INTRODUCTION

Blood is the medium for exchanging oxygen, nutrients, and waste products throughout the body, and consists of plasma, blood cells (red blood cells, white blood cells), and platelets. Platelets play an important role in clotting, while white blood cells are responsible for inflammation, and red blood cells carry oxygen and nutrients to all tissues of the body and carry waste products away from the organs. Any abnormality of these blood components can result in hematologic disorders. While disorders involving platelets and coagulation that can lead to thrombosis and/or bleeding are of primary concern for most cardiologists, disorders involving red blood cells and platelets can also affect the mechanics of blood flow and blood viscosity. Our understanding of hematologic disorders has advanced steadily in recent years, particularly with the development of genetics and molecular biologic techniques. Here we provide a focused overview of nononcologic blood disorders and their potential impact on the arterial circulatory system as common phenotypes, including myocardial infarction, ischemic stroke, and peripheral arterial occlusive events. Venous thromboembolism is employed in our discussion as a clinical template. We also provide practical steps and guidance for diagnostic testing and management in routine clinical practice.
BLOOD DISORDERS OF COAGULATION

Venous thromboembolism is an important and growing public health problem. An estimated 900 000 patients present with clinically evident VTE in the United States each year, resulting in an estimated 300 000 deaths from pulmonary embolism. The urgent task for clinical cardiologists is to understand the burden of disease and potential causes of VTE, which has enormous potential to prevent and reduce death and morbidity from VTE.

INHERITED THROMBOPHILIAS

The World Health Organization/International Society of Thrombosis and Hemostasis in 1995 defined thrombophilia as an unusual tendency toward thrombosis, which is characterized by features such as early age of onset; recurrent episodes; strong family history; unusual, migratory, or widespread locations; and severity out of proportion to any recognized stimulus. It also refers to hypercoagulable states which are the end result of diseases, disorders, or conditions that heighten one’s propensity to form blood clots within the venous, arterial, and/or microcirculatory systems. Primary characteristics for common inherited thrombophilias are summarized in Table 1.

Antithrombin Deficiency

Antithrombin is a single-chain glycoprotein belonging to the serine protease inhibitor (serpin) super family that plays a key anticoagulant role by preventing inappropriate, excessive, or mislocalized clotting of blood, which may cause thrombotic disorders. To date, up to 228 distinct mutations have been described in the SERPINC1 gene associated with antithrombin deficiency, with a reported prevalence of antithrombin deficiency of 1 in 500 to 1 in 5000 in the overall population. Antithrombin deficiency is associated with increased risks of pulmonary embolism and upper and lower extremity deep VTE, but VTE can also occur in unusual sites such as cerebral or sinus, mesenterial, portal, hepatic, renal, and retinal veins. A metaanalysis of observational studies reported that antithrombin deficiency significantly increased the risk of first VTE with odds ratio (OR) 8.73 (95% confidence interval [CI] 3.12-24.42), and recurrent VTE with OR 3.37 (95% CI 1.57-7.20). Despite its clear relationship with VTE, the patients with heterozygous antithrombin deficiency may be at risk for arterial ischemic stroke or mesenteric artery thrombosis. Another systematic review reported a pooled OR of 6.49 (95% CI 2.96-14.27) for arterial ischemic stroke among the patients with protein C deficiency. However, there is still no evidence of association between early signs of atherosclerotic alterations (intima-media thickness, ankle/brachial pressure index) and protein C deficiency. Considered collectively, protein C deficiency may be a risk factor for arterial ischemic stroke, particularly in patients younger than 55 years.

Protein S Deficiency

Protein S is a Vitamin K-dependent glycoprotein that is 40% unbound and active in the circulation, and acts as the principle co-factor of activated protein C, increasing the protein’s affinity for negatively charged phospholipids. The resulting membrane-bound activated protein C-protein S complex produces a marked increase in Factor Va and VIIIa inactivation. Hereditary protein S deficiency is an autosomal dominant disorder with almost 200 different PROS1 mutations resulting in loss of function identified.

Although protein S deficiency is uncommon in the general population, it is found in approximately 2% of unselected patients and 1%–13% of thrombophilic patients with VTE respectively. Individuals with protein C deficiency experience a heightened risk for VTE and recurrent VTE. A metaanalysis reported that protein S deficiency significantly increased the risk of first VTE, with an OR of 5.77 (95% CI 3.07-10.85), and recurrent VTE with an OR of 3.76 (95% CI 1.76-8.04). In a large cohort of families with hereditary protein S deficiency, the annual incidences of recurrent VTE were 8.4% (95% CI 5.8-11.7). The results from a large family cohort study also showed that subjects with protein S deficiency have a higher risk (hazard ratio [HR] 4.6, 95% CI 1.1-18.3) for arterial thrombosis.

Table 1
Summary of Main Characteristics of Inherited Thrombophilias

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Mutations</th>
<th>Prevalence</th>
<th>Manifestation</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATD</td>
<td>SERPINC1 gene</td>
<td>1/500–1/5000</td>
<td>+</td>
</tr>
<tr>
<td>PCD</td>
<td>Protein C gene</td>
<td>1/200–1/5000</td>
<td>+</td>
</tr>
<tr>
<td>PSD</td>
<td>PROS1</td>
<td>0.03%–2%</td>
<td>+</td>
</tr>
<tr>
<td>APC resistance</td>
<td>FV Leiden (A506G); FVR2 (H1299R); FV Cambridge (R306T) and FV Hong Kong (R306G)</td>
<td>4%–6%</td>
<td>+</td>
</tr>
<tr>
<td>Prothrombin G20210A</td>
<td>Prothrombin G20210A</td>
<td>23%–4%</td>
<td>+</td>
</tr>
</tbody>
</table>

−: no evidence; +: the risk increases; APC, activated protein C; AT, arterial thrombosis; ATD, antithrombin deficiency; FV, factor V; PCD, protein C deficiency; PSD, protein S deficiency; RVTE, recurrent venous thromboembolism; VTE, venous thromboembolism.
Activated Protein C Resistance

Activated protein C exerts anticoagulant effects beyond inactivating factor Va by cleaving at R306 and R506, generating inactive factor V (FVai). In addition, activated protein C generates an anticoagulant molecule (FVac) by cleaving full-length factor V (FV) at R506; this FVac acts as a cofactor with activated protein C to degrade factor VIIa. The most common mutation in the FV gene is a single point mutation that results in the replacement of Arg506 in one of the activated protein C cleavage sites with a Gln. This FV Leiden mutation accounts for 90% to 95% of all causes of activated protein C resistance and is the most prevalent hereditary thrombophilia, occurring in 4% to 6% of the general population. It is rare or absent in populations from Far East Asia, black Africans, and indigenous populations of America and Australia. Less common FV mutations also affect activated protein C resistance. Of these, FVR2 (H1299R) reduces activated protein C cofactor activity and leads to an increased thrombotic risk when present in compound heterozygotes with FV Leiden. FV Cambridge (R306T) and FV Hong Kong (R306G) are rare mutations that exhibit only mild activated protein C resistance and have not been associated with increased risk of thrombosis.

Heterozygosity for FV Leiden yields a lifelong hypercoagulable state associated with an approximate 3- to 7-fold increased risk of venous thrombosis, and is also predictive of recurrent VTE. In addition to pulmonary embolism and deep venous thromboembolism, FV Leiden significantly increases the risk of first cerebral vein thrombosis with OR of FV 3.38 (95% CI 2.27-5.05). The FV Leiden mutation accounts for 90% to 95% of all causes of activated protein C resistance and is the most prevalent hereditary thrombophilia, occurring in 4% to 6% of the general population.

Antiphospholipid Syndrome

Antiphospholipid syndrome is an autoimmune disorder characterized by the clinical association of antiphospholipid antibody with a condition of hypercoagulability, and poses high risk for both VTE and arterial thrombosis. Antiphospholipid antibody syndrome is associated with myocardial infarction, intracardiac thrombosis, and pulmonary hypertension resulting from the predisposition to thrombosis, and, less frequently, with valvular heart disease and atherosclerosis of peripheral and coronary arteries. The latter might be explained by antibody-mediated proinflammatory and procoagulant effects exerted directly on endothelial cells. Antiphospholipid syndrome patients have significantly worse cardiovascular outcomes.

DIAGNOSTIC STRATEGIES FOR VENOUS AND ARTERIAL THROMBOSIS

When venous or arterial thrombosis occurs and the suspicion of an acquired thrombophilia is raised, screening tests for lupus anticoagulant are usually performed. Current antiphospholipid syndrome diagnostic criteria require a positive test in the antiphospholipid antibodies panel test (lupus anticoagulant, moderate or high titer anticardiolipin antibodies, and/or anti-β2GP1 antibodies) on 2 separate occasions at least 12 weeks apart, in the setting of thrombosis or pregnancy complications. A workup for inherited thrombophilia is usually indicated only in patients with a history of multiple thromboembolic episodes, thromboembolism at a young age, family history of thromboembolism, thrombosis in an unusual site, or VTE without any obvious risk factor. The diagnosis of inherited thrombophilias can be approached employing the following steps: a) functional amidolytic assays should be performed in each of the abovementioned inherited thrombophilias except for the prothrombin G20210A gene mutation, which can be tested directly using genetic analysis; b) functional tests are performed to exclude antithrombin deficiency, protein C deficiency, and protein S deficiency; and c) genetic testing is required for the detection of specific gene mutations such as FV Leiden. Functional assays are preferably avoided in the setting of acute thrombosis and best performed before or several days after cessation of heparin and/or oral anticoagulation therapies, as acute thrombosis and anti-coagulation therapy may affect the results. However, genetic assays for G20210A or FV Leiden can be performed at any time. All causes of acquired thrombophilias should be excluded before classifying a person with abnormal test results as having an inherited thrombophilia. Testing among patients with arterial thrombosis, including the common phenotypes of myocardial infarction, ischemic stroke and/or peripheral arterial occlusive events should be individualized, with a primary focus on traditional risk factors, systemic diseases associated with atherosclerotic vascular disease, and antiphospholipid syndrome with or without a circulating Lupus anticoagulant prior to embarking on testing for hereditary thrombophilias in patients younger than 55 years.

ACQUIRED THROMBOPHILIAS

The most common acquired factors which predispose to thrombosis are presence of an antiphospholipid antibody and malignancy. Antiphospholipid syndrome will be reviewed here.

FACTOR II (Prothrombin) G20210A Gene Mutation

Prothrombin G20210A is a gain-of-function mutation located in the 3′ untranslated region of the prothrombin gene (nucleotide 20210 G to A), leading to increased plasma levels of prothrombin and a hypercoagulable state. Prothrombin G20210A is the second most common inherited risk factor for VTE. Its prevalence depends on geographic location and ethnic background. It is found in 2% to 4% of the general population, and in 5% to 8% of patients with a history of VTE. There is a strong association between prothrombin G20210A mutation and an increased risk of VTE, with patients having the mutation having a 2- to 3-fold increased risk of VTE. Genetic testing is required for the detection of prothrombin G20210A mutation, which can be performed directly using genetic analysis. Functional tests are performed to exclude antithrombin deficiency, protein C deficiency, and protein S deficiency. Genetic testing is required for the detection of specific gene mutations such as prothrombin G20210A.
Inherited thrombophilias because of the increased risk of hemorrhage.

Prophylaxis in high-risk settings: Heparin or low-molecular-weight heparin should be considered strongly for thromboprophylaxis when individuals with inherited thrombophilias and prior arterial thrombosis find themselves in high-risk settings, including major surgery, trauma, or management of pregnancy, labor, and delivery.

Venous and arterial thrombosis treatment: The initial management of coronary arterial thrombosis in patients with an inherited thrombophilia should proceed according to the standard of care, with anticoagulant and platelet-directed therapy as indicated. Consideration of long-term anticoagulant therapy must be individualized in the absence of randomized studies. The management of VTE is usually not different from that of VTE in other patients without inherited thrombophilias.

The cornerstone of management for acquired thrombophilias is treatment of the underlying disease. Patients who are persistently positive for antiphospholipid antibodies, and who have a documented history of either VTE or arterial thromboembolism, are at increased risk of recurrence. Long-term oral anticoagulant therapy is the mainstay of treatment, with a target international normalized ratio of 2.0 to 3.0. There is no general consensus on the prophylactic treatment of antiphospholipid antibody carriers who have not experienced vascular/thrombotic or obstetric manifestations.

Acetylsalicylic acid prophylaxis may be sufficient in low-risk settings.

DISORDERS OF PLATELETS

Heparin-induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT), an immune reaction in response to platelet factor 4-heparin complexes, can occur in 0.1% to 5% of patients receiving heparin, depending on the patient population, source and formulation of heparin, and dose and duration of treatment. HIT occurs more frequently in surgical patients than in medical patients, and more often with unfractionated heparin than with low molecular weight heparin. HIT is characterized by thrombocytopenia and a strong propensity for paradoxical thrombosis, manifesting either arterial, microvascular, or VTE, the latter being more common.

HIT is diagnosed using a combination of clinical and laboratory criteria. Two principal criteria are essential for establishing a clinical diagnosis: development of thrombocytopenia and/or clinical thrombosis in temporal association with heparin therapy (typically within 5 to 14 days of heparin exposure), and exclusion of other causes of thrombocytopenia. Detection of HIT antibodies is necessary, but not sufficient, for the diagnosis because only a subset of individuals who develop heparin antibodies actually develop HIT. There are several available assays to detect HIT antibodies, including the serotonin release assay (SRA), enzyme-linked immunosorbant assay (ELISA), or enzyme immunoassay (EIA).

Heparin cessation and initiation of an alternative anticoagulant should occur immediately after clinical suspicion is aroused and even before the result of any serologic test becomes available. Alternative anticoagulants include the direct thrombin inhibitors lepirudin, argatroban, and bivalirudin, and the anti-Xa agent fondaparinux. The use of warfarin anticoagulation has been linked with an increased risk of thrombosis and hemorrhage. The American College of Chest Physicians consensus statement recommends that platelet counts should be monitored every 2 to 3 days beginning on the 4th day after initiation of therapy, until the therapy is discontinued or until the 14th day of heparin exposure.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening multisystem disorder caused by platelet and von Willebrand factor deposition in arterioles and capillaries which, in turn, prompts widespread organ ischemia, particularly affecting the brain, heart, and kidneys. Microangiopathic hemolytic anemia ensues as the red blood cells pass through the affected vessels and break into fragments called schistocytes. A rare condition resulting from the deficiency of ADAMTS13, TTP affects approximately 1000 persons per year in the United States, is much more prevalent among women, and the incidence among African Americans is 9 times higher than in other ethnicities.

The classic pentad of thrombocytopenia, hemolytic anemia, fever, renal dysfunction, and neurologic symptoms is present in only a minority of TTP patients.

The clinical laboratory picture is similar to that of disseminated intravascular coagulation, although prothrombin time and activated partial thromboplastin time are rarely abnormal. ADAMTS–13 activity assays have advanced the diagnosis of TTP, with sensitivities ranging from 89% to 100% and specificity greater than 91%. Plasma exchange or infusion is the mainstay of treatment for TTP. Glucocorticoids, cyclosporine, vincristine, splenectomy, and, more recently, rituximab (monoclonal antibody to CD20) have all been used in combination with plasma exchange to treat TTP, although randomized clinical trial data are lacking.

On the other hand, some have suggested a role for the therapeutic use of antilplatelet agents in conjunction with plasma exchange despite significant thrombocytopenia. Similarly, a previous standard of care held that platelet transfusion was contraindicated in TTP, but a recently published review concludes that it is still uncertain whether this practice is harmful or not.

Immune Thrombocytopenia

Immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia (platelet count $150 \times 10^9/L$), in the absence of other causes of thrombocytopenia. Although the development of autoantibodies against platelet glycoproteins remains central in the pathophysiology of ITP, several abnormalities involving the cellular mechanisms of immune modulation have been identified. It appears both platelet survival and production are impaired in ITP. An analysis from the General Practice Research Database in the United Kingdom showed that the current estimate of the incidence of ITP is 3.3 per 105 adults/year for adults. Feudjo-Tepie et al. reported the prevalence of ITP in the years 2002–2006 for adults and the overall population was 23.6 and 20.3, respectively, per 100 000 in the United States. The symptoms and signs are highly variable and range from the completely asymptomatic patient to severe bleeding.
frank hemorrhage from any site, the most serious of which is intracranial. Even if the platelet count is low, myocardial infarction and ischemic stroke can occur in some patients.47 The diagnosis of ITP is made by excluding other causes of thrombocytopenia. The basic diagnostic approach to ITP includes a patient history, physical examination, complete blood count, detection of antiplatelet antibodies and examination of a peripheral blood smear. Bone marrow aspiration in patients older than 60 years is appropriate to rule out leukemia, infiltrative disease and aplastic anemias.

Treatment of patients with ITP must take into account the age of the patient, the severity of the illness, and the anticipated natural history. Adult patients, particularly those older than 60 years, have a higher incidence of major or fatal bleeding than children. However, specific therapy may not be necessary unless the platelet count is <20 × 10^9/L or there is extensive bleeding. In fact, the current treatment for ITP is considered appropriate for symptomatic patients and for those at risk of bleeding.48 Provided the patient’s situation is not life threatening, corticosteroids are the standard initial treatment for the ITP. Intravenous immune globulin is generally recommended for patients unresponsive to corticosteroids. The platelet count also can be supported by anti-D immunoglobulin, which is active only in Rh-positive patients and is in the pre-splenectomy setting.48 splenectomy is traditionally considered to be the second-line treatment in adults with ITP in whom achieving a safe platelet count with initial prednisone therapy has failed, and it is effective for most patients. The treatment of chronic ITP has advanced in recent years. These advances include the incorporation of immunomodulatory therapy (rituximab, anti-CD20 monoclonal antibody) and the development of thrombopoietic stimulating agents (romiplostim, eltrombopag), which has been used in clinical trials and showed some good benefits,49 but any long-term adverse impact is unknown.

Following percutaneous coronary interventions, patients with ITP have risk for bleeding or thrombotic complications when antiplatelet treatment is given or spared, respectively. Given the paucity of data on ITP and stenting, no strict recommendations can be made.48 There is a need for adequately powered randomized phase III trial. The STAMINA-HeFT study, a double-blind, randomized, placebo-controlled, multicenter trial, showed a nonsignificant trend toward a lower risk of all-cause mortality or first heart failure hospitalization in darbepoetin-alfa–treated patients, compared with placebo (HR 0.68; 95% CI 0.43, 1.08; P = .10).55 However, the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT) reported that the use of darbepoetin-alfa in patients with diabetes, chronic kidney disease, and moderate anemia who were not undergoing dialysis did not reduce the risk of either of the primary composite outcomes (ie, death or a cardiovascular event and death or a renal event) and was associated with an increased risk of stroke.56 Accordingly, the optimal threshold at which therapy should be initiated and the extent of correction considered safe and desirable in the individual patient with heart failure have not been established. The second mortality and morbidity trial, Reduction of Events With Darbepoetin alfa in Heart Failure (RED-HF), is in progress and is likely to provide more answers.57 More recently, the Reduction of Infarct Expansion and Ventricular Remodeling With Erythropoietin After Large Myocardial Infarction (REVEAL) trial led by Rao et al., a randomized, double-blind, placebo-controlled, multicenter trial, is evaluating the effects of epoetin α on infarct size and left ventricular remodeling in patients with large myocardial infarctions. Its results, presented at the American Heart Association 2010 Scientific Sessions in Chicago, show that an intravenous injection of erythropoietin following successful primary or rescue percutaneous coronary intervention did not reduce infarct size in ST-segment-elevation myocardial infarction patients.58 The available evidences show that the routine use of either transfusions or bone marrow stimulating agents do not benefit, and may in fact do harm to, patients with myocardial infarction or heart failure, even those with concomitant renal insufficiency.59

Sickle Cell Disease

Sickle cell disease (SCD) is an inherited genetic disorder characterized by a hemoglobin abnormality called “hemoglobin S” (HbS). It refers to a group of hemolytic anemias in which HbS is present in either a homozygous state (HbSS) or a compound heterozygous state, such as when combined with hemoglobin C (HbSC) or B-thalassemia (HbS-B-thalassemia). SCD is caused by homozygosity for a single nucleotide mutation in codon 6 of the HBB globin gene, GAG > GTG, resulting in the substitution of valine for glutamic acid (Glu6Val). SCD is one of the most common genetic diseases in the United States, occurring in 1 in 2400 births. Among African Americans, SCD affects approximately 1 in 400 births and it is estimated that there are 100 000 individuals in the United States with SCD.60

Among the multiple cardiovascular pathologies associated with this disease, a sickle red cell-endothelial interaction has been implicated as one of the major potential initiating mechanisms. SCD is a prototype of a condition in which the erythrocyte is under ischemic, oxidative, or shear stress that results in changes in the erythrocyte morphology, predisposing to polymerization and consequent deformation (“sickling”). This change leads to enhanced erythrocyte-endothelial cell adhesion. The endothelial dysfunction is characterized by reduced nitric oxide (NO)
bioavailability, pro-oxidant and pro-inflammatory stress and coagulopathy, leading to vasomotor instability and ultimately producing a proliferative vasculopathy. Endothelial damage and inflammation make a significant contribution to the pathophysiology of SCD and the β-thalassemia syndromes

The most common manifestation of SCD is vaso-occlusive crisis, characterized by intermittent, unexpected episodes of pain. Hemodynamic stressors to the heart can present as cardiomegaly and myocardial ischemia. Pulmonary hypertension is another known consequence of sickle cell anemia. It occurs in 30% to 40% of patients with SCD, and is associated with increased mortality. The most common premorbid conditions among patients with SCD include acute chest syndrome/pneumonia (58.1%), pulmonary hypertension (41.9%), systemic hypertension (25.6%), congestive heart failure (25.6%), myocardial infarction (20.9%), and arrhythmias (14.0%).

SCD is suggested when the abnormal sickle-shaped cells in the blood are identified under a microscope. Testing is typically performed on a smear of blood using a special low-oxygen preparation. Other prep tests can also be used to detect the abnormal HbS, including solubility tests performed on tubes of blood solutions. The disease can be confirmed by specifically quantifying the types of hemoglobin present using a hemoglobin electrophoresis test.

The bulk of the current evidence suggests that hydroxyurea, pro-oxidant and pro-inflammatory stress and coagulopathy, leading to vasomotor instability and ultimately producing a proliferative vasculopathy. Endothelial damage and inflammation make a significant contribution to the pathophysiology of SCD and the β-thalassemia syndromes

**CONCLUSIONS**

Our understanding of hematologic disorders has advanced steadily over the past two decades, stimulated by rapid growth in molecular biology, genetics, and contemporary diagnostic platforms. We have provided a focused overview of nononcological blood disorders involving plasma coagulation proteins, platelets, and red blood cells and their potential impact on the cardiovascular system, including the common phenotypes of myocardial infarction, ischemic stroke, and peripheral arterial occlusive events. Venous thromboembolism was highlighted as well, serving as a clinical template to heighten awareness of a common problem faced by all clinicians, including general cardiologists, and to clearly distinguish blood disorders which are unique to the venous as compared to the arterial circulatory systems. Finally, practical steps and general guidance for diagnostic testing and management in routine clinical care were offered to foster safe, effective, and cost-efficient patient care.

**CONFLICTS OF INTEREST**

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