CME

Etiology and Assessment of Hypercoagulability with Lessons from Heparin-Induced Thrombocytopenia

Roman M. Sniecinski, MD,* Marcie J. Hursting, PhD,† Michael J. Paidas, MD,‡ and Jerrold H. Levy, MD, FAHA*

Hypercoagulability, or thrombophilia, is a condition associated with an abnormally increased tendency toward blood clotting. Affected individuals are prone to developing venous or arterial thrombosis and often require thromboprophylaxis. Hypercoagulability can be generally classified as either an inherited or acquired condition. Patients with an inherited thrombophilia have genetic variances that alter the quality or quantity of proteins involved with hemostasis. Hypercoagulability may also be acquired and develop as an exaggeration of normal physiologic responses to major tissue injury, or an abnormal response to various prothrombotic clinical factors. Careful assessment for hypercoagulability is important because effective management strategies, often involving anticoagulation, may be available. Heparin-induced thrombocytopenia is an example of an acquired hypercoagulable state that has been well studied and, when recognized, responds to appropriate therapy. In this article, we review the etiology, risks, and assessment of thrombophilia, with emphasis on the clinical lessons learned from heparin-induced thrombocytopenia. (Anesth Analg 2011;112:46–58)

There is a delicate balance between 2 competing forces intravascularly. The coagulation system ensures that bleeding does not continue indefinitely after vascular injury. At the same time, this system is balanced by thromboresistant forces that use anticoagulant proteins to regulate clot formation and fibrinolytic proteins to remove clots once vascular injury has been repaired. The proper balance between these systems must be maintained to ensure blood fluidity.

Hypercoagulability, also known as thrombophilia, pre/prothrombotic state, or "vulnerable blood," is a condition in which blood clots more readily than normal. It is the result of tilting the normal equilibrium of procoagulant and thromboresistant forces in favor of coagulation.[1] Although arterial and venous thrombi were once thought to be distinct problems, patients with hypercoagulability can be at risk for both, and it has been suggested that the condition represents a spectrum of diseases rather than separate clinical entities.[2–4] Clinicians, particularly those in the operating room, are usually concerned about the risk of bleeding in patients; however, hypercoagulability is also a potential cause of adverse outcomes but is often overlooked.[5,6]

Risk factors for hypercoagulability are broadly classified as either inherited or acquired.[7] Effects are exerted by either increasing procoagulant activity or decreasing anticoagulant or fibrinolytic activity and both can act synergistically. These risk factors have an important role in the development of disease and it is estimated that 80% of patients with venous thrombosis have an underlying risk factor.[8] Because of this increased risk, hypercoagulable patients are often treated prophylactically with anticoagulation therapy, which clinicians need to consider.[9,10]

Herein, we review the inherited and acquired risk factors for hypercoagulability, their clinical impact, and approach to diagnosis. Additionally, we discuss the diagnosis and treatment of heparin-induced thrombocytopenia (HIT), which offers representative lessons in the management of a potentially catastrophic hypercoagulable state.

INHERITED RISK FACTORS

Patients with inherited hypercoagulability are particularly prone to venous thromboembolic events that occur early in life, and even in utero.[11–14] Some conditions, such as inherited antithrombin deficiency, have been recognized for decades,[15] whereas others, prothrombin G20210A mutation, for example, have only recently been identified.[16,17] With the help of genetic testing, variants that contribute to hypercoagulability are continually being discovered.[18] The inherited risk factors described herein are grouped according to whether they enhance procoagulant effects, reduce natural anticoagulation, impair fibrinolysis, or have some other unique effect. Figure 1 presents an overview of the coagulation/fibrinolytic pathways and where each inherited risk factor has an effect.

Enhancement of Procoagulant Effects

For venous thrombosis, the most common inherited risk factors are factor V Leiden and prothrombin G20210A mutation, present respectively in approximately 5% and 2% of Caucasians.[19,20] The factor V Leiden gene mutation leads to an amino acid substitution that renders the activated procoagulant factor V resistant to cleavage (and thus inhibition) by activated protein C. The thrombotic risk for

From the *Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia; †Clinical Science Consulting, Austin, Texas; and ‡Department of Obstetrics and Gynecology, Yale School of Medicine, New Haven, Connecticut.

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Address correspondence to Jerrold H. Levy, MD, FAHA, Emory Hospital, 1364 Clifton Rd., Atlanta, GA 30322. Address e-mail to jlevy01@emory.edu.

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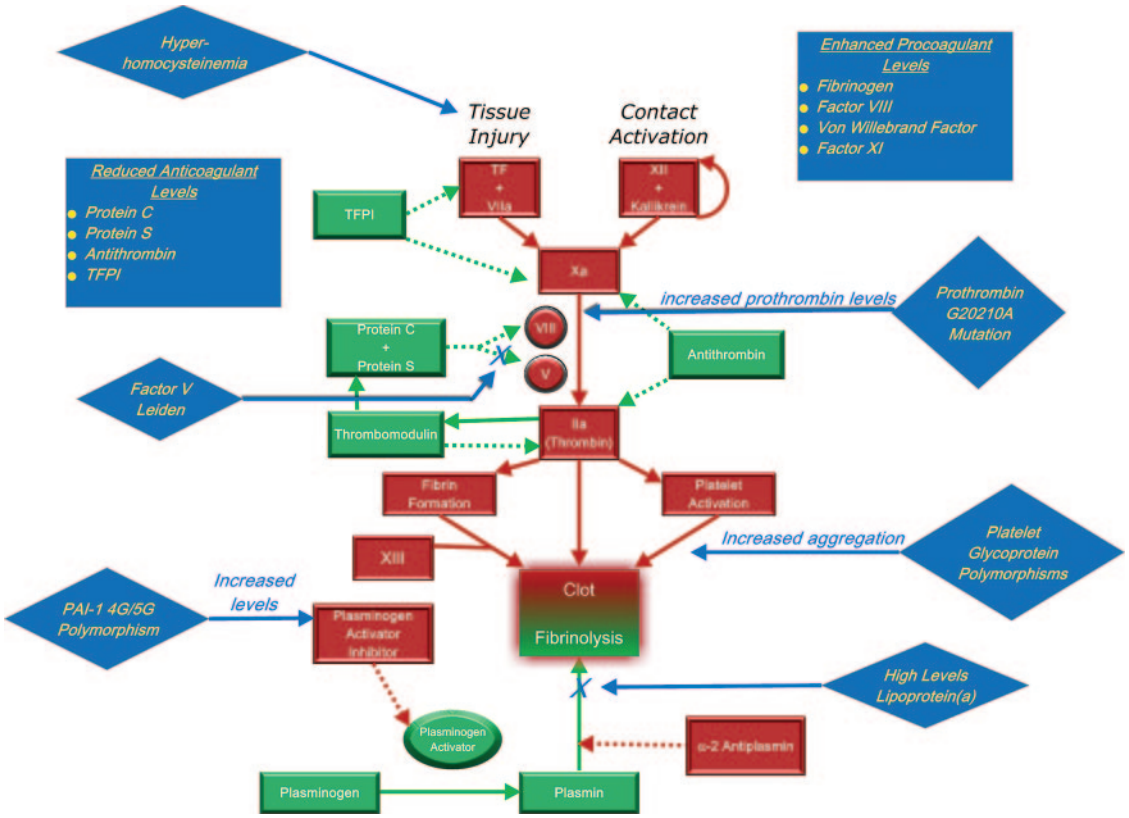

Figure 1. Inherited risk factors for hypercoagulability. Procoagulant forces (red) and natural anticoagulant/fibrinolytic forces (green) are diagrammed. Dashed lines indicate an inhibitory effect. Inherited risk factors are presented in blue boxes with yellow lettering and arrows indicating the mechanism for the hypercoagulable effect. "Xs" denote a specific block in a pathway. See text for full details. TF = tissue factor; TFPI = tissue factor pathway inhibitor; PAI = plasminogen activator inhibitor.

individuals with factor V Leiden, compared with individuals lacking the mutation, is increased approximately 3-fold in heterozygotes, 18-fold in homozygotes, and 9-fold overall.[21,22] Individuals who are heterozygous for the prothrombin G20210A mutation have increased messenger RNA stability for the protein and thus higher plasma levels of prothrombin. This results in an approximate 3-fold increased risk of venous thrombosis, relative to individuals lacking the mutation.[16,22] Approximately 7% of patients diagnosed with venous thrombosis have this prothrombin variant.[23] Individuals who are homozygous for the G20210A mutation are extremely rare, with only 70 cases (patient age: neonate to 74 years) published before 2006.[24] Factor V Leiden and prothrombin G20210A can be found together in some individuals.[25]

The association of factor V Leiden and prothrombin G20210A with arterial thrombosis is controversial. However, a large meta-analysis showed a small yet significant association of each with myocardial infarction (respective per-allele relative risks, 1.2 and 1.3).[26] Prothrombin G20210A has also been linked to a 5-fold–higher incidence of thrombotic cerebrovascular disease,[27] and, when combined with the factor XIII Leu34 polymorphism, which leads to increased levels of the clot-stabilizing protein factor XIII, there is a 12-fold–higher risk of myocardial infarction.[28]

Fibrinogen abnormalities can result in hypercoagulability by causing levels to be too high (hyperfibrinogenemia) or causing structural variants that are less susceptible to breakdown (dysfibrinogenemia). Individuals in the highest tercile of plasma fibrinogen concentration have nearly twice the risk of arterial thrombosis as do those in the lowest tercile.[29] Additionally, stroke patients with initial fibrinogen levels ≥450 mg/dL have poorer functional outcomes.[30] Hyperfibrinogenemia also increases the risk for venous thrombosis, although to a smaller extent.[31,32] Dysfibrinogenemias, although often associated with bleeding diatheses, can also cause hypercoagulability if the resulting fibrin molecules fail to inhibit thrombin or are less susceptible to cleavage by plasmin.[33,34] This condition is frequently present in patients who develop chronic thromboembolic pulmonary hypertension after acute thromboembolism.[35]

Other prothrombotic risk factors include elevated levels of specific coagulation factor levels, as well as von Willebrand factor. Factor VIII, an acute phase reactant, is increased in up to 25% of patients with unexplained venous thrombosis.[36] Independent of inflammatory markers, however, an increased factor VIII level remains a risk factor for venous thrombosis and arterial vascular events.[37,38] In a large, nested case-control study, elevated levels of factor XI were associated with an increased risk of venous thromboembolism (odds ratio, 1.8; 95% confidence interval, 1.3–2.7).[39] von Willebrand factor is involved with platelet adhesion, and the risk of myocardial infarction is approximately 3-fold greater in individuals

with levels in the highest quartile compared with the lowest quartile.[40]

Reduction of Natural Anticoagulation

Protein C and protein S are vitamin K–dependent proteins that inhibit the activated procoagulant factors V and VIII. Inherited qualitative or quantitative deficiencies of these natural anticoagulants are strong genetic risk factors for venous thrombosis, increasing the risk at least 5- to 10-fold.[41–43] Homozygous protein C deficiency often results in fatal thrombosis in the newborn.[44]

Antithrombin, formerly referred to as antithrombin III, is a serine protease inhibitor with a particularly strong affinity for thrombin in the presence of heparin-like glycosaminoglycans on the endothelium or exogenously administered heparin.[45] Heterozygous antithrombin-deficient patients typically have thrombin inhibition of only 50% of normal and are at increased risk for thrombotic events.[46] Similar to protein C–deficient individuals, being homozygous for the trait is almost always fatal in the newborn or in utero. Although congenital deficiencies in these natural coagulants are rare (≤0.2% in the general population),[47] they may also be acquired from certain clinical conditions, as discussed below.

Tissue factor pathway inhibitor neutralizes both factors VIIa and Xa. A very low level of tissue factor pathway inhibitor is an independent risk factor for myocardial infarction, with an estimated 7-fold increase in events among individuals in the lowest 10th percentile, and polymorphisms of the protein may be associated with increased risk of venous thrombosis.[40,48] Associations have been equivocal between thrombosis and polymorphisms/deficiencies of other natural anticoagulants such as thrombomodulin, endothelial protein C receptor, or heparin cofactor II.[48,49]

Reduction of Fibrinolysis

Lipoprotein (a) is a serum lipoprotein that has high homology with plasminogen and competitively inhibits fibrinolysis. Levels of lipoprotein (a) are highly heritable, and genome-wide linkage studies have identified genomic regions that influence its concentration.[50] Plasma lipoprotein (a) levels >300 mg/L are significantly associated with venous thromboembolism (odds ratio, 2.1), and increased levels are also considered a risk factor for cardiovascular disease.[51,52]

Plasminogen activator inhibitor-1 (PAI-1) is a serpin that down-regulates fibrinolysis. A deletion/insertion (4G/5G) polymorphism in its gene promoter region correlates with higher plasma levels.[53] In a meta-analysis of published data (22 articles) regarding the PAI-1 4G/5G polymorphism, the 4G mutation was associated with a significant increase in risk of venous thromboembolism, but only in patients having another genetic risk factor for hypercoagulability (per-allele odds ratio, 1.833; 95% confidence interval, 1.325–2.536).[54] However, when only studies of patients with a nongenetic risk factor for venous thromboembolism were considered, insignificant results were obtained, suggesting that the polymorphism is only important in patients with other predisposing genetic defects. Elevated levels of tissue plasminogen activator, which paradoxically may reflect impaired fibrinolysis because of assay methodologies in use, are associated with a 2- to 3-fold increased risk of myocardial infarction and thrombotic stroke.[48,54,55] Inherited deficiencies of plasminogen and polymorphisms affecting plasma levels of thrombin-activatable fibrinolysis inhibitor are reported, yet their associations with thrombotic risk remain unclear and complex.[56]

Other Inherited Conditions

Hyperhomocysteinemia has been linked to increased arterial or venous thrombosis, perhaps via endothelial damage; however, results are variable and some data suggest that elevated plasma levels of homocysteine may be a response to ischemic events.[57,58] Polymorphisms in the gene for methylene tetrahydrofolate reductase, an enzyme involved in homocysteine metabolism, may lead to hyperhomocysteinemia.[59] Hyperhomocysteinemia may also be acquired in individuals with folic acid deficiency.

Polymorphisms for a variety of platelet glycoproteins, including Ib/IX (von Willebrand factor receptor), Ia/IIa (collagen receptor), and IIb/IIIa (fibrinogen receptor), have been described. Study results of platelet glycoprotein genetic variants have been inconsistent regarding association with thrombosis, although some suggest a link with cardiovascular risk.[5,48] Genome-wide association studies have already identified 11 risk alleles explaining 20% of the heritability of myocardial infarction or coronary artery disease, and particular attention is now being given to better characterizing loci related to platelet function, number, or volume.[60]

ACQUIRED RISK FACTORS

Acquired risk factors are often transient, yet may confer higher thrombotic risk than genetic polymorphisms. Similar to inherited factors, some acquired conditions enhance procoagulant forces (e.g., HIT) whereas others decrease levels of natural anticoagulants (e.g., antiphospholipid antibodies). However, most acquired risk factors are likely multifactorial and have mechanisms that remain to be fully characterized. We have grouped the acquired risk factors into broad categories of disease states, clinical scenarios, and pharmacologic causes. How the major acquired risk factors affect the coagulation and fibrinolytic systems is presented in Figure 2.

Disease States

Various antiphospholipid antibodies, including lupus anticoagulants, anticardiolipin antibody, and anti–β 2 glycoprotein I antibody, are associated with increased risk of venous or arterial thrombosis.[61–63] Literature review indicates that the presence of lupus anticoagulants confers an odds ratio of 8.6 to 10.8 for arterial thrombosis, 4.1 to 16.2 for venous thrombosis, 5.7 to 7.3 for any thrombosis, and 3 to 4.8 for recurrent miscarriage and fetal death.[62,64] Potential mechanisms explaining hypercoagulability with antiphospholipid antibodies include down-regulation of thrombomodulin expression, increased tissue factor expression, and impairment of the protein C anticoagulant pathway.[65] Antiphospholipid antibody may be induced during acute infection or inflammation and be short-lived, i.e., detectable for 2 to 3 months; however, in some patients,

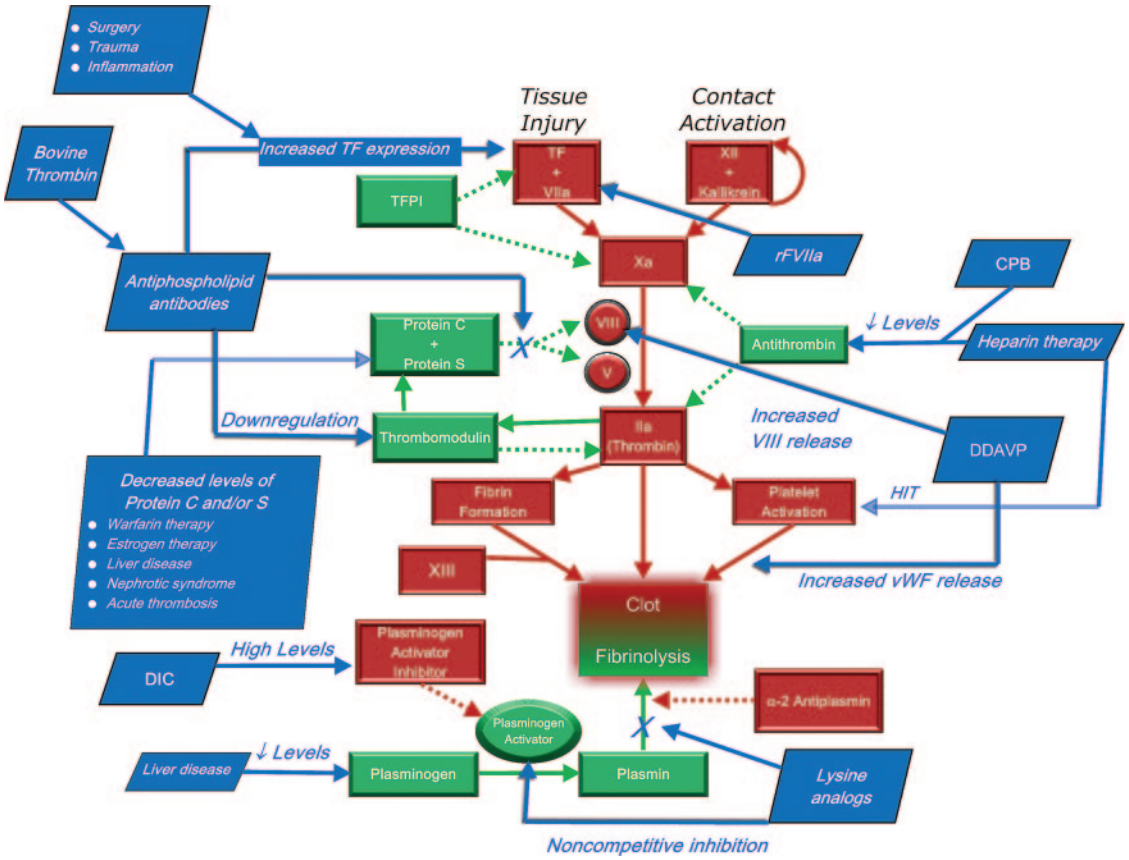

Figure 2. Acquired risk factors for hypercoagulability. Procoagulant forces (red) and natural anticoagulant/fibrinolytic forces (green) are diagrammed. Dashed lines indicate an inhibitory effect. Acquired risk factors are presented in blue boxes with white lettering and arrows indicating the mechanism for the hypercoagulable effect. "Xs" denote a specific block in a pathway. Note that some acquired risk factors have multiple effects; see text for full details. TF = tissue factor; TFPI = tissue factor pathway inhibitor; CPB = cardiopulmonary bypass; DDAVP = desmopressin; HIT = heparin-induced thrombocytopenia; vWF = von Willebrand factor; DIC = disseminated intravascular coagulation.

persistent or pathologic antibodies develop in response to infection.[13,66,67] Patients with thrombosis (arterial or venous) or repeated pregnancy loss plus antiphospholipid antibody detected on at least 2 occasions at least 12 weeks apart meet diagnostic criteria for antiphospholipid syndrome.[68] This syndrome is a well-established risk factor for recurrent thrombotic events, and indefinite anticoagulation is often recommended.[47,69,70]

Although liver and kidney disease are more frequently viewed as risks for bleeding, both can also contribute to hypercoagulability. In cirrhosis, protein C, protein S, antithrombin, and plasminogen levels are all decreased.[71] Although procoagulant factors are also lower because of impaired synthesis, prothrombin levels tend to be proportionately higher, setting up the potential for a hypercoagulable state. Additionally, endothelial dysfunction, particularly in the pulmonary and portal vasculature, increases platelet aggregation and promotes activation of coagulation.[72] It has been known for years that in nephrotic syndrome, fibrinogen synthesis is increased and antithrombin levels are below normal.[73,74] Similar to liver disease, there is also a component of endothelial dysfunction, particularly in the renal vasculature, which contributes to the 35% overall incidence of renal vein thrombosis.[75]

Many conditions associated with blood stasis, such as immobility from paralysis or low intracardiac flow caused by heart failure, are considered risk factors for hypercoagulability. Although abnormal blood flow is one of the classic components of Virchow triad, it alone does create thrombosis. The importance of Virchow's other 2 factors, vessel wall abnormalities and dysfunctional blood constituents, is just starting to be appreciated at the molecular level. The so-called "metabolic syndrome," which includes abdominal obesity, hypertension, elevated glucose, and unfavorable cholesterol levels, is associated with endothelial dysfunction and increased platelet aggregation.[76] Patients with heart failure have reduced nitric oxide release from the endothelium, promoting platelet aggregation.[77] Cancer cells release microparticles that promote fibrin deposition.[78] Even advancing age, although hardly considered a disease state, is associated with procoagulant changes including elevated fibrinogen,[79] increased factor VII,[80] impaired fibrinolytic activity,[81] and increased platelet aggregation.[82] Clearly, these factors represent complex interactions that are just beginning to be understood.

Clinical Scenarios

Although there is an obvious need for hemostasis after tissue injury caused by trauma or surgery, hypercoagulability can occur during the healing process. In the absence of preventive therapy, thrombosis will occur in up to 50%

of patients who undergo surgery, particularly orthopedic surgery, and up to 60% of trauma patients.[83,84] Levels of tissue factor in circulation as well as that exposed on the affected endothelium increase.[85,86] Disseminated intravascular coagulation can occur after severe tissue damage and is both a bleeding and thrombotic condition. Although disseminated intravascular coagulation promotes thrombin generation and fibrin deposition, the fibrinolytic system is severely impaired because of high levels of PAI-1.[87,88] Furthermore, in trauma patients who receive no anticoagulant prophylaxis, markers of thrombin generation increase within 24 hours of the injury and stay increased for approximately 5 days, without an early, compensatory increase in tissue factor pathway inhibitor.[84] This has led to the recent recommendation that all surgical patients, with the exception of ambulatory patients undergoing minor procedures or those patients at high bleeding risk, receive anticoagulant thromboprophylaxis with drugs other than aspirin alone.[9]

Cardiac surgery using cardiopulmonary bypass (CPB) results in a wide range of hematologic insults. In addition to consumptive and hemodilutional losses of procoagulant factors, anticoagulant factors become low as well.[89,90] After prolonged CPB, transfusion of hemostatic blood products is typical, but this can result in excessive thrombin generation and many case reports in the literature describe catastrophic thromboses after platelet, cryoprecipitate, and protamine administration.[91] Given the possibility of hypercoagulability, hemostatic drugs should probably be used with caution in patients with other known risk factors for thrombophilia (see below).

Pharmacologic Causes

The use of oral contraceptives or hormone replacement therapy is associated with increased risk of thrombosis.[3,92] The prothrombin 20210A mutation or factor V Leiden may increase risk for atherothrombotic cardiovascular disease in women receiving estrogen replacement therapy.[93] Estrogen intake may lead to an acquired protein S deficiency and hence decreased natural anticoagulation. Normal pregnancy, a hyperestrogenic state, is associated with decreased free protein S antigen, with mean levels in the second and third trimester of 39% and 31%, respectively.[94]

The lysine analogs tranexamic acid and aminocaproic acid are antifibrinolytics frequently used in cardiac surgery that competitively inhibit plasminogen activator and noncompetitively inhibit plasmin. Thrombotic events, including retinal artery or vein obstruction (tranexamic acid) and glomerular capillary thrombosis (aminocaproic acid), are reported after therapy, and patients with a history of thromboembolic disease appear at increased risk.[95] Aprotinin, a broad-spectrum serine protease inhibitor with antifibrinolytic effects, was recently removed from marketing (still available for compassionate use), and further analysis of the Blood Conservation Using Antifibrinolytics in a Randomized Trial (BART) is underway.[96]

The hemostasis-enhancing drugs desmopressin acetate and recombinant factor VIIa (rFVIIa) are frequently used for prevention or treatment of bleeding in various settings, but these agents may contribute to hypercoagulability in some patients. Desmopressin, a vasopressin analog, stimulates release of procoagulant (factor VIII and von Willebrand factor), thromboresistant (tissue plasminogen activator), and vasodilatory (prostacyclin) factors from the endothelium. This agent is a treatment of choice for many patients with von Willebrand disease, mild hemophilia A, some congenital platelet function defects, and uremia.[97] There have been reports of thrombotic events after infusion of desmopressin, and the Food and Drug Administration (FDA) recommends using the drug with caution in patients predisposed to thrombosis.[98,99] In one meta-analysis, desmopressin was associated with a 2.4-fold greater risk of perioperative myocardial infarction, with minimal reduction in perioperative bleeding.[100] The risk of thrombotic sequelae with rFVIIa is relatively low in its licensed indications, i.e., treatment of bleeding in patients having hemophilia A or B with inhibitors, acquired hemophilia, or congenital factor VII deficiency; or prevention of bleeding in surgical interventions or invasive procedures in the same patient types.[101] However, rFVIIa has also been used off-label extensively in patients with refractory, life-threatening bleeding not in those categories. Across 13 studies of rFVIIa therapy for coagulopathy secondary to anticoagulant therapy, cirrhosis, or severe traumatic injury, thrombotic adverse events occurred in 6.0% of rFVIIa-treated patients (45 of 748 patients) and 5.3% of placebo-treated patients (23 of 430 patients) ($P = 0.57$).[102] In a study in patients with massive postpartum hemorrhage, rFVIIa therapy reduced maternal mortality and no thromboembolic events were reported.[103] Nevertheless, close monitoring of rFVIIa-treated patients for signs or symptoms of thrombosis is warranted.

Fibrin sealant (a widely used, multicomponent system of fibrinogen and thrombin), bovine thrombin, and recombinant human thrombin are topical aids to tissue adhesion and hemostasis, but may lead to life-threatening thromboembolic events if administered intravascularly.[104] Furthermore, exposure to bovine thrombin during cardiovascular surgery has been linked to the development of antiphospholipid antibodies that are associated with thrombotic risk.[105,106]

Acquired antithrombin deficiency may result from heparin therapy. In 250 patients administered heparin during and after percutaneous coronary intervention, the mean decrease in antithrombin activity was 7.5% during the 1- or 2-hour procedure and 4% between the end of the procedure and the next morning, and the level remained significantly less than normal until heparin had been discontinued for ≥20 hours.[107] Heparin therapy leads to the hypercoagulable condition of HIT in approximately 1% to 5% of patients administered unfractionated heparin and <1% of patients administered low-molecular-weight heparin.[108] Approximately 8% of heparin-treated patients experience a nonimmune-mediated, asymptomatic transient decrease in the platelet count (sometimes known as "HIT type I"); however, the term "HIT" now preferably refers to the hypercoagulable state. HIT is strongly associated with venous and arterial thrombosis (odds ratio, 12–37) and is more fully discussed below as an example of acquired hypercoagulability.[109]

Table 1. Laboratory Evaluation of Hypercoagulability

Risk factor(s) to be investigated	Consensus guideline[10,160]
Factor V Leiden, functional protein C, functional protein S, functional antithrombin, and prothrombin G20210A mutation	Appropriate for patients with VTE (particularly idiopathic VTE) who are younger and/or have a family history of thrombosis. Not recommended for patients with arterial thrombotic disease associated with atherosclerosis or adults with stroke. Consider in certain unusual situations such as patients with unexplained arterial thrombosis without atherosclerosis or young patients.
Antiphospholipid antibodies (e.g., anticardiolipin antibodies and lupus anticoagulants)	Appropriate for patients with VTE, if the VTE is idiopathic or associated with autoimmune disease or in the absence of a family history of venous thrombosis. Consider for patients with arterial thrombosis, particularly in a young person or a person with no documented atherosclerosis. Consider for patient with unexplained stroke or cerebral venous thrombosis, particularly in a young person with autoimmune disease.
All of the above	Appropriate for patients with a history of recurrent VTE; patients with VTE before the age of 50 y or with a family history of VTE; patients with VTE that is unprovoked, at an unusual site, or secondary to pregnancy, oral contraceptives, or hormone replacement therapy.
Homocysteine	Consider for patients with VTE, documented atherosclerotic arterial occlusive disease, documented stroke, or existing cerebrovascular disease.
Suspected inherited defect	May be worthwhile before pregnancy or oral contraceptive use in asymptomatic females who are first-degree relatives of a proband with defined inherited thrombophilia.
HIT	Consider in patient in whom the platelet count decreases ≥50%, or new thrombosis develops, 5–14 d after heparin initiation, even if the patient is no longer receiving heparin.

VTE = venus thromboembolism; HIT = heparin-induced thrombocytopenia.

ASSESSMENT OF HYPERCOAGULABILITY

Clinical suspicion is paramount in assessing a patient's risk of hypercoagulability. Whereas most perioperative physicians readily uncover risks for bleeding, risks for thrombosis are less sought after. A careful personal and family history of thrombosis or fetal loss and a thorough review of pharmacologic factors that predispose to hypercoagulability should be taken. What must be realized is that, although any single risk factor might not lead to a thromboembolic event, risks are cumulative and patients with an inherited risk at baseline can experience poor outcomes when placed in clinical situations that can also result in acquired risks. For example, a patient with factor V Leiden may be asymptomatic, but when exposed to antifibrinolytics and prolonged CPB, catastrophic thrombosis can result.[110,111]

Unfortunately, screening for inherited risk factors is problematic because of their infrequent prevalence in the general population. In mathematical modeling using even the highest level of testing specificity, there would likely be at least 1 to 4 false positives for every true positive result, and the ratio could be as high as 100:1.[112] Therefore, indiscriminate testing in unselected individuals, even after a first episode on a deep venous thrombosis, is not recommended.[113] In general, testing for inherited risk factors is only recommended for young patients with unprovoked or recurrent thromboembolism or patients with arterial thrombosis who do not have known atherosclerotic disease. Consensus guidelines for testing various conditions are summarized in Table 1.

Testing for acquired hypercoagulability is also problematic. As demonstrated in Figure 2, acquired conditions can exert their effects at many different points along the coagulation–fibrinolysis cascades. Therefore, any laboratory testing should be tailored to the patient's clinical situation. General laboratory markers of a persistent hypercoagulable state include elevated levels of prothrombin fragment 1.2, thrombin-antithrombin complexes, plasmin-antiplasmin complexes, fibrinopeptide A, fibrin monomer, and D-dimer.[114,115] Among these, D-dimer is arguably the best studied for routine clinical application, and clinical trial data support its utility for determining the need for prolonged anticoagulation in patients with unprovoked venous thromboembolism.[116,117] Soluble P selectin and measurement of thrombin generation show promise as biomarkers of a prothrombotic state but require additional prospective testing.[118]

Of course, the ideal test for hypercoagulability would allow clinicians to assess a patient's risk of thrombosis before it actually happened. Unfortunately, 2 of the most frequently ordered plasma tests, prothrombin time and activated partial thromboplastin time, have failed to show any correlation with thrombotic events in orthopedic, trauma, or general surgery patients.[119–121] This is not surprising because each provides only limited information on stages of clot formation and none on platelet function or fibrinolytic activity. One whole blood assay that provides a comprehensive view of the clotting and fibrinolytic pathways is thromboelastography (TEG®). Both TEG® and rapid-TEG® (which differs by the addition of tissue factor) have gained interest for the evaluation of hypercoagulability.[122–125] However, a recent review of the literature found that the test's predictive accuracy for postoperative thrombotic events was "highly variable," in part because of the lack of reference standards.[126] More studies using TEG® with respect to hypercoagulability seem warranted.

HIT: AN ACQUIRED HYPERCOAGULABLE STATE

Overview and Pathogenesis

HIT is an adverse reaction to heparins that leads to an increase in thrombotic risk. Although the odds ratio for

Table 2. Estimated Risk of Heparin-Induced Thrombocytopenia for Different Patient Populations

Estimated risk of HIT[10]	Patient population
>1% (up to approximately 5%)	Postoperative patients receiving prophylactic-dose UFH >4 d
	Postoperative patients receiving therapeutic-dose UFH >4 d
0.1% to 1%	Medical/obstetric patients receiving prophylactic-dose UFH >4 d
	Medical/obstetric patients receiving therapeutic-dose UFH >4 d
	Postoperative patients receiving LMWH ≥4 d
	Postoperative/critical care patients receiving UFH flushes >4 d
	Medical/obstetric patients receiving LMWH after first receiving UFH
<0.1%	Medical/obstetric patients receiving LMWH >4 d
	Medical/obstetric patients receiving only heparin flushes
	Any patient receiving UFH or LMWH <4 d

HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin.

thrombosis in HIT depends in part on how the thrombocytopenia is assessed, i.e., absolute platelet count <150 × 10^9/L (odds ratio, 37) versus 50% relative decrease in platelet count beginning after 5 days of heparin (odds ratio, 12), the risk is comparable to, if not greater than, that associated with lupus anticoagulants and the more common inherited hypercoagulable states.[127] Regardless, HIT provides a good example to illustrate the clinical approach to diagnosis and management of prothrombotic states.

HIT is unique as a hypercoagulable state in that it paradoxically occurs during (or soon after) therapy with an anticoagulant, specifically heparins. The paradox is explained by the pathogenesis of HIT in which procoagulant forces are substantially enhanced via immune-mediated mechanisms.[128,129] In HIT, antibodies to a complex of heparin and platelet factor 4 (PF4) bind to the platelet surface and induce platelet activation. Activated platelets release PF4, which furthers complex formation, releasing microparticles that increase generation of thrombin, which in turn activates more platelets. This cycle contributes to thrombocytopenia and thrombosis. Antibody-mediated endothelial injury contributes further to the hypercoagulable state. Bleeding is a rare complication in HIT, consistent with its hypercoagulable nature. Recent data suggest that HIT may be a misplaced immune-host defense, mimicking immunity against repetitive antigens such as seen in microbial defense.[130] The risk of HIT for various patient populations is summarized in Table 2. There may be an increased risk with the use of bovine versus porcine heparin.[131]

Diagnosis

Like all hypercoagulable states, the evaluation for HIT must begin with suspicion. HIT should be suspected whenever the platelet count decreases ≥50% within 5 to 14 days after heparin introduction, even if the patient is no longer receiving heparin.[10] In patients with recent (≤100 days) previous heparin exposure, a more rapid onset (≤24 hours) of thrombocytopenia may occur, often in association with acute systemic reactions.[132] In a patient acquiring HIT after CPB, the platelet count either may not increase after 3 to 4 days (i.e., the time by which CPB-related thrombocytopenia would have typically resolved) or may decrease 3 to 4 days after bypass.[133] Less frequently, the onset of HIT may be delayed up to 20 days and manifest after the patient has been discharged from the hospital.[134] The thrombocytopenia of HIT is usually moderately severe (median nadir, 50 to 70 × 10^9/L), although a relative 50% decrease in platelet count is more indicative of HIT than the absolute count. Other causes of thrombocytopenia, including sepsis, mechanical destruction via intraaortic balloon pump, or another drug-induced thrombocytopenia, should be considered and excluded.

HIT may first be suspected after a thrombotic event such as deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, or limb artery occlusion.[135] Hemorrhagic-like skin lesions at heparin injection sites, systemic symptoms such as hypotension or flushing after heparin administration, and heparin resistance (i.e., related to PF4 release leading to heparin binding) should also prompt suspicion. Venous events predominate over arterial events, except in cardiac surgery patients.[136] Approximately 38% to 76% of affected patients have a thromboembolic complication within a month, typically within the first few days.[137] Nearly 10% of patients with HIT and thrombosis lose a limb, and mortality is approximately 20% to 30%.[138]

Laboratory testing is recommended when HIT is suspected, although results may not be available for hours to days, so it is useful to estimate the pretest probability using the "4 Ts" system. The exact scoring method is reviewed elsewhere, but involves the criteria of thrombocytopenia, timing of platelet count decline, thrombosis, and other causes for low platelets.[139] The resultant score seems most useful for excluding HIT. Antigenic immunoassays for the heparin-PF4 antibodies are frequently used and have a >90% sensitivity, but poor specificity because they also detect nonplatelet-activating antibodies. With immunoassays for heparin-PF4 antibodies, the optical density may be more informative than a simple positive or negative result because a higher optical density (e.g., at least >1.0) is associated with increased likelihood of a strongly positive serotonin release assay (see below) and with an increased thrombotic risk in HIT.[140] Whereas heparin-PF4 immunoassays typically detect immunoglobulin (Ig)G, IgA, and IgM classes, assays for only the IgG class have become commercially available and may improve clinical specificity for HIT. However, overdiagnosis of HIT can still occur if a positive immunoassay result alone is considered confirmatory of HIT, irrespective of the clinical scenario.[141]

Functional assays such as the serotonin release assay have greater sensitivity (95%) and specificity (95%) than immunoassays, but are technically demanding and usually performed only as a confirmatory test. Most patients with HIT elicit a strong positive result (i.e., at least >50% release, where >20% is considered positive) with the serotonin

release assay.[142] Still, not all heparin-PF4 antibodies have platelet-activating capabilities, and most seropositive patients do not develop HIT. In a study of cardiac surgery patients receiving unfractionated heparin postoperatively, heparin-PF4 antibodies were detected by immunoassay in 50% of the patients, platelet-activating heparin-PF4 antibodies were detected by serotonin release assay in 20%, and HIT occurred in 1%.[143] This illustrates that, similar to all hypercoagulable states, clinician awareness and judgment are paramount in diagnosis.

Treatment

When HIT with or without thrombosis is strongly suspected, all heparins should be discontinued and a fast-acting, nonheparin anticoagulant should be initiated promptly, without delay for laboratory confirmation.[10] Heparin cessation alone is inadequate treatment because of the persistent hypercoagulability and increased thrombotic risk for at least a month. Three anticoagulants, each a direct thrombin inhibitor, are FDA approved for use in HIT patients in the noninterventional setting (lepirudin, argatroban) or during percutaneous coronary intervention (argatroban, bivalirudin). Additionally, danaparoid (a heparinoid unavailable in the United States) and fondaparinux (a selective factor Xa inhibitor) have been suggested as alternative anticoagulants, although neither is FDA approved in this setting.[10] Warfarin should be avoided during acute HIT because it is slow acting and also because its earlier reduction of protein C and protein S levels, as compared with factor X, factor IX, and prothrombin levels, may actually promote thrombosis.

The direct thrombin inhibitors are routinely monitored using the activated partial thromboplastin time or, at higher levels of anticoagulation, activated clotting time. In historical controlled studies, lepirudin and argatroban each significantly reduced adverse outcomes, particularly new thrombosis, in patients with HIT.[144] Lepirudin is renally cleared, and doses should be reduced in patients with renal impairment. Patients often develop antilepirudin antibodies and, rarely, patients reexposed to lepirudin have anaphylactoid reactions.[10] Argatroban is hepatically metabolized, and doses should be reduced in patients with hepatic impairment or conditions associated with hepatic hypoperfusion. Argatroban profoundly prolongs the prothrombin time/international normalized ratio, and published approaches to monitor the transition from argatroban to warfarin should be followed.[10] Retrospective data suggest that bivalirudin at doses much less than those used during coronary intervention may be effective and safe in patients with HIT in the noninterventional setting; however, no prospective study has been published. Bivalirudin is cleared by renal and enzymatic mechanisms, and doses should be reduced in renal impairment.

HIT during pregnancy, although rare, poses unique risks because of the potential adverse fetal effects.[145] For treating HIT in a woman who is pregnant, reported experience is sparse for the direct thrombin inhibitors (lepirudin, argatroban) and is also limited, yet encouraging, for danaparoid and fondaparinux.[146–151] Each of these alternative anticoagulants is a pregnancy category B drug.

The data on alternative anticoagulants during cardiac surgery are sparse. Because HIT antibodies have a relatively short half-life, the ideal situation is to delay elective cardiac surgery until heparin-PF4 antibody assays are negative, which should occur after 3 months.[10,132] The operation can then proceed with heparin anticoagulation and protamine reversal during the operative period only, with alternative anticoagulants used for pre- and postoperative management as needed.[10] If cardiac surgery cannot be delayed, use of an alternative anticoagulation is recommended. Small case series of CPB with lepirudin and argatroban have been reported,[152,153] although bivalirudin has been studied more extensively for this purpose.[154,155] Bivalirudin also seems to have become the anticoagulant of choice for off-pump cardiac surgery, with reduced dosing comparable to that used in the cardiac catheterization laboratory.[156,157]

The optimal duration of alternative, nonheparin anticoagulant therapy has not been established. Consideration should be given to providing treatment for at least a month in HIT patients without thrombosis and 3 to 6 months in HIT patients with thrombosis.[137,158] Warfarin may be initiated after adequate parenteral nonheparin anticoagulation is achieved and the platelet count is $>150 \times 10^9$/L, and warfarin and parenteral anticoagulation should be overlapped until a therapeutic international normalized ratio is achieved for at least 2 consecutive days.[10] In a patient with current or previous HIT, heparin should be avoided at least as long as heparin-PF4 antibodies are detectable by a sensitive assay.

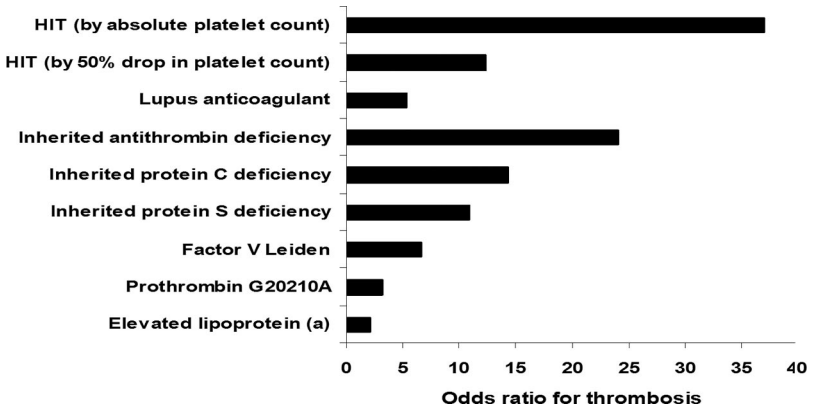

Figure 3. Odds ratio for thrombosis in selected hypercoagulable states. Because a range of odds ratios have been reported across studies and sources for these hypercoagulable states, the data are representative only. The odds ratios were extracted from a single source,[159] with exception of data for lipoprotein (a) and prothrombin G20210A.[22,52] The reported odds ratios for thrombosis in heparin-induced thrombocytopenia (HIT) were estimated using as criteria for thrombocytopenia either an absolute platelet count $<150 \times 10^9$/L or a 50% relative decrease in the count beginning after 5 days of heparin.

CONCLUDING REMARKS

Physicians in the operating room are acutely aware of the dangers of excessive bleeding, but thrombotic complications, which can be equally as devastating, are often ignored. Hypercoagulability can be inherited or acquired and, as shown in Figure 3, significantly increase the risk of thrombosis. The first step in improving management of these situations is to make perioperative physicians aware of these risks, which we have attempted to do in this review. Careful, watchful assessment for hypercoagulability is important because effective management strategies, often involving anticoagulation, may be available. HIT is one such hypercoagulable state that can be successfully diagnosed and treated now that there is a strong awareness of it. In the future, it is likely that new inheritable risk factors will be identified by genome-wide analyses, the mechanism(s) by which acquired risk factors exert their effects will be better elucidated, and management strategies, possibly involving newer antithrombotic drugs, for hypercoagulability will be refined.

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