficiency of AT; in this case, heparin concentration determination alone would fail to identify the lack of anticoagulant effect after heparin administration.

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 the entire spectrum of clot formation in whole blood from early fibrin strand generation through clot retraction and fibrinolysis. The early TEG developed by Hartert in 1948 has evolved into two independent viscoelastic monitors: the modern TEG (TEG 5000 Thromboelastograph Hemostasis Analyzer System, Haemoscope, Braintree, MA) and ROTEM (TEM Systems, Durham, NC).[133] In the case of the 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.[134]

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. The R value may be prolonged by a deficiency of one or more plasma coagulation factors or inhibitors such as heparin. Maximum amplitude provides a measure of clot strength and may be decreased by either qualitative or quantitative platelet dysfunction or decreased fibrinogen concentration. The α angle and K (BiKoatugulierung 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 coagulation activation. Specific activators differ from that of the TEG with resulting quantitative measures termed (1) coagulation time (seconds), (2) α angle (clot formation time; seconds), (3) maximal clot firmness (MCF; millimeter), and (4) lysis time (LT; second)(Fig. 50.5 on TEG in attached file).

In contrast to TEG and ROTEM, an alternative viscoelastic measure of coagulation (Sonoclot Analyzer, Sienco Inc., Arvada, CO) 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.[133] 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 TEG and ROTEM have been demonstrated to reduce blood administration.[135,136] More widespread application of viscoelastic monitoring has been hindered by lack of specificity associated with abnormal findings and qualitative assay interpretation.[137] 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 are 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.[138] Lack of standardized quality controls necessitates use of local donor blood to establish normal control ranges. Complicating assessment further is the fact that platelets are highly susceptible to activation or desensitization during sample collection, transport, storage, and processing.

The technique for platelet aggregometry was developed in the 1960s and soon became the gold standard for assessment of platelet function.[139] The classic method involves centrifugation of patient blood to obtain platelet-rich plasma, which is then analyzed in a cuvette at 37°C placed between a light source and photocell. Addition of platelet agonists such as ADP, epinephrine, collagen, and ristocetin, stimulates platelet aggregation, which in turn results in a decrease in turbidity of the solution and an increase in light transmission. Patterns based upon the kinetics and amplitude of response to these various agonists are associated with specific platelet disorders and aid in diagnosis.[140] In an effort to decrease the labor required to prepare the platelet rich plasma solution as well as to include the effect of RBCs and plasma proteins on platelet function, a technique for whole blood aggregometry was developed.[141] Whole blood aggregometry uses platinum electrodes onto which platelets adhere. Platelet aggregation induced by agonists results in increased adhesion of aggregates to the electrodes, raising the impedance which is measured over time. A multichannel system (Multiplate Analyzer, Roche Diagnostics, Indianapolis, IN) is available and is used to diagnose platelet dysfunction as well as monitor anti-platelet therapy.[142] Flow cytometry employing fluorescent-labeled antibodies provides another sensitive method for quantitating platelet activation, responsiveness, and surface receptor availability.[143] Despite representing standards of care, these measurements remain technically challenging, costly, and time-consuming laboratory-based assays.

Although viscoelastic measures of coagulation (i.e., TEG or ROTEM) may detect platelet dysfunction, the sensitivity and specificity are limited. Incorporation of a platelet mapping assay into TEG provides a method for viscoelastic measurement of drug-induced platelet inhibition with reasonable correlation to optical aggregometry.[134]

Fortunately, an increasing array of platelet function assays specifically designed as point-of-care instruments are becoming available.[140] As a measure of primary hemostasis, a platelet function analyzer (PFA-100, Siemens, Tarrytown, NY) increasingly has replaced the bleeding time in assessment of hemostasis. The PFA-100 incorporates high-shear conditions to simulate small vessel injury in the presence of either ADP or epinephrine, both potent platelet activators.[144] Time to clot-mediated aperture occlusion is reported as closure time. The PFA-100 has proven effective in detecting vWD 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.

Many other different point-of-care platelet function testing devices are on the market today. It is important to keep in mind that monitors from different manufacturers measure differing aspects of platelet-mediated or plasma-mediated hemostasis. When 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 are essential to inform patient care. Also, in considering any point-of-care coagulation testing, it must be recognized that results will not necessarily mirror those reported from laboratory-based

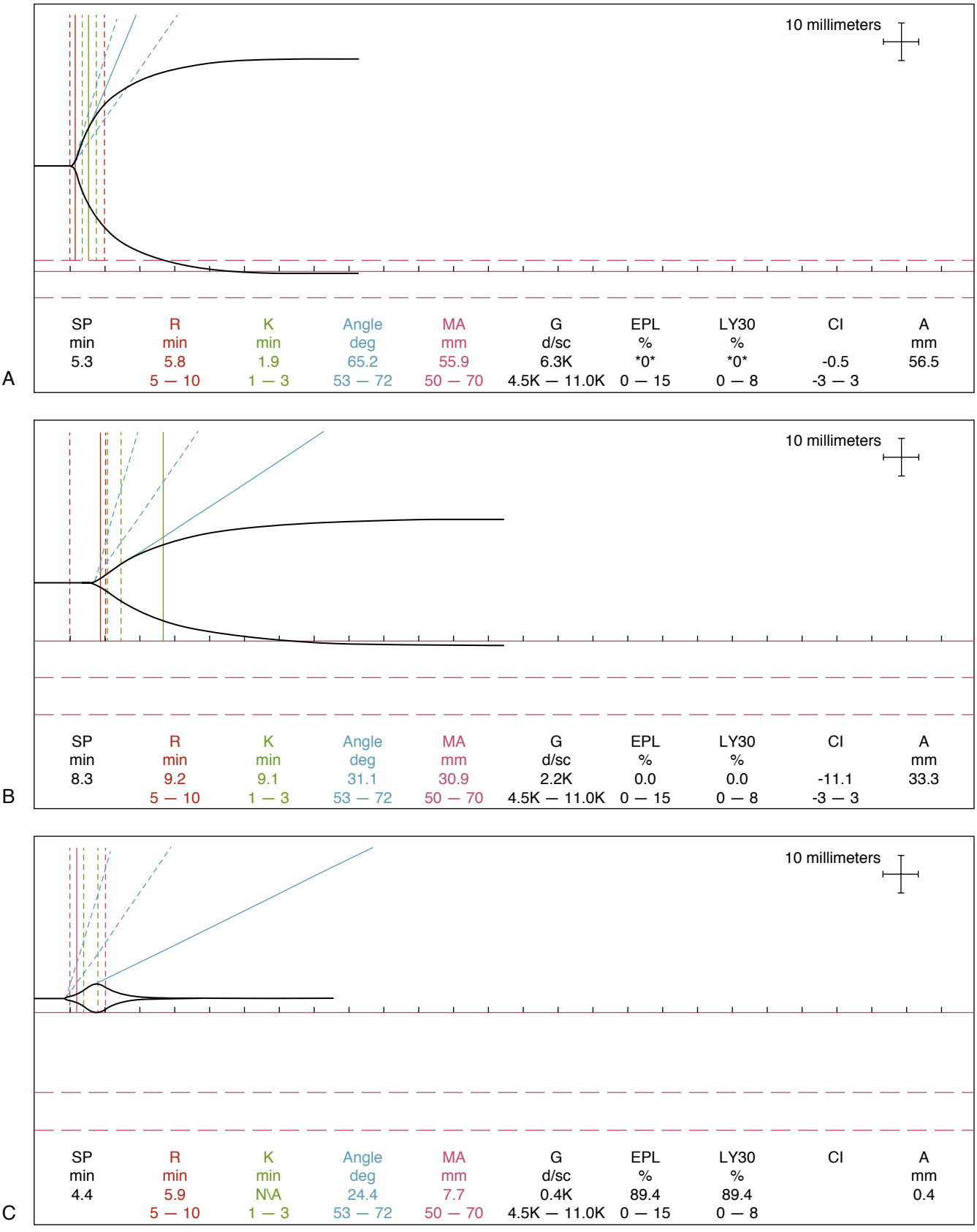

Fig. 50.5 Thromboelastographs from kaolin-activated samples analyzed using a TEG 5000 system depicting (A) normal coagulation, (B) hypofibrinogenemia, and (C) hyperfibrinolysis .

testing because of differences between using whole blood samples for testing as opposed to plasma or processed platelets. Reagent sensitivities can vary across manufacturers and lots. Hopefully, further advances in point-of-care coagulation monitoring will offer the opportunity for clinicians to make informed, bedside decisions about transfusion therapy and hemostatic drug administration to minimize perioperative bleeding and adopt effective patient blood management practices.

Antithrombotics, Thrombolytics, and Procoagulant Drugs

In the following sections, we will briefly review some common medications used to decrease or increase clot formation and then examine perioperative management strategies to reverse anticoagulants. This is not intended to be an exhaustive list of all FDA-approved drugs, so only more commonly used medications are discussed here.

Starting with antithrombotic drugs, these drugs are usually used to reduce the formation of blood clots in the setting of coronary or cerebral atherosclerosis or after vascular thrombosis. They can be further subdivided into antiplatelet agents and anticoagulants (Table 50.1).

TABLE 50.1 Common Classes of Antithrombotics, Thrombolytics, and Procoagulants

Category	Subcategory	Generic Drug Names
Antiplatelet agents	Cyclooxygenase inhibitors	Aspirin, NSAIDS
	P2Y12 receptor antagonists	Ticlopidine, clopidogrel, prasugrel, cangrelor, and ticagrelor
	Platelet GPIIb/IIIa antagonists	Abciximab, eptifibatide, and tirofiban
Anticoagulants	Vitamin K antagonists	Warfarin
	Heparin	UFH, LMWH, fondaparinux
	Direct thrombin inhibitors	Argatroban, bivalirudin (IV) Desirudin (SQ) Dabigatran (PO)
	Factor Xa inhibitors	Rivaroxaban, apixaban, edoxban
Thrombolytics	Fibrin-specific agents	Alteplase, reteplase, tenecteplase
	Non-fibrin-specific agents	Streptokinase
Antifibrinolytics	Lysine analogs	Tranexamic acid, epsilon-aminocaproic acid
Factor Replacements	Recombinant Factor VIIa	
	Factor VIII-vWF	
	Prothrombin complex concentrates	3-factor PCC; 4-factor PCC, activated PCC, FEIBA
	Fibrinogen concentrates	

FEIBA, Factor VIII Bypass Activity; *IV,* intravenous; *LMWH,* low-molecular-weight heparin; *NSAIDS,* nonsteroidal antiinflammatory drugs; *PCC,* prothrombin complex concentrate; *PO,* per os, by mouth; *SQ,* subcutaneous; *UFH,* unfractionated heparin; *vWF*, von Willebrand factor.

ANTIPLATELET AGENTS

Antiplatelet agents inhibit thrombus formation by inhibiting platelet aggregation and/or adhesion to clot or damaged endothelium. Depending on the drug, they can work either reversibly or irreversibly. Most common antiplatelet agents can be divided into: (1) cyclooxygenase (COX) inhibitors, (2) P2Y12 receptor antagonists, and (3) platelet GPIIb/IIIa antagonists, although there are several other classes available such as phosphodiesterase inhibitors, protease-activated receptor-1 antagonists, adenosine reuptake inhibitors, and thromboxane inhibitors.

Cyclooxygenase Inhibitors

Aspirin and NSAIDS are the two primary members of this class. There are two forms of the cyclooxygenase enzyme: COX-1 and COX-2. COX-1 maintains the integrity of the gastric lining and renal blood flow and initiates the formation of thromboxane A_2 (TxA_2), which is important for platelet aggregation. COX-2 is responsible for synthesizing the prostaglandin mediators in pain and inflammation.

Aspirin

Aspirin is a non-selective and irreversible COX inhibitor. It acetylates a serine residue on COX-1 and prevents the production of TxA_2 in platelets.[145] COX-2, which leads to antiinflammatory and analgesic effects, is 170 times less sensitive than COX-1 to aspirin so only at high doses can aspirin irreversibly inhibit both COX-1 and COX-2.[146] Because platelets are anuclear, they are unable to synthesize new COX-1 once aspirin has irreversibly inhibited the enzyme. Consequently, despite its short half-life of approximately 15 to 20 minutes, aspirin's inhibitory effect persists through the platelet lifespan of 7 to 10 days.[147]

The recovery of platelet function after aspirin depends on platelet turnover. Generally, megakaryocytes generate 10% to 12% of platelets daily, so near normal hemostasis is expected in 2 to 3 days after the last dose of aspirin with typical platelet turnover. High platelet turnover diseases, which result from increased production (e.g., essential thrombocythemia) or increased consumption (e.g., inflammation), may require more frequent than once daily aspirin dosing.[148] Immediate reversal of aspirin for emergencies can be achieved with platelet transfusions.

NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Most NSAIDS are nonselective, reversible COX inhibitors and therefore provide antipyretic, analgesic, and antiplatelet aggregation effects.[149] Platelet function normalizes 3 days after discontinuing the use of NSAIDS. Selective COX-2 antagonists such as celecoxib were introduced in the late 1990s to provide antiinflammatory, analgesic, and

antipyretic activity without the gastrointestinal complications,[150] but clinical trials with selective COX-2 antagonists have reported increased risks for cardiovascular complications.[151] COX-2 specific inhibitors do not affect platelet function because platelets do not express COX-2. The increased cardiovascular risk is thought to be due to inhibition of PGI_2 without inhibition of TxA_2, thus tipping the balance toward thrombosis. Current recommendations are to use COX-2 inhibitors only when necessary for pain and then with the lowest effective dose possible after weighing the risks and benefits.[152]

P2Y12 RECEPTOR ANTAGONISTS

These drugs (ticlopidine, clopidogrel, prasugrel, cangrelor, and ticagrelor) interfere with platelet function by inhibiting the P2Y12 receptor, which inhibits platelet adhesion and aggregation by preventing the expression of GPIIb/IIIa on the surface of activated platelets.[153] Ticlopidine, clopidogrel, and prasugrel are members of a class known as thienopyridines, and are pro-drugs requiring hepatic metabolism to generate the active metabolite that then irreversibly inactivates the ADP-binding site of the P2Y12 receptor.[154] Ticagrelor and cangrelor are reversible inhibitors.

Clopidogrel (Plavix) is the most commonly prescribed agent in this class. Platelet functions normalize 7 days after discontinuing clopidogrel and 14 to 21 days after discontinuing ticlopidine. Because clopidogrel is a pro-drug and requires CYP2C19 for activation, it has wide interindividual variability in inhibiting ADP-induced platelet function. Although many factors may be involved in this variability, genetic polymorphism of CYP2C19 along with ABCB1, which affects the intestinal permeability and oral bioavailability of clopidogrel, are thought to play a significant role.[155] Patients treated with clopidogrel who have decreased CYP2C19 and ABCB1 activity were shown to have increased risk of major cardiovascular events.[156] The FDA put a black box warning on clopidogrel to make patients and healthcare providers aware that CYP2C19-poor metabolizers, representing up to 14% of patients, are at high risk of treatment failure and that genotype testing may be helpful prior to drug initiation.[157]

Ticagrelor binds to the P2Y12 receptor at a different site than the thienopyridines, and causes a conformational change of the receptor.[158] While ticagrelor needs to undergo metabolism to an active metabolite, both the parent drug and the active metabolite have anti-platelet effects.[159] Genetic polymorphisms do not appear to be clinically relevant for this drug.[160] Because it is much shorter acting than clopidogrel, ticagrelor must be dosed twice daily, which may be of benefit prior to surgery.

The newest drug in this group is cangrelor. It is the only one available for intravenous administration, and like ticagrelor, it changes the conformation of the P2Y12 receptor, resulting in inhibition of ADP-induced platelet aggregation.[158] It received FDA approval in 2015 for adult patients undergoing percutaneous coronary intervention (PCI). This drug has the fastest onset of action (seconds), and platelet function normalizes within 60 minutes after drug discontinuation.[161] This rapid onset may allow for bridging therapy in patients with drug-eluting stents who require surgery.

GLYCOPROTEIN IIB/IIIA INHIBITORS

Glycoprotein IIb/IIIa inhibitors (GPI) (abciximab, eptifibatide, and tirofiban) work to prevent platelet aggregation by decreasing the binding of fibrinogen and vWF to glycoprotein IIb/IIIa receptors on the surface of activated platelets.[162] They are given intravenously in order to: (1) stop ongoing arterial thrombosis or (2) eliminate excessive platelet reactivity in diseased vessels so that occlusive thrombi and restenosis do not occur. Their use was highly touted in the past with balloon angioplasty where acute closure was a feared complication. Now with the introduction of stents and P2Y12 receptor antagonists, GPI have become less popular in routine PCI because of the associated bleeding risk and their use is only recommended in a subset of patients with high risk angiographic features or those not loaded adequately with dual antiplatelet agents.[163] Although abciximab has a short plasma half-life (approximately 10 minutes), its effects on platelet function can be seen for much longer, even after the infusion has been stopped. One rare, but serious side effect to be aware of, abciximab can produce thrombocytopenia immediately after drug administration in a small proportion of patients. Mild thrombocytopenia (platelet count $<100 \times 10^9$/L) developed more frequently in patients treated with the drug than control subjects (4.2% vs. 2.0%; $P < .001$).[164]

ANTICOAGULANTS

Vitamin K Antagonists

Warfarin, the most frequently used oral VKA in the United States, inhibits the vitamin K-dependent carboxylation of coagulation factors II, VII, IX, and X and proteins C and S. Warfarin is highly effective in reducing the risk of venous and arterial thromboemboli, and is still the anticoagulant of choice for patients with valvular atrial fibrillation and mechanical heart valves despite the popularity and increased utilization of DOACs for nonvalvular atrial fibrillation. [165]

Warfarin has a long half-life (40 hours) and the complete anticoagulant effect can take 3 to 4 days to emerge because of the long half-lives of the preexisting coagulation factors. Prothrombin (factor II) has the longest half-life (~60 hours). Factor VII and protein C have the shortest half-lives (3-6 hours).[166] Because of this long initiation period, patients at high risk for thromboembolism must be bridged with another anticoagulant (usually UFH or LMWH) until the target INR is achieved. Also, early reductions in the anticoagulant protein C can cause an imbalance toward a hypercoagulable state if warfarin is started alone, resulting in thrombosis or warfarin-induced skin necrosis.

Warfarin is monitored using the INR, and the therapeutic range for warfarin anticoagulation is generally an INR of 2.0 to 3.0, except for patients with mechanical heart valves, where higher values are necessary (INR 2.5-3.5). The INR is not calibrated to evaluate non-warfarin deficiencies such as liver disease and should not be used to evaluate therapeutic effects of other anticoagulants. Warfarin has a very narrow therapeutic window and can be easily affected by drug-drug interactions and patient variability. The need for frequent laboratory monitoring makes warfarin a difficult drug for patients to maintain compliance and the reported

time in therapeutic range is only about 65% ± 20% in patients with atrial fibrillation.[167]

Warfarin's pharmacology can be affected by genetic variations in the metabolism of the drug (CYP2C9) and in the production of a vitamin K epoxide reductase enzyme (VKORC1), which reduces vitamin K after it has been oxidized. Recent meta-analyses of randomized trials found that pharmacogenetics testing for polymorphisms unfortunately did not reduce rates of bleeding or thromboembolism.[168] Current recommendations are to only perform pharmacogenetics testing in patients who consistently have INRs outside the therapeutic range or who have an adverse event while on therapy.[169]

Unfractionated Heparin

UFH can be isolated from porcine or bovine intestines and is a mixture of different length polysaccharides with a high molecular weight (mean molecular weight around 15,000 daltons or 35-45 polysaccharide units).[170] UFH binds to AT and indirectly inhibits thrombin (factor IIa) and factor Xa. Benefits of heparin are its short half-life and full reversibility with protamine. Heparin does not have any fibrinolytic activity, so it will not lyse an existing clot.

Full-dose heparin for cardiac surgery is administered as an intravenous bolus of 300 to 400 U/kg. An ACT greater than 400 to 480 seconds is usually considered safe for initiation of CPB. Patients may be resistant to UFH if they have a hereditary deficiency of AT or an acquired deficiency of AT from prolonged heparin administration. The incidence of heparin resistance during CPB is reported at approximately 21%.[171] Simply increasing the dose of heparin in patients with an AT deficiency is often not effective. For these patients, treatment should be with fresh frozen plasma (FFP) transfusions or AT concentrate, which will replenish AT levels and restore heparin response.[172] Other causes of heparin resistance can be due to increased heparin clearance, increased levels of heparin-binding proteins, or elevations of fibrinogen and factor VIII levels.

Low Molecular Weight Heparin and Fondaparinux

LMWH, produced by cleaving UFH into shorter fragments (mean molecular weight approximately 4000 daltons, approximately 15 saccharide units)[173] and fondaparinux, a synthetic pentasaccharide (mean molecular weight 1700 daltons) of the AT binding region of heparin, act more specifically via AT to inhibit factor Xa. LMWH and fondaparinux do not affect the aPTT assay, and coagulation testing is usually not needed. Anti-factor Xa activity levels may be necessary in patients who may have unpredictable drug levels (e.g., renal failure, pregnancy, and body weight less than 50 kg or more than 80 kg).

LMWH has a longer half-life than heparin and can be administered subcutaneously either once or twice daily. LMWH is primarily excreted by the kidney, so its half-life is prolonged in patients with renal failure. Approximately 25% to 50% of LMWH molecules contain 18 or more saccharide units and can inhibit factor Xa and thrombin, while the remaining 50% to 75% of LMWH molecules contain <18 saccharide units and only inhibit factor Xa. [174] Protamine requires more than 14 saccharide units in the heparin molecule for interaction. [175] Therefore, protamine is only partially effective in reversing LMWH. It does not completely abolish the anti-Xa activity, but it may neutralize the higher molecular weight fractions of LMWH.

Fondaparinux has a much longer half-life (17-21 hours) and can be dosed daily.

Because it is only 5 saccharide units, protamine is not effective for reversing fondaparinux.[176] Because antigen formation by the PF4/heparin complex requires a polysaccharide chain of at least 8 to 10 saccharides, fondaparinux-associated HIT is unlikely to occur,[177] and only eight cases of possible fondaparinux-associated HIT have been reported in the literature.[178] Currently, fondaparinux is not FDA approved for use in HIT, but there is considerable positive anecdotal experience in the literature (e.g., decreased bleeding risk) when compared with DTIs.[179]

Direct Thrombin Inhibitors

DTIs bind directly to thrombin and do not require a cofactor such as antithrombin to exert their effect. All DTIs inhibit thrombin in its free (soluble) and fibrin-bound (insoluble) states, unlike heparin, which only has effect on free thrombin. Other advantages over heparin include: lack of binding to other plasma proteins that leads to a more predictable anticoagulant effect, and no concern for developing an immune-mediated thrombocytopenia.

Hirudin is a naturally occurring anticoagulant found in leeches, while argatroban and bivalirudin are synthetic agents. Argatroban, with a half-life of 45 minutes, is the preferred DTI in patients with renal insufficiency because it is eliminated by the liver. It reversibly binds to the active site on thrombin. Argatroban is FDA approved for the prophylaxis and treatment of thrombosis and for PCI anticoagulation in patients with HIT. Clinical effects are usually monitored with aPTT or ACT in the operating room. Dosing goals are to maintain an aPTT 1.5 to 3 times baseline. Because argatroban prolongs thrombin-dependent coagulation, the PT and INR will be prolonged as well, which can complicate transition to warfarin therapy for long-term anticoagulation.[180]

Bivalirudin, a 20-amino acid synthetic analogue of hirudin, is a reversible DTI, and is metabolized by proteolytic cleavage and hepatic metabolism.[181] It has the shortest half-life among the intravenous DTIs and is the drug of choice for patients with both renal and hepatic dysfunction, although dose adjustments are still necessary. In studies, bivalirudin has been shown to have better efficacy in preventing primary outcomes with lower bleeding rates when compared with UFH for percutaneous transluminal coronary angioplasty for unstable or postinfarction angina,[182] and for use as an alternative to heparin in patients with HIT undergoing PCI.[183]

Desirudin was approved in 2010 and is the only DTI available for subcutaneous administration. An early, small, open label study (16 patients) showed that desirudin may be a potentially cost-effective alternative to argatroban for patients with suspected HIT.[184] Desirudin also has more predictable pharmacokinetics, and dosage adjustments and aPTT monitoring may be unnecessary in patients with a creatinine clearance greater than 30 mL/min.[185]

Direct Oral Anticoagulants

Several new oral anticoagulants have been introduced into the market over the past 10 years. These new drugs have more predictable pharmacokinetics and pharmacodynamics

and fewer drug-drug interactions, allowing them to be dosed without daily laboratory monitoring. The drawback has been the lack of specific antidotes for anticoagulation reversal, but this is slowly changing with the introduction of idarucizumab.

Most DOACs are approved for prevention of venous thromboembolism after hip or knee replacement surgery, treatment and secondary prevention of venous thromboembolism, and prevention of stroke in nonvalvular atrial fibrillation. Many are also being studied for use in secondary prevention of coronary events after acute coronary syndrome, prevention of thrombosis in elective PCI, and prevention of thrombus formation on mechanical heart valves. The results from early preclinical trials have been positive and encourage further randomized trials, so increased impact of these agents in the future is expected.[186] The DOACs have a shorter half-life than warfarin and have demonstrated noninferior efficacy to warfarin. A meta-analysis of phase II and phase III randomized clinical trials comparing DOACs with VKAs in patients with atrial fibrillation showed that use of DOACs was associated with a significant reduction in major bleeding (Relative risk [RR] 0.86, 95% CI 0.72-1.02) and a significantly decreased risk of intracranial hemorrhage (RR 0.46, 95% CI 0.39-0.56).[187]

Dabigatran (Pradaxa), an oral DTI, was the first new antithrombotic agent approved for the prevention of ischemic stroke in patients with non-valvular atrial fibrillation since warfarin. When given at a dose of 150 mg twice daily, dabigatran was shown to reduce the risk of stroke while having a similar bleeding risk as warfarin at an INR of 2.0 to 3.0.[188] Although the bleeding risk is similar, the bleeding profile does differ between the two drugs. Dabigatran increases the risk of major gastrointestinal bleeding but lowers the risk of intracranial bleeding when compared with warfarin.[189] Dabigatran is predominantly eliminated by the kidneys, so the dose should be reduced in patients with a creatinine clearance less than 30 mL/min.

Monitoring of dabigatran therapy is difficult because the perfect laboratory test does not exist. The aPTT does not become linear until dabigatran concentrations are quite high (>200 ng/mL).[190] The TT is very sensitive to dabigatran, so while it is useful to detect any presence of the drug, it cannot be used to quantify the amount of drug present.[191] If available, dilute TT or ecarin clotting time are both linear at clinically relevant dabigatran concentrations and are the tests of choice if monitoring is necessary.[192]

Direct Xa inhibitors, rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) are agents whose activity is directed against the active site of factor Xa. Factor Xa inhibitors have been associated with fewer strokes and embolic events, fewer intracranial hemorrhages, and lower all-cause mortality compared with warfarin.[193] A comparison of apixaban versus warfarin in patients with atrial fibrillation showed a reduction in stroke risk along with a significant reduction in major bleeding.[194] The anti-factor Xa assays are the tests best suited for monitoring the effects of the direct Xa inhibitors, but assays must be individually calibrated for each drug.[192]

THROMBOLYTICS

Thrombolytic therapy is used to break up or dissolve blood clots. These medications are most commonly used during acute myocardial infarctions, strokes, massive pulmonary embolus, arterial thromboembolism, and venous thrombosis. Thrombolytics may be given through an intravenous line systemically or directly to the site of the blockage. Most thrombolytic agents are serine proteases that work by converting plasminogen to plasmin. Plasmin then lyses the clot by breaking down fibrinogen and fibrin. Fibrinolytic agents are divided into two categories: (1) fibrin-specific agents and (2) non–fibrin-specific agents. Fibrin-specific agents are alteplase (tPA), reteplase, and tenecteplase. They theoretically produce less plasminogen conversion in the absence of fibrin and result in less fibrinogen depletion. Non–fibrin-specific agents (e.g., streptokinase) catalyze systemic fibrinolysis. Streptokinase, produced by beta-hemolytic streptococci, is highly antigenic and can cause immunologic sensitization and allergic reactions, particularly with repeat administration even several years after previous exposure.[195] Streptokinase is not widely used in the United States but is still used internationally because of its lower cost.

t-PAs are both thrombolytics and anticoagulants because as mentioned earlier, fibrinolysis generates increased amounts of circulating fibrin degradation products, which inhibit platelet aggregation. Surgery or puncture of noncompressible vessels is contraindicated within a 10-day period after the use of thrombolytic drugs.

Time is usually of the essence when administering these drugs. Medical providers should quickly obtain a history and physical exam, review absolute and relative contraindications, (Table 50.2), order relevant laboratory tests, request necessary consultations, and proceed with decision making. Many studies have investigated the use of thrombolytics in acute pulmonary embolus, ST-elevation myocardial infarction (STEMI), and ischemic stroke. Thrombolytics are indicated in the setting of hemodynamic instability due to acute pulmonary embolus.[196] A meta-analysis in patients with massive pulmonary embolism found that systemic thrombolytic therapy decreased the composite endpoint of death and recurrent thromboembolism (9.4% vs. 19%, odds ratio 0.45, 95% CI 0.22-0.92).[197] Primary PCI is the preferred treatment for patients with acute STEMI if it can be performed by an experienced operator within 2 hours from presentation to the emergency department, but fibrinolytic therapy remains an important modality in hospitals with limited primary PCI

TABLE 50.2 Absolute and Relative Contraindications for Thrombolytics

Absolute Contraindications	Relative Contraindications
Vascular lesions	Ischemic stroke >3 months prior
Severe, uncontrolled hypertension (SBP > 185 or DBP > 110)	Active peptic ulcer
Recent cranial surgery or trauma	Current use of anticoagulant drugs
Brain tumor	Pregnancy
Ischemic stroke <3 months prior	Prolonged/traumatic CPR <3 weeks prior
Active bleeding	Major surgery <3 weeks prior

CPR, Cardiopulmonary resuscitation; *DBP,* diastolic blood pressure; *SBP,* systolic blood pressure.

availability. Early thrombolysis was associated with a lower mortality rate. When compared between less than 2 hours versus greater than 4 hours from time of symptom presentation to thrombolysis administration, 30-day mortality was decreased with earlier administration (5.5% vs. 9%).[198] For stroke care, the primary goal is to restore blood flow to ischemic regions in order to reduce stroke-related disability and mortality. Alteplase is the recommended therapy for treatment of acute ischemic stroke if treatment can be initiated within 4.5 hours of symptom onset.[199] Mechanical thrombectomy should still be considered even if thrombolysis has been administered for ischemic stroke.

PROCOAGULANT DRUGS

Anesthesiologists may use procoagulant drugs for individuals at risk of bleeding to help control blood loss during surgery. These drugs can be divided into two different classes: antifibrinolytics and factor replacements. (see Table 50.1).

Antifibrinolytics

There are two types of antifibrinolytics, the lysine analogs, epsilon-aminocaproic acid (EACA) and TXA, and a SERPIN, aprotinin. Aprotinin was removed from the US market due to concerns of renal and cardiovascular toxicity and is now only available in Europe and Canada. The lysine analogs act by competitively inhibiting the binding site on plasminogen, leading to inhibition of plasminogen activation as well as preventing plasminogen binding of fibrin, therefore impairing fibrinolysis.[200] TXA has been more thoroughly studied than EACA, but aside from subtle differences, both agents appear to have similar efficacy and have been shown to decrease perioperative blood loss.

TXA has been studied in the large CRASH-2 trial of patients admitted after trauma and was associated with a reduction in all-cause mortality (14.5% vs. 16%, P = .0035), including the risk of death due to bleeding (4.9% vs. 5.8%, P = .0077), without an increase in vascular occlusive events.[100] Subgroup analysis of the CRASH-2 data showed that early treatment (≤1 hour) after traumatic injury significantly reduced the risk of death due to bleeding events in the TXA group (RR 0.68; 95% CI, 0.57-0.82; P < .0001). RR was also lower 0.79 (95% CI, 0.64-0.97; P = .03) if TXA was administered between 1 and 3 hours; however, treatment after 3 hours seemed to increase death due to bleeding, with a RR of 1.44 (95% CI, 1.12-1.84; P = .004).[101]

Aside from trauma, there are also trials studying use of TXA in cardiac surgery, orthopedic surgery, neurosurgery, hepatic surgery, and obstetric and gynecology surgery. The World Maternal Antifibrinolytic Trial (WOMAN) found that administration of TXA reduced death due to bleeding in women with postpartum hemorrhage, especially if given within 3 hours of birth, and was not associated with an increase in adverse effects.[201] In a recent meta-analysis in surgical patients, TXA reduced the probability of receiving a blood transfusion by a third (risk ratio 0.62; 95% CI, 0.58-0.65; P < .001). [202] Fewer deaths occurred in the TXA group (risk ratio 0.61; 95% CI, 0.38-0.98; P = .04), but the effect of TXA on myocardial infarction (risk ratio 0.68; 95% CI, 0.43-1.09; P = .11), stroke (risk ratio 1.14; 95% CI, 0.65-2.00; P = .65), deep vein thrombosis (risk ratio 0.86; 95% CI, 0.53-1.39; P = .54), and pulmonary embolism (risk ratio 0.61; 95% CI, 0.25-1.47; P = .27) was inconclusive. A Cochrane review also found that TXA significantly reduced blood transfusions by 39%; however, TXA was not associated with decreased mortality in all surgeries in their analysis.[203]

Overall, the lysine analogs (TXA and EACA) appear to be inexpensive and low risk adjunctive agents that should be considered for use in major surgery or critical bleeding. The rate of thrombosis does not appear to be elevated, but further studies are necessary before this can be definitively concluded. In terms of side effects, there is a reported dose-response relationship of high-dose TXA and seizures in patients undergoing cardiac surgery.[204] The reported mechanism is TXA binding to $GABA_A$ receptors, subsequently blocking $GABA_A$-mediated inhibition in the central nervous system.[205]

Factor Replacements

Recombinant Factor VIIa. Recombinant factor VIIa (rFVIIa) increases the generation of thrombin via the intrinsic and extrinsic pathways to enhance hemostasis. The drug was originally FDA approved for use in hemophilia patients. It binds to tissue factor at the site of vessel injury and to the surface of the activated platelet, leading to activation of factor X. Both mechanisms result in a "burst" of thrombin and fibrin generation, which leads to clot formation. The half-life of rFVIIa is only 2 to 2.5 hours, so the initial dose may require repeating until the bleeding is controlled.

Successful use of rFVIIa in hemophilia patients with inhibitors generated a great deal of interest in the drug's ability to enhance hemostasis in hemorrhaging patients without a preexistent coagulation disorder. This off-label use of rFVIIa had been quite varied, and included patients with intracranial hemorrhage,[206,207] trauma,[208,209] and traumatic brain injury,[210] and patients undergoing cardiac surgery[211] and liver transplantation.[212,213] While treatment with rFVIIa reduced the progression of the hematoma following intracranial hemorrhage and reduced the risk of acute respiratory distress syndrome (risk reduction, −0.05; 95% CI, −0.02 to −0.08) in trauma patients, mortality or functional outcomes were not improved in any patient subset.[211]

As the off-label use of rFVIIa increased, there were more troubling reports of arterial and venous thromboses. A review studying the safety of off-label rFVIIa reported a higher rate of arterial thromboembolic events with the use of rFVIIa compared with placebo (5.5% vs. 3.2%, P = .003), and an increased observed rate for coronary events (2.9% vs. 1.1%, P = .002). [214] This rate was noted to be increased with age (for patients aged 65-74 years, OR 2.12; 95% CI: 0.95-4.71 and for those ≥75 years, OR 3.02, 95% CI: 1.22-7.48), as well as higher doses. Considering that no randomized controlled trial has been able to demonstrate a significant benefit in terms of intensive care stay, hospital stay, or mortality, guidelines currently recommend that rFVIIa no longer be used for the off-label indications of prevention and treatment of bleeding in patients without hemophilia.[215] Each clinician will have to weigh the risk of thromboembolic events against the benefit for the refractory bleeding patient where the "last ditch" use of rFVIIa in massive hemorrhage has not been formally assessed.

Prothrombin Complex Concentrate. PCCs are commercially available purified concentrates containing varying amounts of vitamin K-dependent coagulation factors. Three-factor PCCs differ from 4-factor PCCs in that they do not contain significant amounts of factor VII. Most of the factors are preserved in the inactive state, with the aim of decreasing thrombogenic risk; however, FEIBA is a 4-factor PCC that contains activated factor VII. The products may also contain coagulation inhibitors such as heparin, AT, protein C, and protein S to mitigate the thrombotic risk by providing more balanced replacement of procoagulant factors and anticoagulant proteins.

While PCCs are derived from human plasma, they are treated with at least one viral reduction process, reducing the risk of transfusion-transmitted infection and the lower administration volume decreases the risk of transfusion-associated circulatory overload (TACO).[216] While PCCs appear to be safe and have low risk of thrombosis, there is accumulating evidence that the level of factor II and its balance with the coagulation inhibitors may be the important key.[217]

Fibrinogen Concentrate. Fibrinogen concentrate is produced from pooled human plasma, but viral inactivation steps are incorporated into the manufacturing. It can be used to correct hypofibrinogenemia with the goals of reducing coagulopathy, bleeding, and transfusion requirements. Fibrinogen concentrate offers benefits over FFP and cryoprecipitate in terms of standardized fibrinogen content, low infusion volume, and faster time to administration due to rapid reconstitution. Alternatively, cryoprecipitate and FFP are cheaper, and they also provide additional procoagulant factors that could be beneficial during massive bleeding. In a recent meta-analysis, seven randomized controlled trials showed a significant reduction in bleeding and transfusion requirements with the use of fibrinogen concentrates, but data on mortality were lacking and there was significant heterogeneity among the trials.[218] While the data are inconclusive, some hospitals have incorporated fibrinogen concentrate into algorithms based on viscoelastic coagulation tests with the goal of reducing transfusion requirements.

Perioperative Management of Anticoagulation

The perioperative management of patients who require chronic anticoagulation or antiplatelet therapy involves balancing the risk of surgical bleeding against the risk of developing postoperative thromboembolism. Patients should be evaluated with enough time prior to elective surgery to perform these necessary risk assessments and make management decisions regarding discontinuation and reinstitution of anticoagulation or antiplatelet therapy.

VITAMIN K ANTAGONISTS

For patients taking VKAs, the current recommendation is to stop VKAs 5 days prior to surgery for those who are at low risk for perioperative thromboembolism (Table 50.3). VKAs should be restarted 12 to 24 hours postoperatively if there is adequate hemostasis. For patients at high risk of thromboembolism, bridging anticoagulation with UFH or LMWH after discontinuation of VKAs should occur. The difficulty arises in defining a plan for patients who are at moderate risk. No definitive evidence exists, so the approach chosen should be based on individual patient and surgical risk factors.[219]

TABLE 50.3 Perioperative Thromboembolism Risk Stratification

Risk	Indication
High	Mechanical heart valve
	Rheumatic valvular heart disease
	CHADS score ≥ 5
	VTE within 3 months or h/o VTE when VKAs are discontinued
Moderate	CHADS score of 3 or 4
	VTE between 3 and 12 months or h/o recurrence
	Active cancer
Low	CHADS score 0-2
	VTE > 12 months prior and no other risk factors

CHADS, Congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, prior stroke; *VKA,* vitamin K antagonists; *VTE,* venous thromboembolism.

HEPARINS

For those patients receiving bridging therapy with UFH, the infusion should be stopped 4 to 6 hours prior to surgery[220] and resumed without a bolus dose no sooner than 12 hours postoperatively. In surgeries with high postoperative bleeding risk, resumption of UFH should be delayed 48 to 72 hours until adequate hemostasis has been achieved. In patients receiving bridging therapy with LMWH, the last dose of LMWH should be administered 24 hours prior to surgery and dosing should be resumed 24 hours postoperatively in low bleeding risk surgery and delayed until 48 to 72 hours postoperatively for surgeries with high bleeding risk.[219]

ASPIRIN

For patients receiving aspirin therapy, risk assessment is based on (1) the patient's risk of a perioperative cardiovascular event; (2) whether the surgery is a minor procedure, major procedure, or cardiac procedure; and (3) the timing and type of stent placement for those patients who have undergone recent PCI. Low-dose aspirin (acetylsalicylic acid, ASA) has been shown to reduce the risk of stroke and myocardial infarction by 25% to 30%,[221,222] and studies report significant increased risk with the withdrawal of low-dose aspirin because of a platelet rebound phenomenon that leads to increased thrombus stability, improved fibrin crosslinking, and decreased fibrinolysis.[223] The decision to discontinue low-dose aspirin must weigh the risks of bleeding versus the benefits of cardiovascular risk reduction. Studies suggest that perioperative aspirin use may lead to a small increase in the risk for major bleeding (2.9% vs. 2.4%, $P = .04$), [222,224] but continuation of perioperative aspirin may confer a significant reduction in myocardial infarction and other major cardiovascular events (1.8% vs. 9.0%, $P = .02$). [225]

Recommendations currently are to continue aspirin for patients who are at moderate to high risk for cardiovascular events requiring noncardiac surgery and only stop aspirin use 7 to 10 days prior to surgery for patients at low risk for cardiovascular events.[226] Patients who are having minor procedures (e.g., minor dental, dermatologic procedures, or cataract surgery) and are on aspirin for the secondary prevention of cardiovascular disease should continue taking it in the perioperative period.

Patients with coronary stents presenting for surgery are problematic because of the concerns for in-stent thrombosis that can occur with stopping antiplatelet therapy. Surgery should be delayed if possible for at least 6 weeks after bare-metal stent placement and for at least 6 months after drug-eluting stent placement.[227] If surgery is required before this time has passed, dual anti-platelet therapy should be continued unless the risk of bleeding is thought to outweigh the risk of stent thrombosis.

Many studies have examined management of aspirin therapy perioperatively; however, there is much less data for management of clopidogrel in the perioperative setting. In most clinical situations, aspirin provides benefit that outweighs the bleeding risk and should be continued unless the patient is undergoing intracranial procedures, transurethral prostatectomy, intraocular procedures, or surgeries with extremely high bleeding risk.[228] The data are inconclusive about use of bridging therapy for patients with coronary stents who require noncardiac surgery. For patients with a very high risk of stent thrombosis, bridging therapy with intravenous, reversible glycoprotein inhibitors or a reversible intravenous P2Y12 inhibitor have been suggested, but concomitant parenteral anticoagulation therapy is not recommended.

NEURAXIAL ANESTHESIA AND ANTICOAGULATION

In addition to surgical bleeding risk assessment, many patients who are on anticoagulant or antiplatelet therapy can potentially benefit from neuraxial anesthetics. Management of perioperative anticoagulation is becoming increasingly more complex with the advent of the DOACs and the number of patients who are now receiving chronic anticoagulation. There is a lack of randomized controlled trials showing safety in the timing of surgical procedures and regional anesthesia because a broad clinical experience with these drugs along with neuraxial techniques does not exist. Most guidelines in the literature are based exclusively on the pharmacokinetics and pharmacodynamics of these drugs.[229] These guidelines and recommendations will continue to be updated as evidence emerges on the bleeding risk and pharmacologic profiles of the newer anticoagulants. In the absence of concrete data, many hospital committees are setting local practice guidelines (Table 50.4). Early preoperative assessment of patients receiving anticoagulation and a multidisciplinary team approach between the patient, primary care physician, surgeon, anesthesiologist, and hematologist is essential to ensure the perioperative safety of these patients. Continued research on thromboembolic events and bleeding risk in the setting of these novel therapies is needed before official recommendations can be made regarding management.

TABLE 50.4 UCSF Guidelines for the Use of Antithrombotic Agents in the Setting of Neuraxial Procedures

Anticoagulant	Minimum Time Between the Last Dose and When Neuraxial Catheter can Occur	Minimum Time After Catheter Placement to Drug Start	Minimum Time Between Last Dose of Drug and Catheter Removal	Minimum Time Between Neuraxial Catheter Removal and When Next Dose can be Given
NSAIDs/ASA	No restrictions for catheter placement or removal			
Heparin SQ BID	No restrictions for catheter placement or removal			
Heparin SQ TID	4 h	2 h	4 h	2 h
Lovenox qD	12 h	6 h	12 h	4 h
Warfarin	5 days and INR < 1.5	Contraindicated while catheter in place		2 h
Clopidogrel	7 days	Contraindicated while catheter in place		2 h
Ticlodipine	14 days	Contraindicated while catheter in place		2 h
Dabigatran	5 days	Contraindicated while catheter in place		6 h
Rivaroxaban	3 days	Contraindicated while catheter in place		6 h
Apixaban	3 days	Contraindicated while catheter in place		6 h
Abciximab	48 h	Contraindicated while catheter in place		2 h
Eptifibatide	8 h	Contraindicated while catheter in place		2 h
Alteplase*	10 days	Contraindicated while catheter in place		10 days

*Full dose for stroke or myocardial infarction. No time restrictions for catheter placement or removal with low dose (2 mg) for catheter clearance

ASA, acetylsalicylic acid; ***BID***, two times a day; ***INR***, international normalized ratio; ***NSAIDs***, nonsteroidal antiinflammatory drugs; ***qD***, once a day; SQ, subcutaneous; ***TID***, three times a day. Adapted from UCSF Guidelines for the use of antithrombotic agents in the setting of neuraxial procedures and Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (third edition). *Reg Anesth Pain Med*. 2010; 35:64–101.

Emergent Reversal of Anticoagulants

VITAMIN K ANTAGONISTS

The incidence of VKA-associated major bleeding is between 1.1% and 8.1% per year depending on the study design.[230,231] Some of these patients will require warfarin reversal for bleeding and other patients will require warfarin reversal prior to emergency surgery. Four-factor PCCs as opposed to three-factor PCCs are now the drug of choice for emergent reversal of oral VKA in place of FFP or rFVIIa,[232] but PCCs only provide a transient correction due to the short half-life of these factors relative to the long half-life of warfarin. Concomitant administration of vitamin K is required to restore carboxylation of the vitamin K dependent factors (VKDFs) by the liver and provide a more sustained correction after the factors in the PCC infusion have been metabolized. Intravenous administration of vitamin K gives a more rapid response than subcutaneous or oral administration.[233] The dose required depends on the clinical situation and the need to be able to re-establish anticoagulation after surgery. For instance, lower doses (3 mg) may allow for warfarin reversal during the acute event, while avoiding warfarin resistance if rapid re-establishment of a therapeutic INR is required.[234]

Rapid reversal of VKA with FFP is difficult and often unrealistic. Time to thaw ABO-compatible units is a concern, but the large volume required to raise the VKDF by 50% is often untenable, especially in a patient population prone to pulmonary, renal, and cardiac disease.[235] There are also concerns for transmission of viral diseases, and transfusion-related complications such as volume overload, TACO, and lung injury (transfusion-related acute lung injury). In a recent randomized controlled trial using 4-factor PCC to reverse VKA prior to surgery or invasive interventions, effective hemostasis was higher (90% PCC vs. 75% FFP), fluid overload was lower (3% PCC vs. 13% FFP), and thromboembolic events were similar compared with patients who received FFP (7% PCC vs. 8% FFP).[236]

DIRECT THROMBIN INHIBITORS

There are no direct reversal agents for intravenous DTIs; however, their half-lives are relatively short, so time and supportive medical care are often sufficient to manage their anticoagulant effect in acute clinical situations. For the DOACs, idarucizumab, a specific antidote for dabigatran, is a humanized antibody fragment that binds to dabigatran with an affinity 350 times greater than thrombin. The drug received FDA approval in 2015 and can completely reverse the anticoagulant effect of dabigatran in minutes.[237] Andexanet alfa, a recombinant derivative of factor Xa, was developed to reverse the factor Xa inhibitors by acting as a decoy. It has a higher affinity for factor Xa inhibitors than intrinsic factor Xa. The drug was recently approved by the FDA for patients who present with an acute hemorrhage while receiving apixaban or rivaroxaban. The indication currently does not cover edoxaban, or enoxaparin.[238,239]

EMERGING AGENTS

There are additional reversal agents in development that may be approved by the FDA soon. Ciraparantag (PER977), a small, synthetic, water-soluble, cationic molecule, binds and neutralizes UFH, LMWH, fondaparinux, dabigatran, and factor Xa inhibitors through hydrogen bonding and charge-charge interactions. Phase I trials have been completed in healthy volunteers.[240] Common anticoagulants and possible reversal agents for emergencies are listed for reference in Table 50.5.

TABLE 50.5 Common Anticoagulants Along with the Required Laboratory Monitoring and Possible Reversal Agents for Emergencies

Antithrombotic Agent	Drug Name	Stop Before Procedure	Monitoring	Reversal Agents
Antiplatelet agents	ASA P2Y12 receptor antagonists GPIIb/IIIa antagonists	7 days 7-14 days 24-72 h	None	Platelet transfusion
Vitamin K antagonists	Warfarin	2-5 days	PT, INR	PCC, FFP, vitamin K
Heparins	Unfractionated heparin (UFH)(IV)	6 h	aPTT	Protamine
	Low-molecular weight heparin (LMWH)	12-24 h	None required, but fXa levels can monitor levels	Partially reversed by protamine
Pentasaccharide	Fondaparinux	3 days (prophylactic dosing)	None required, but fXa levels can monitor levels	None
Direct thrombin inhibitors	Argatroban, Bivalirudin	4-6 h 3 h	aPTT or ACT	None
	Dabigatran	2-4 days (longer if renal impairment)	None required, thrombin time can monitor levels	Idarucizumab
FXa inhibitors	Rivaroxaban, Apixaban, Edoxaban	2-3 days 2-3 days 2-3 days	None required, but fXa levels can monitor levels	Andexanet alfa for rivaroxaban and apixaban

ACT, activated clotting time; *aPTT*, activated partial thromboplastin time; *ASA*, acetylsalicylic acid; *FFP*, fresh frozen plasma; *INR*, international normalized ratio; *IV*, intravenous; *PCC*, prothrombin complex concentrate; *PT*, prothrombin time.

Conclusion

The coagulation system remains exceedingly complex, but an understanding of the fundamental principles of hemostasis will allow the anesthesia provider to identify patients at risk of bleeding preoperatively, and safely manage blood loss and treat acquired coagulopathy both intraoperatively and postoperatively. Given the abundance of different antithrombotic and anticoagulant medications, perioperative management is becoming increasingly challenging. Early preoperative assessment of patients receiving anticoagulation and a multidisciplinary team approach between the patient, primary care physician, hematologist, surgeon, and anesthesiologist is essential to ensure the perioperative safety of these patients.

Complete references available online at expertconsult.com.

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