The Scientific Basis for Evaluation and Management of Thrombotic Disorders

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Thrombotic disorders include qualitative and quantitative abnormalities of platelets, coagulation factors, or their regulatory mechanisms. These disorders can be either congenital or acquired. For the thoracic surgeon, a sound knowledge of the pathogenesis and treatment of these diseases is paramount. To prevent the thrombotic complications associated with these disorders, patients are frequently prescribed anticoagulants or antiplatelet agents. The perioperative management of such patients centers on their risk of bleeding intraoperatively or postoperatively should these agents be continued versus their risk of thrombosis upon cessation of such therapies. In this article, the authors discuss the background and pathogenesis of thrombogenic disorders and highlight the important factors to be considered in the perioperative management of the prothrombotic patient.

Coagulation cascade

Over the past 2 decades, our understanding of coagulation biochemistry has changed dramatically. In 1964, a model of coagulation was proposed that consisted of a series of sequential reactions in which zymogen clotting factors, once activated, in turn activated subsequent clotting factors, leading to the well-known coagulation cascade [1,2]. This paradigm was later modified after the discovery that some of the previously identified zymogens were actually cofactors of coagulation. The cascade was also split into the “intrinsic” and “extrinsic” pathways of coagulation, with common convergence on the activation of Factor X. In the laboratory, the activated prothrombin time (aPTT) reflects the activity of factors in the extrinsic and common pathways, whereas the activated partial thromboplastin time (aPTT) measures that of the intrinsic and common pathways.

The intrinsic system was confined to factors in the circulating blood, whereas the extrinsic pathway was limited to the tissues, hence the naming of “tissue” factor (TF), the receptor for Factor VII. It became evident that there were obvious flaws with the classic cascade model. Patients deficient in Factor XII, prekallikrein, and high-molecular-weight kininogen lack any clinical bleeding tendency, despite demonstrating an elevated aPTT. Furthermore, the intact extrinsic pathway does not overcome the serious, life-threatening bleeding exhibited by hemophiliacs. Although the concept of two separate pathways converging on activation of a common pathway provides a valuable scheme for diagnostic purposes, recent research reveals that these pathways are intimately interrelated in vivo, because the TF/VIIa complex can activate both Factors IX and X. In addition, the concept that lipid membranes of different cellular surfaces both localize and amplify the biochemical reactions of coagulation has revolutionized our perspective on hemostasis [3,4].
The key elements of coagulation in vivo are platelets, the endothelium, and circulating coagulation factors. This trio works in concert to allow for the initiation, propagation, and amplification of the coagulation cascade. In vivo, endothelial disruption exposes TF and collagen to circulating clotting factors and platelets. This permits TF to initiate coagulation by activating Factor VII [5,6]. The TF/VIIa complex then activates Factors IX and X. Concurrently, the wounded endothelium, with its exposed collagen and von Willebrand factor (vWF), allows for the activation of circulating platelets. Once activated, the platelets alter their morphology, and in so doing display their densely anionic and procoagulant phospholipid membranes. The platelet plug that results allows for further amplification and propagation of the clotting cascade [7].

The injured, TF-bearing endothelial cell facilitates the formation of the prothrombinase complex, consisting of Factor Xa, activated by TF/VIIa, and Cofactor Va, activated by Factor Xa. The prothrombinase complex produces thrombin, Factor IIa, from prothrombin, Factor II. The thrombin generated by the prothrombinase complex, Xa/Va, participates in downstream feedback amplification. Thrombin activates both platelets and Cofactors V and VIII on activated platelet surfaces. The activation of Factor VIII mediates additional release of vWF by dissociating it from Factor VIII, leading to further platelet adhesion and aggregation at the site of injury. Factor IXa, activated by TF/VIIa at the initiation of coagulation, moves to nearby activated platelet surfaces, with exposed Cofactors Va and VIIIa. The VIIIa/IXa complex, otherwise known as the tenase complex, yields more Factor Xa. The assembly of multiple tenase and prothrombinase complexes on the exposed phospholipid membranes of activated platelet surfaces allows for the propagation phase of coagulation to occur, resulting in a burst of thrombin generation, and ultimately, the clotting of fibrinogen [3,4,8,9]. The thrombin generated during this burst also activates Factor XIII to form XIIIa, leading to the cross linkage of fibrin and clot maturation.

Control mechanisms exist to confine clot formation to the site of vessel wall injury and to prevent widespread thrombosis [9]. These include TF pathway inhibitor (TFPI) [10], the protein C/protein S/thrombomodulin (TM) system, Antithrombin III (ATIII) and the fibrinolytic system. ATIII and TFPI inhibit any Factor Xa that dissociates from the TF-bearing cell. Likewise, excess thrombin that escapes into the general circulation is inhibited by ATIII. Adjacent normal endothelium binds thrombin via thrombomodulin. This thrombin/thrombomodulin complex activates protein C (APC). Along with its cofactor protein S, APC inactivates Factors Va and VIIIa escaping from the injured endothelial cell surface. Plasmin, crucial to the fibrinolytic system, is proteolytically activated by a Factor XII-dependent pathway or by plasminogen-activators (PA), including tissue-type PA (t-PA) and urokinase-like PA (u-PA). Plasmin both degrades fibrin and interferes with its polymerization. The affinity of t-PA for fibrin makes it a useful therapeutic reagent, because it targets the fibrinolytic activity of plasmin to sites of recent clotting. These inhibitory mechanisms not only help localize thrombin formation to the site of vessel wall injury, but also prevent extension of clot to uninjured endothelial surfaces or occlusion of the vessel lumen.

**Thrombotic disorders**

*Inherited thrombophilias*

Patients who have inherited thrombogenic tendencies are at greater risk for thromboembolic events. Their elevated thrombosis threshold makes them more susceptible to thrombosis, even following minor acquired triggers. Importantly, it is well-recognized that the perioperative period independently increases the risk of venous thromboembolism (VTE). The various inherited thrombogenic tendencies are discussed below, with emphasis placed on the various thrombosis thresholds for these disorders compared with the general population. Most of the inherited hypercoagulable disorders predispose patients to VTE, although some also have an association with arterial thromboembolic events and arteriosclerotic disease.

The incidence of VTE is approximately 2 million per year, with 60,000 deaths from resulting pulmonary embolism annually [11]. Inherited thrombophilias are detected in 40% to 50% of cases following a VTE event [12,13]. The inherited thrombotic disorders can be divided into those that have decreased levels of antithrombotic proteins, including ATIII deficiency, protein C (PC) deficiency and protein S (PS) deficiency; and those that have increased levels of prothrombotic proteins, including Factor V Leiden (also termed APC resistance), thrombomodulin gene mutation G20210A, and increased levels of certain clotting Factors (VII, XI, IX, VIII, vWF) [12–16].
The inherited deficiencies of ATIII, PC, and PS were among the first identified causes of thrombophilia, and result in a lack of key anticoagulants for crucial steps in the clotting cascade, tipping the balance in favor of thrombosis [17–20]. Overall, deficiencies in ATIII, PC, and PS are rare, detectable in less than 1% of the general population and in fewer than 10% of patients who have VTE [21–23]. When compared with the wild type, the risk of VTE is fivefold to eightfold higher among carriers of deficiencies of these anticoagulant proteins [24–27].

The prothrombin gene mutation G20210A is also relatively rare, being present in only 2% of the general population. Of patients who have VTE, 7% will possess a prothrombin gene mutation [28–30]. The single nucleotide change (G to A transition) in the 3'-untranslated region of the prothrombin gene is associated with elevated prothrombin levels, leading to the observed increased risk of thrombosis. Although the risk of VTE for heterozygotes is twofold to threefold higher compared with the general population, the risk of VTE in probands increases with age, and can be up to 19 fold higher after age 60 [28,31].

Factor V Leiden is predominantly restricted to whites, with a prevalence of 5% in the general population, making it the most common inherited thrombophilia [32,33]. Among patients who have VTE, approximately 10% will possess the Factor V Leiden mutation [32,33]. The mutation is caused by a substitution of glutamine for the normal arginine residue at position 506 of Factor V. The mutant Factor V cannot be inactivated by cleavage at the usual arginine residue, making it resistant to the anticoagulant effect of APC. The risk of VTE is twofold to sevenfold higher among heterozygotes and 40 to 80 fold higher among homozygotes [25,26,31,34–36].

Hyperhomocysteinemia is a metabolic defect associated with a risk of VTE. In recent years, the relationship between arterial thrombosis and hyperhomocysteinemia has been elucidated [37]. Homocysteine is derived from the metabolism of methionine. Homocysteine is common among individuals who have a variant of the methylene tetrahydrofolate reductase (MTHFR) enzyme, particularly in the homozygous state. This variant has a prevalence of 12% in the general population [38], similar to its prevalence in patients who have VTE. It is felt that homocysteine may cause endothelial dysfunction through the formation of reactive oxygen species, and appears to interfere with the vasodilator and antithrombotic functions of nitric oxide [39]. Poor dietary intake of folate, vitamin B6, and vitamin B12 may contribute to and exacerbate hyperhomocysteinemia.

Antiphospholipid syndrome (APS) is an acquired procoagulant state characterized by recurrent venous and arterial thromboembolism [40]. APS exists in both primary and secondary forms. The primary form exists in the absence of systemic lupus erythematosus (SLE), whereas the secondary form occurs in those who have SLE. Some patients who have SLE produce autoantibodies to phospholipid-complexed plasma proteins. A variety of protein substrates have been implicated, including prothrombin, PS, PC, and beta-2-Glycoprotein I; anticardiolipin antibodies are also increased. Some of these antibodies prolong in vitro coagulation tests, leading to the term "lupus anticoagulant." This prolongation fails to correct with normal plasma, indicating the presence of the inhibitory autoantibodies. Although the lupus anticoagulant displays an anticoagulant effect in vitro, it leads to a prothrombotic state in vivo, manifesting as both recurrent cerebrovascular accidents and recurrent miscarriages. This constellation of clinical features in association with the lupus anticoagulant is referred to as APS. Both forms of APS are strongly associated with VTE. The secondary form is associated with a fourfold increased risk of VTE compared with the general population [16,41]. Among patients who have SLE, those who have anticardiolipin antibodies have a twofold increased risk of VTE compared with those who do not have such antibodies [42].

Acquired thrombophilies

Patients who have atrial fibrillation (AF) and those who have mechanical heart valves represent additional patient populations at risk for arterial thromboembolic events. These patients are frequently anticoagulated, which often mandates adjustment of their anticoagulation regimen before planned surgical procedures.

Approximately 2 million patients in the United States have AF, and 40% of these patients are anticoagulated with oral agents. The risk of stroke in patients who have AF who are not anticoagulated is 4.5% per year [43]. This risk is increased in patients who have suffered prior AF-related strokes, and can be as high as 12% in these patients. Of note, strokes caused by AF are more disabling, more likely to recur, and are more likely to cause death than strokes from other causes [44,45]. Anticoagulation reduces the risk of stroke in AF by 66%.
Evidence shows that the risk of stroke is most effectively reduced with an international ratio (INR) in the range of 2.0 to 3.0 [47,48].

Prosthetic valve thrombosis has an incidence ranging from 0.03% to 5.7%, and is most associated with inadequate anticoagulation and a mechanical valve placed in the mitral position [49–52]. The arterial thromboembolic events associated with prosthetic valve thrombosis are fatal in 15% of cases. The various prosthetic valves possess varying levels of thrombogenic potential, which is determined by the type of valve (mechanical versus bioprosthetic), design of valve (caged ball versus disc), and the position in which it is placed (mitral versus aortic) [49]. Although homografts require no anticoagulation, the recommended INR is 2.5 to 3.5 for patients who have mechanical prosthetic valves, and 2.0 to 3.0 for those who have bioprosthetic valves [53].

**Heparin-induced thrombocytopenia**

Heparin can cause thrombocytopenia via immune (Type II) and nonimmune mechanisms (Type I) [54–57]. Because heparin-induced thrombocytopenia (HIT) Type I does not involve the production of heparin-dependent antibodies, it is also referred to as heparin-associated thrombocytopenia (HAT). HIT Type II can induce an acquired prothrombotic state via the induction of platelet-activating antibodies [58]. A high binding affinity exists between heparin and platelet factor 4 (PF4). Although neither heparin nor PF4 is antigenic by itself, the heparin-PF4 binding interaction elicits conformational changes in both molecules, exposing highly antigenic epitopes. In some patients, these epitopes induce antibody formation against the heparin-PF4 macromolecular complexes. The resulting antibodies promote a prothrombotic state by activating platelets through activation of the platelet FcRIIA receptors. This ultimately leads to the destruction of platelets and the release of prothrombotic platelet-derived microparticles into the circulation. These microparticles promote a state of hypercoagulability by activating thrombin, accounting for the observed increased thrombogenicity seen in HIT.

HIT manifests as a decrease in the patient's platelet count by 30% to 50% within 5 to 15 days of heparin treatment, and develops in 3% of patients treated with unfractionated heparin for more than 4 days [59]. The appearance of thrombocytopenia may be accelerated in the setting of prior heparin sensitization, and has been reported to occur within hours of heparin exposure in the preceding 3 months [55]. The platelet count rarely decreases to lower than 20,000; however, in spite of the associated thrombocytopenia, the predominant clinical picture is paradoxically one of thrombosis, not hemorrhage. The association of thrombocytopenia with thrombosis results in the clinical syndrome known as heparin-induced thrombocytopenia with thrombosis (HITT). Both venous and arterial thromboembolic complications can be seen in 50% to 70% of patients who have HITT, and include deep venous thrombosis, pulmonary embolism, adrenal vein thrombosis, cerebral sinus thrombosis, lower extremity thrombosis, myocardial infarction, stroke, and end-organ thromboses (ie, mesenteric, renal, brachial) [60–62]. The most common of these is deep venous thrombosis; compared with medical patients, the risk of VTE from HIT is greater in high-risk surgical patients. Without treatment, HITT has a mortality of 20% to 30% [63,64].

The treatment for HIT begins with immediate cessation of heparin and all heparin-containing products. Management focuses on prevention of the thromboembolic complications, observed in more than 50% of patients, and requires anticoagulation with non-heparin-containing agents. The discontinuation of heparin is not enough to prevent these complications, because the heparin dependent antibodies are detectable in the serum for up to 50 to 85 days [65]. Warfarin should not be used alone in the management of HIT. The direct thrombin inhibitors and the low molecular weight heparinoids, danaparoid, are drugs used in the treatment of HIT. Specifically, the direct thrombin inhibitors play a major role in the management of HIT by targeting the enhanced thrombin generation. The direct thrombin inhibitors are lepirudin, argatroban, bivalirudin, and desirudin [54].

**Miscellaneous acquired thrombotic states**

Other medical conditions and disease states are also associated with an increased prothrombotic tendency, including pregnancy, cancer, blood dyscrasias, and hematological malignancies. Although it is outside the scope of this article to discuss the various factors contributing to the evaluation and management of the hypercoagulable state in these specialized clinical scenarios, the reader is directed elsewhere for additional information [12].
Perioperative management of thrombotic disorders

Preoperative considerations

Patients who have prothrombotic tendencies are frequently on chronic anticoagulation therapy with warfarin. Before planned surgical intervention, decisions must be made regarding perioperative duration of such therapy. The risks of bleeding from the operative site versus the potential for increased risk of thromboembolic events secondary to cessation of anticoagulation must be considered. Decision-making should be centered on the original indication for anticoagulation and the likelihood of the patient suffering a thromboembolic event [12]. It should be noted that arterial thromboembolism has a higher morbidity and mortality compared with venous thromboembolism. Arterial thromboembolism causes death in 40% of events and major disability in 20% of cases [66], whereas venous thromboembolism causes sudden death in 6% and major permanent disability in fewer than 5% of cases [67]. Given the different risks, patients chronically anticoagulated for the prevention of recurrent arterial thromboembolism should be considered distinct from those patients whose indication for anticoagulation is the prevention of venous thrombosis.

Surgery itself is estimated to increase the risk of VTE by 100-fold. In patients who have concurrent hypercoagulable states, this risk of VTE is higher, and varies with the associated condition. Exclusive of these factors, estimates have been derived to predict the rate of thromboembolism in the absence of anticoagulation, and to determine the risk reduction for such thromboembolic events in the presence of anticoagulation [66]. For acute venous thrombotic events, the thromboembolic rate without anticoagulation is 40% per month in the first month and decreases to 10% at 2 months. In this setting, the risk reduction with anticoagulation is 80% in the first month and increases to 90% thereafter. For cases of recurrent VTE, the rate of thromboembolism without anticoagulation is 15% per year, with a 90% risk reduction if the patient is anticoagulated [66].

In patients who have a history of arterial thromboembolic events, the rate of thromboembolism in the absence of anticoagulation is 4.5% a year in nonvalvular atrial fibrillation (NVAF), 12% a year in those who have NVAF and a history of previous embolism, 8% a year in those who have mechanical heart valves, and 15% a month in patients having suffered an acute arterial embolism from a noncardiac source. In all scenarios, the risk reduction with anticoagulation is 75% [66].

Bridging therapy, in the form of unfractionated heparin (UFH) or low molecular weight heparin (LMWH), can be used both pre- and postoperatively. Bridging therapy refers to the use of therapeutic doses of UFH or LMWH during the period of time when the INR is subtherapeutic. Although there have been no randomized trials to evaluate the efficacy of bridging therapy, this management strategy is usually employed in the highest risk patients [68–70]. The half-life of warfarin is 22 hours. The INR begins to decline approximately 30 hours after the last dose of warfarin. Before surgery, this translates into initiating the preoperative bridge approximately 60 hours after the last dose of warfarin [71–73]. The bridge may be administered as intravenous UFH, which is stopped 6 hours before surgery and requires hospital admission. Alternatively, the bridge may consist of LMWH, with the last dose given no less than 18 hours preoperatively if BID dosing is used or 30 hours preoperatively if a daily regimen is employed [74,75]. LMWH may be conveniently administered on an outpatient basis. For patients who have an INR maintained in the 2.0 to 3.0 range, it takes around 4 days for the INR to fall to less than 1.5. For those kept between 2.5 and 3.5, it takes approximately 5 days for the INR to fall into an acceptable range.

In the setting of prior VTE, the indication for anticoagulation is to prevent recurrence. The risk for recurrence is highest during the 3 months following an acute episode [12,66,76,77]. As mentioned previously, the risk of recurrent VTE is as high as 40% in the first month following the original event should anticoagulation be stopped. Thus, it is preferable to delay surgery until the patient has received anticoagulation therapy for at least 1 month before the planned procedure. Ideally, surgery should be postponed for 3 months to make the risk of recurrence in the absence of anticoagulation as low as possible. In this scenario, the warfarin need only be held and no bridge is required; however, if surgery needs to be performed within the 1-month window following the initial VTE, bridging therapy should be employed when the INR is less than 2.0. In the event that surgery is required within the 2 weeks following the original VTE, not only is bridging
therapy recommended, but also consideration should be made for pre- or intraoperative vena caval filter placement.

Patients on longer-term anticoagulation therapy (ie, greater than 3–6 months) for prevention of VTE recurrence have usually had either multiple VTE episodes or have experienced a single event in the absence of known temporary risk factors (ie, recent surgery). Either patient group may have an inherited or acquired hypercoagulable state. Again, it is preferable to defer surgery until the initial 3 months of anticoagulation therapy have been completed.

Anticoagulation therapy for the prophylaxis of arterial thromboembolism is usually employed in the setting of atrial fibrillation or valvular heart disease (native or prosthetic). A prior history of arterial thromboembolism is the most important risk factor for stroke in patients who have NVAF and in those who have prosthetic heart valves. In this subgroup of patients, the duration of time the individual is subtherapeutically anticoagulated should be minimized. Bridging therapy can be used in those patients at highest risk for thromboembolic events, but the evidence suggests that it may not be very effective at stroke prevention in patients who have AF [68–70,78–80].

Postoperative considerations

The factors governing anticoagulation in the postoperative period differ markedly from the preoperative period in several respects. Surgery itself is associated with a 100-fold increase in the short-term risk of VTE. This has to be weighed against the verifiable risk for postoperative bleeding in the setting of anticoagulation. Among the anticoagulating agents, UFH and LMWH are associated with more bleeding than warfarin, at both therapeutic and prophylactic doses [81–84]. Although anticoagulant-induced bleeding has less overall case-fatality compared with an episode of thromboembolism [85,86], the lower overall absolute risk of thromboembolism in the absence of anticoagulation can make the risk of anticoagulation prohibitively high, especially if the surgery is associated with an even modest increase in the risk of bleeding.

Surgery is a major risk factor for VTE. All surgical patients, regardless of their preoperative risk for VTE, are placed on some sort of postoperative VTE prophylaxis. Patients who have a history of VTE within 3 months of surgery are at highest risk to suffer a recurrence postoperatively.

If bleeding risks are acceptable, bridging therapy is recommended until an INR of 2.0 is achieved [66]. In the absence of a prior VTE history, the usual prophylactic dose of subcutaneous UFH or LMWH is recommended.

For patients at highest risk for arterial thromboembolism, postoperative bridging therapy is recommended. Either intravenous UFH, initiated 12 hours postoperatively titrated to appropriate aPTTs with no bolus, or therapeutic subcutaneous LMWH, initiated 24 hours postoperatively, may be selected; however, if a moderate to high risk of postoperative bleeding exists, prophylactic dose UFH or LMWH is recommended, even to those patients at highest risk for arterial thromboembolic events.

Summary

The hemostatic mechanisms at work in the body involve a complex series of interactions between platelets, the endothelium, and the coagulation cascade. Much has been learned regarding the molecular mechanisms governing these intricate processes. The hypercoagulable state involves a disruption of the normal homeostatic equilibrium. This state may be either inherent or acquired. The prevention of associated thromboembolic complications requires therapeutic anticoagulation. A broader understanding of the factors contributing to these prothrombotic tendencies and the subtleties involved in their management provides the surgeon with another weapon in the armamentarium to promote better and safer patient outcomes.

References


