Clinicians are faced with the challenge of navigating the precarious balance between bleeding and clotting. Bleeding disorders or failure to obtain adequate hemostasis during surgery may lead to severe hemorrhage. However, if thrombotic complications occur (eg, thromboembolic stroke), they may be far more difficult to treat. To achieve a stable equilibrium between bleeding and clotting, the treating physician should have a fundamental understanding of coagulation biology.

In this article, we review the physiological role of the vascular endothelium in maintaining an antithrombogenic environment at baseline and a prothrombotic state after injury. Commonly used hemostatic and anticoagulant drugs and their mechanism of action are examined in this context. This is followed by a review of the most common inherited and acquired bleeding and clotting disorders, as well as the mechanism by which they lead to defects in coagulation biology. The approach to a bleeding patient is then discussed, including the interpretation of the most frequently used coagulation tests. Finally, we analyze mechanical assist device therapy as an extreme case of an acquired bleeding and clotting diathesis.

Coagulation Cascade

The concept of blood coagulation dates back to the 1960s, when Davie, Ratnoff, and Macfarlane published articles in Nature and Science outlining the fundamental principle of a cascade of proenzymes activated through proteolytic cleavage that in turn activate “downstream” enzymes. Schematically, the coagulation system is divided into the extrinsic and intrinsic pathways (Figure 1 and Movie I in the online-only Data Supplement). The extrinsic pathway is triggered in response to tissue trauma and is initiated with exposure of tissue factor. The role of the intrinsic pathway is less clear in vivo but becomes important when the extrinsic pathway is activated through contact with artificial surfaces, such as a cardiopulmonary bypass circuit or a mechanical circulatory assist device (MCAD).

These pathways are interconnected on many levels and converge at the prothrombinase complex, which consists of factors Xa and Va bound together by calcium ions on a phospholipid membrane. The prothrombinase complex converts prothrombin (factor II) to thrombin (factor IIa). Thrombin activates factor XIII to XIIIa, which stabilizes the fibrin clot by covalently cross-linking fibrin.

Endothelium as Modulator of Anticoagulation and Coagulation

Anticoagulation

The endothelium is in direct contact with blood and modulates both anticoagulation and coagulation. In its healthy state, it exhibits antplatelet, anticoagulant, and fibrinolytic properties (Figure 2 and Movie II in the online-only Data Supplement).

Antiplatelet Properties of the Endothelium

There are 2 independent pathways of platelet activation. The first is a tissue factor–dependent pathway, in which constitutively expressed tissue factor on the vessel wall is activated by disulfide isomerases, subsequently leading to thrombin generation. Thrombin then cleaves the platelet thrombin receptor Par4, activating platelets. This pathway does not require disruption of the endothelium. The second pathway is dependent on the exposure of subendothelial matrix proteins after endothelial disruption. The exposed collagen interacts with platelet glycoprotein VI, von Willebrand factor (vWF), and glycoprotein Ib-V-IX, leading to platelet capture and activation.

Moreover, adenosine diphosphate (ADP) activates platelets through binding to the platelet surface receptors P2Y1 and P2Y12. This enables platelet aggregation and adhesion to subendothelial structures via fibrinogen, fibrin, vWF, and vitronectin. ADP also triggers the release of the contents stored in α and dense granules. The endothelium expresses ectonucleotidase enzymes that degrade ADP by dephosphorylation. Furthermore, endothelial cells synthesize and release nitric oxide, which inhibits platelet adhesion and acts synergistically with prostacyclin to inhibit platelet aggregation (Figure 2).

Antiplatelet Drugs

Common antiplatelet agents can be grouped into 3 categories: aspirin, glycoprotein IIb/IIIa inhibitors, and P2Y12 antag-
platelet pool by the bone marrow to recover effective platelet function. The drug dose given, bone marrow turnover, and size of the circulating platelet pool (itself related to patient size and platelet count) may explain the interpatient variability of the recovery of platelet function. Transfusion of multiple platelet units may be required to achieve hemostasis after cardiopulmonary bypass.

Reversible receptor binding is seen with the glycoprotein IIb/IIIa inhibitors eptifibatide and tirofiban (both of their half-life periods are \( \approx 2 \) hours, with recovery of platelet function occurring 4 to 8 hours after discontinuation) and the P2Y12 receptor antagonist ticagrelor (half-life of 7 to 8 hours and recovery of platelet function after 12 hours). The elimination half-life of these drugs is important to consider because free drugs will bind to and inhibit transfused or native platelets. All approved agents are cleared renally, and renal impairment approximately doubles the time until platelet function recovery. Even though the not-yet-approved drug ticagrelor is cleared mainly through the liver, it has been associated with an increase in creatinine and should be avoided in patients with renal dysfunction.\(^{10,11}\)

**Anticoagulant Properties of the Endothelium**

The endothelial surface is coated with heparin-like glycosaminoglycans, which act as cofactors in stimulating antithrombin to inactivate thrombin. Antithrombin also inhibits factors VIIa, IXa, Xa, and XIa. The administration of heparin (eg, during cardiopulmonary bypass) takes advantage of this mechanism by augmenting the inhibitory action of antithrombin. In patients who appear unresponsive to high doses of heparin, antithrombin deficiency should be suspected. Thrombomodulin and the recently characterized Z-dependent protease inhibitor are part of 2 other important anticoagulant systems of the endothelium described in more detail in Figure 2. In addition, tissue factor pathway inhibitor suppresses the extrinsic pathway (see below) by directly inhibiting factor Xa and the tissue factor/VIIa catalytic complex.\(^{12}\)

**Antifibrinolytic Properties of the Endothelium**

Tissue plasminogen activator is constitutively synthesized and released from endothelium. Tissue plasminogen activator catalyzes the proteolytic cleavage of plasminogen to plasmin, which then degrades fibrin.

**Antifibrinolytic Drugs**

Pharmacological agents used to inhibit conversion of plasminogen to plasmin include the lysine analogs Amicar (\( \epsilon \)-aminocaproic acid) and Cylvlokapron (tranexamic acid). Trasylol (aprotinin) acts by inhibiting plasmin and was used extensively in cardiac surgery until its recent withdrawal from the US market.\(^{13}\)

**Coagulation**

Injured endothelial cells quickly become prothrombotic. Activated platelets and damaged endothelial cells provide a platform of negatively charged phospholipids, which bind coagulation factors and convert inactive zymogens to their active serine proteases. In addition, endothelial cells release stored vWF, which promotes platelet adhesion to subendothelial collagen via the platelet surface glycoprotein Ib. This
mechanism is taken advantage of clinically when desmopressin (1-deamino-8-D-arginine vasopressin), a synthetic analog of arginine vasopressin, is administered to a bleeding cardiac patient. It causes a rapid elevation of plasma levels of vWF by stimulating its release from Weibel-Palade bodies in endothelial cells and increases levels of factor VIII. After injury, endothelial cells also cease expressing antithrombogenic molecules, such as thrombomodulin, but secrete tissue factor (thromboplastin). This activates the extrinsic clotting pathway and plasminogen activator inhibitor type I, which indirectly slows fibrin degradation.

Inherited and Acquired Bleeding and Clotting Disorders

Inherited Bleeding Disorders

Von Willebrand Disease
Von Willebrand disease (vWD) is the most common inherited bleeding disorder and affects up to 1% of the population. It results from mutations that directly hinder the synthesis and function of vWF. vWD may also be an acquired disorder and has been associated with antibody formation, proteolysis, increased factor clearance, and, most notably, decreased synthesis or degradation, resulting from increased shear stress in patients with aortic valve stenosis (see below). In addition to platelet adhesion and aggregation, vWF also acts as a carrier protein for factor VIII, which would otherwise have a greatly shortened half-life. vWF is synthesized by megakaryocytes and endothelial cells and circulates as a series of high-molecular-weight multimers. Patients with vWD generally suffer from prolonged bleeding time, though the severity and location of the bleeding varies with the specific type of vWD.

Hemophilias
Hemophilia A and B are X-linked recessive inherited bleeding disorders. Hemophilia A is marked by factor VIII deficiency, whereas hemophilia B is characterized by a lack of
factor IX. In mild to moderate forms of the disease, patients have 1% to 5% of normal factor activity, and in severe forms patients have <1% of the normal factor concentration. The combined incidence rate of both types is \( \approx 1 \) in 5000 male births.

### Acquired Bleeding Disorders

**Vitamin K Deficiency**

Vitamin K is essential for the synthesis of factors II, VII, IX, and X. Deficient states of vitamin K (eg, secondary to malabsorption syndromes) therefore increase patients’ bleeding tendencies. Coumadin (warfarin) inhibits vitamin K epoxide reductase, which is necessary to "recycle vitamin K" to its reduced state. Only in its reduced state can vitamin K participate in the vital carboxylation of glutamic acid residues of the coagulation factors II, VII, IX, and X in the liver.\(^{17}\)

**Liver Disease**

Because the liver is responsible for synthesizing most coagulation factors, hypoperfusion ("shock liver") or advanced liver disease decreases circulating procoagulant factors, reflected in a prolonged prothrombin time (PT).

**Intraoperative Metabolic Abnormalities**

Clinicians must also consider hypothermia, acidosis, anemia, and hypocalcemia. Hypothermia has been shown to inhibit coagulation enzymes, decrease platelet count and function, and stimulate fibrinolysis, whereas acidosis impedes fibrin polymerization. Anemia further aggravates bleeding diathesis because red cells are thought to assist in platelet margination against an injured vessel wall.\(^{18}\) Hypocalcemia from citrate toxicity in massively transfused patients must be corrected to permit enzymatic reactions of the coagulation cascade.

**Disseminated Intravascular Coagulation**

Initiated by massive tissue destruction and endothelial injury, disseminated intravascular coagulation leads to the release of tissue factor, which triggers widespread thrombus formation in the microcirculation. This further exacerbates endothelial injury by depleting coagulation factors and platelets while also activating the fibrinolytic system, resulting in a consumptive coagulopathy. Fragmentation of erythrocytes generates schistocytes and hemolysis. Elevated D-dimers, thrombocytopenia, a prolonged PT, partial thromboplastin time, and thrombin time, and decreased fibrinogen levels are therefore noted.

**Inherited Clotting Disorders**

The most common inherited thrombophilias are mutations in the factor V gene, also known as factor V Leiden, and a G20210A mutation in the prothrombin gene. Predominantly found in whites with a prevalence of 5% to 8% in most European studies, factor V Leiden renders factor V resistant to degradation by activated protein C and is associated with 20% to 40% of all venous thromboses.\(^{19,20}\) Found in \( \approx 2\% \) of the white population, the prothrombin 20210A variant increases plasma prothrombin concentration, thereby increasing the risk of thromboembolic events.

**Hyperhomocysteinemia**

Hyperhomocysteinemia constitutes a risk factor for atherosclerosis and possibly thrombotic events. The enzyme methylenetetrahydrofolate reductase reduces 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is used to convert homocysteine to methionine. The C677T mutation of methylenetetrahydrofolate reductase causes a mild enzymatic dysfunction, and a coinheritance of MTHRF mutation with factor V Leiden is associated with an increased incidence of venous thromboembolism.\(^{21}\)

**Protein C and Protein S Deficiency**

Other less common inherited causes of thrombosis include deficiencies in protein C and protein S and, rarely, antithrombin.

### Acquired Clotting Disorders

Most cases of thromboembolism occur when a patient with 1 or more predispositions to clotting suffers a precipitating event. Such events include surgery, trauma, immobilization after surgery, pregnancy and the puerperium, neoplasia, myeloproliferative disorders, and use of contraceptives or hormone replacement therapy.

**Antiphospholipid Syndrome**

Second to smoking, the most common acquired thrombophilia is antiphospholipid syndrome, in which autoantibodies (anticardiolipin antibodies or lupus anticoagulant) that recognize anionic phospholipids can inhibit protein C and protein S, as well as activate prothrombin.\(^{22}\) This acquired disorder predisposes affected patients to venous as well as arterial thromboses and often manifests as repeated miscarriages. Paradoxically, it is noted by an abnormally elevated partial thromboplastin time in conjunction with a normal PT due to a selective in vitro effect of the antibodies. The diagnosis of antiphospholipid syndrome can be confirmed with specialized lupus anticoagulant panels.

**Heparin-Induced Thrombocytopenia**

Heparin-induced thrombocytopenia type II is mediated by antibodies to a combined heparin/platelet factor 4 antigen capable of activating platelets. In contrast to heparin-induced thrombocytopenia type I, which causes a transient mild thrombocytopenia, heparin-induced thrombocytopenia type II may also lead to thrombosis; it is then referred to as heparin-induced thrombotic thrombocytopenia. The treatment of heparin-induced thrombotic thrombocytopenia requires cessation of all heparin exposure and initiation of an alternative anticoagulant; the direct thrombin inhibitors argatroban and bivalirudin are typically used.

### Practical Considerations of Antithrombotic Therapy

Many patients who present for cardiac surgery are likely to have received anticoagulation therapy for prophylaxis or treatment of venous thromboembolism, atrial fibrillation, prosthetic valves, acute coronary syndrome, or heparin-induced thrombocytopenia.

Before choosing a specific agent for anticoagulation, the physician must answer 4 crucial questions: (1) How can this particular drug be reversed? (2) If no effective reversal agent exists (as is the case for most of these drugs), should surgery be delayed until the effect has cleared? (3) If no antidote
exists and surgery is delayed, what is the drug’s half-life of elimination? (4) How is the particular agent cleared? Cardiogenic shock, for instance, reduces renal clearance, thus prolonging the effect of drugs that are cleared renally. For emergent cases and in the setting of intractable bleeding, increasing clearance of particular drugs with hemofiltration, hemodialysis, or plasmapheresis and increasing thrombin generation with recombinant activated factor VII or prothrombin complex concentrates should be considered for rescue therapy. The individual features of antithrombotic agents are detailed in the Table.

Intravenous unfractionated heparin therapy is familiar to most clinicians and is rapidly reversible with protamine sulfate. Low-molecular-weight heparin is much less likely to induce heparin-induced thrombocytopenia than unfractionated heparin and is dosed subcutaneously as a fixed dose by body weight, but its clearance is dependent on renal function, and it is only partially reversed by protamine. Low-molecular-weight heparin therapy can lead to perioperative hemorrhage and ideally should be discontinued 24 hours before cardiac surgery. Bivalirudin and argatroban are direct thrombin inhibitors used for the treatment of heparin-induced thrombocytopenia; bivalirudin is approved by the US Food and Drug Administration for use during percutaneous coronary intervention. Recent data suggest that fondaparinux is also safe for venous thromboprophylaxis and the treatment of heparin-induced thrombocytopenia, but a prolonged half-life and dependence on renal elimination warrant caution for perioperative use. Newly developed oral agents such as apixaban and rivaroxaban are nearing approval in the United States and are also included in the Table.

**Approach to the Patient With a Bleeding Diathesis**

The fundamental causes of abnormal bleeding are failures in primary hemostasis (platelet inhibition/dysfunction, thrombocytoypenia, and vWD), failure to generate thrombin (procoagulant factor deficiency), and failure to form a stable fibrin clot (hypofibrinogenemia or dysfibrinogenemia and excessive fibrinolysis). We will briefly discuss the PT, activated partial thromboplastin time (aPTT), mixing studies, and platelet function testing such as thromboelastography as some of the most important diagnostic tests available to the cardiac surgeon and anesthesiologist.

**PT and aPTT**

The PT indicates the relative functionality of the extrinsic and common pathways by timing how long it takes plasma to clot after the addition of tissue factor. It is markedly prolonged in the absence of vitamin K and is dependent on factors II, V, VII, and X. On the other hand, aPTT measures the effectiveness of the intrinsic and common pathways. The test is “partial” because of the absence of tissue factor from the method of testing. In the following section, we will discuss a systematic approach to the interpretation of these coagulation tests (Figure 3).

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**Table. Characteristics of Important Anticoagulants**

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Route</th>
<th>Elimination Half-Life</th>
<th>Clearance</th>
<th>Current FDA Approval</th>
<th>Cautions</th>
<th>Reversal Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin</td>
<td>Low-molecular-weight heparin anti-FXa, anti-FIIa</td>
<td>Subcutaneous</td>
<td>4.5–7 h; FXa activity persists for 12 h after a prophylactic dose</td>
<td>Liver, 10% renal</td>
<td>VTE prophylaxis, treatment of DVT and PE, treatment of NSTEMI</td>
<td>Hepatic impairment</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Anti-FXa synthetic oligosaccharide</td>
<td>Subcutaneous</td>
<td>17–21 h</td>
<td>Renal</td>
<td>VTE prophylaxis, treatment of DVT and PE</td>
<td>Hepatic impairment, renal impairment, advanced age, small size</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Direct thrombin inhibitor</td>
<td>Intravenous</td>
<td>25 min; 57 min if CrCl &lt;30 mL/h and 3.5 h if ESRD</td>
<td>Enzymatic 80%, renal 20%</td>
<td>Anticoagulation for PCI with or without HIT</td>
<td>Renal impairment, hypothermia</td>
</tr>
<tr>
<td>Argatroban</td>
<td>Direct thrombin inhibitor</td>
<td>Intravenous</td>
<td>39–51 min; 118 min with hepatic impairment</td>
<td>Liver</td>
<td>Prophylaxis or treatment of thrombosis or PCI in patients at risk of HIT</td>
<td>Hepatic impairment</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Direct thrombin inhibitor</td>
<td>Oral</td>
<td>12–14 h after multiple doses</td>
<td>80% excrated renally</td>
<td>Approved in Europe and Canada for VTE prophylaxis</td>
<td>Not recommended if CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Direct FXa inhibitor</td>
<td>Oral</td>
<td>5–9 h</td>
<td>36% excrated renally</td>
<td>Approved in Europe and Canada for VTE prophylaxis</td>
<td>Not recommended if CrCl &lt;30 mL/min</td>
</tr>
<tr>
<td>Apixaban</td>
<td>Direct FXa inhibitor</td>
<td>Oral</td>
<td>8–15 h</td>
<td>25% excrated renally</td>
<td>Not yet approved for commercial use</td>
<td>Currently under investigation</td>
</tr>
</tbody>
</table>

FXa indicates factor Xa; FIIa, factor IIa; VTE, venous thromboembolism; DVT, deep venous thrombosis; PE, pulmonary embolism; NSTEMI, non–ST-segment elevation myocardial infarction; CrCl, creatinine clearance; ESRD, end-stage renal disease; PCI, percutaneous coronary intervention; and HIT, heparin-induced thrombocytopenia.
Bleeding With Normal PT and aPTT

If PT, aPTT, and platelet count are normal in a patient with a history of mucocutaneous bleeding, then primary hemostasis should be investigated (eg, with the platelet function analyzer PFA-100 [Dade Behring, Inc, Deerfield, Ill], which can also screen for vWD). Specifically, testing platelet aggregation/function and analyzing platelet morphology are necessary to single out rare cases of inherited disorders of platelet function, including Bernard-Soulier syndrome, Glanzmann thrombasthenia, and the various storage pool diseases, in addition to antiplatelet drug effects.

Bleeding With Abnormal PT or aPTT

A normal PT and prolonged aPTT are indicative of a problem with the intrinsic pathway (factors XI, XII, VIII, IX), whereas a prolonged PT and normal aPTT indicate a disorder of the extrinsic pathway, most likely a result of reduced factor VII from Coumadin therapy, vitamin K deficiency, and liver disease. It should be noted that vitamin K deficiency and liver disease can present with elevation of both PT and aPTT. When a patient presents with prolonged PT and aPTT but normal platelet count and function, the physician should rule out a fibrinogen abnormality by measuring the thrombin time or testing for D-dimers and other fibrin degradation products. Fibrinogen levels need to be <80 mg/dL in order to be the sole cause of a prolonged PT and aPTT. Generalized reduction in procoagulant factor concentration with a mixed PT/aPTT pattern can be the result of a long cardiopulmonary bypass run.

Mixing Studies

Diagnosis of Coagulation Factor Deficiency

To perform a mixing study, the patient’s blood sample is mixed with pooled normal plasma in vitro, and the coagulation screen is repeated. If the assay is normal after mixing, then a coagulation factor deficiency can be diagnosed. For preoperative diagnostic purposes, the specific factor deficiency can be sought by serially adding patient plasma to factor-deficient plasma. The plasma deficient in the same factor as the patient will be the only one not to correct the clotting time. Liver disease and vitamin K deficiency lead to a marked decrease in the synthesis of prothrombin (factor II) and factors VII, IX, and X. Factor V production, however, is independent of vitamin K, and therefore a deficiency of this factor indicates a hepatic synthetic dysfunction. The exact biosynthetic origin of factor VIII is still a matter of debate, and the extent to which factor VIII is generated in hepatocytes versus endothelium is not clear. Factor VIII is elevated in hepatic necrosis and reduced in disseminated intravascular coagulation (secondary to thrombin-induced proteolysis by activated protein C). An isolated factor VIII deficiency rules out vitamin K deficiency and liver disease.
Diagnosis of Coagulation Factor Inhibitor

If the assay remains abnormal after mixing, then an inhibitor of coagulation is present. Immediate acting inhibitors include lupus anticoagulants that recognize phospholipid-protein cofactors. A longer incubation of up to 2 hours may be necessary for slower binding inhibiting antibodies to recognize coagulation factor proteins. Therefore, laboratory reports of this test include both an immediately obtained and an incubated value.

Inhibitors are rare but can develop after repeated exposure to factor concentrates used to treat preexisting deficiencies, such as hemophilia A (factor VIII) or B (factor IX), or they can develop de novo (acquired inhibitors). The most common is a spontaneous, acquired factor VIII inhibitor that is associated with liver disease, pregnancy, autoimmune disease, and malignancy. However, pertinent to cardiac surgery is the development of antibodies after exposure to bovine thrombin used as a topical hemostatic agent. These antibodies cross-react with human thrombin and factor V, leading to a prolonged thrombin time and a significant bleeding diathesis during subsequent surgeries. Platelet transfusions can specifically treat isolated factor V inhibitors because platelet degranulation delivers factor Va to a site of injury, but achieving hemostasis in the presence of inhibitors requires the use of a bypassing agent. Prothrombin complex concentrates or recombinant factor VIIa can generate thrombin despite the upstream inhibition. Longer-term treatment of inhibitors requires plasmapheresis or long-term immunosuppression until the autoantibody does not recur.

Thromboelastography

Thromboelastography determines clot formation and lysis within a given blood sample by measuring the shear elastic modulus of whole blood samples during clot formation (Figure 4). However, it does not measure the effect of aspirin, thienopyridines (P2Y12 platelet receptor inhibitors), or low-molecular-weight heparin. Thromboelastography provides a global assessment of hemostatic function in whole blood, preserving the interplay between erythrocytes, platelets, coagulation factors, and fibrinogen. Thromboelastography has been demonstrated to be remarkably accurate when used to predict postoperative hemorrhage, with a success rate of 87%, whereas the activated clotting time and coagulation profile posted accuracy rates of 30% and 51%, respectively. Addition of a heparinase reagent allows diagnosis of abnormal coagulation potential during heparinization.

The Implantable MCAD: An Extreme Case of Acquired Bleeding and Clotting

The implantation of vascular grafts or devices, such as MCADs, introduces a foreign body into the patient that is in constant contact with the blood. Because the endothelium is missing on artificial surfaces, it cannot exert its antithrombotic actions, increasing the risk for occlusive thrombosis or thromboembolic events. Because of the relative lack of organs available for heart transplant, MCADs, such as the left ventricular assist device, will become a much more commonly employed therapy for patients with end-stage heart failure and may benefit 30 000 to 60 000 patients per year in the future. However, among the major complications of implantable MCADs are bleeding and thrombosis.

Bleeding Complications With MCAD Therapy

In the immediate postoperative period, the risk of bleeding predominates over thrombosis and is compounded by concomitant renal and hepatic dysfunction and possible technical difficulties of a redo sternotomy (Figure 5 and Movies IV and V in the online-only Data Supplement). In the later postoperative period, bleeding continues to predominate. It is hypothesized that because of the high shear stress generated by left ventricular assist devices, the vWF multimers are elongated, and thus cleavage sites become exposed to metalloproteinase ADAMTS13, which then cleaves the hemostatic high-molecular-weight vWF multimers. Similar to Heyde’s syndrome, this leads to acquired vWD.

Thromboembolic Complications With MCAD Therapy

Whereas bleeding is much more common with current left ventricular assist device technology, thrombosis and embolic strokes are potentially more catastrophic and difficult to treat. In a recent prospective multicenter study of 281 patients treated with a second-generation continuous-flow device, >50% of patients suffered from bleeding complications, but only 1% of patients died of bleeding. In contrast, ~1% of patients died because of device thrombosis, and 5% suffered ischemic strokes, half of those with fatal outcomes. Of note, end-stage heart disease itself predisposes to bleeding and thromboembolism, although patients treated with MCADs have been significantly more likely to suffer from these adverse events than those on optimal medical management.

Therefore, most patients receive some form of long-term...
Figure 5. Molecular pathways of bleeding and clotting on the blood-contacting surface of a MCAD. Left to right, High-molecular-weight kininogen (HMWK) adsorbs to the titanium surface and initiates the intrinsic coagulation pathway (contact activation). The surface is also populated with blood-derived monocytes and macrophages, which express tissue factor (TF) and activate the extrinsic coagulation pathway. At the same time, platelets adhere and become activated (AP), releasing α granules containing coagulation factor V, which further contributes to thrombus formation. Top to bottom, The fibrinolytic system is also activated through the cleavage of prekallikrein to kallikrein via factor XIIa (FXIIa). Kallikrein in turn converts plasminogen to plasmin, which cleaves fibrin. Fibrin degradation products cause platelet dysfunction through their inhibitory effect on platelet receptors, compounding the bleeding risk. Center, Moreover, the high shear stress may elongate vWF multimers, thus exposing vulnerable cleavage sites that lead to defunctionalized vWF molecules. FXII indicates factor XII; FV, factor V; and GP, glycoprotein.
anticoagulation during left ventricular assist device support, although concurrent coagulopathies require careful dosing of anticoagulants and antiplatelet drugs.

Spanier et al found significant thrombin generation and fibrinolysis in patients with textured-surface MCADs that caused a phenomenon of "compensated coagulopathy." Furthermore, they demonstrated progressive population of the MCAD surface by activated macrophages and monocytes expressing tissue factor and proinflammatory cytokines, as well as persistently elevated levels of tissue factor in the circulation (Figure 5 and Movie III in the online-only Data Supplement).

Because of these risks, MCAD design has focused on engineering a device with higher flow, such as the current HeartMate II (Thoratec, Pleasanton, Calif). However, as described above, high flow within the HeartMate II device causes bleeding complications, possibly as a result of acquired vWD. Furthermore, the artificial titanium surface of MCADs, which is thought to sequester platelets, may also play a role in the observed postimplantation thrombocytopenia requiring transfusion or contributing to reoperation. Because it has become feasible to isolate endothelial progenitor cells from peripheral blood, it may be possible to engineer "biogenic MCADs" in the future, which are lined with the patients’ own, blood-derived endothelial progenitor cells. Such a lining may prevent platelet adhesion and thrombus formation in areas of low flow and stasis and possibly ameliorate the dreaded side effects of infection and bleeding.

Conclusion

The vascular endothelium has a variety of innate mechanisms that steer the coagulation system toward either the prevention of clot formation or thrombosis. As such, it plays a crucial role in maintaining normal blood flow. On the other hand, the lack of a functioning endothelium contributes both directly and indirectly to bleeding and clotting disorders. In addition, implantable artificial devices, which lack an endothelial lining entirely, are prone to cause coagulation abnormalities through contact activation. In the future, it may be possible to bioengineer a confluent lining of the patients’ own endothelial cells to cover the blood-contacting surface of such devices.

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References


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