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Update: Systemic Diseases and the Cardiovascular System (VI)

Hematologic Diseases: From Within the Heart

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ABSTRACT

The fundamental relationship between blood disorders and the cardiovascular system originates within multiple points of interface, ranging from the heart and its structural constituents to include heart chambers, valves, coronary arteries, coronary veins, and the cerebrovascular and peripheral vasculature. While the cellular components of circulating blood derive their primary origin from multipotent progenitor cells, plasma-based components, which include coagulation proteins, are mostly born of hepatic synthesis and endothelial cells. Here we provide a focused overview of nononcological 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.

Enfermedades hematológicas: desde dentro del corazón

Palabras clave:
Hemoglobinopatías
Trombocitopenia
Trombofilias
Trombosis

RESUMEN

La relación fundamental entre los trastornos sanguíneos y el sistema cardiovascular tiene su origen en múltiples puntos de contacto, que van del corazón y sus componentes estructurales, como las cámaras cardiacas, las válvulas, las arterias coronarias y las venas coronarias, a los vasos sanguíneos cerebrovasculares y periféricos. Mientras que los componentes celulares de la sangre circulante proceden inicialmente de células progenitoras pluripotenciales, los componentes plasmáticos, que incluyen las proteínas de la coagulación, se originan principalmente en la síntesis hepática y las células endoteliales. Presentamos aquí una revisión centrada en los trastornos hematológicos no oncológicos y sus posibles repercusiones en el sistema circulatorio arterial en forma de fenotipos frecuentes, como el infarto de miocardio, el ictus isquémico y los episodios de oclusión arterial periférica. En nuestro análisis utilizamos la tromboembolia venosa como patrón de referencia clínico. Presentamos también unos pasos prácticos y una guía para las pruebas diagnósticas y el manejo en la práctica clínica habitual.

Abbreviations

HIT: heparin-induced thrombocytopenia
ITP: immune thrombocytopenia
SCD: sickle cell disease
TTP: thrombotic thrombocytopenic purpura
VTE: venous thromboembolism

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, 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, including the common phenotypes of myocardial infarction, ischemic stroke, and peripheral arterial occlusive events. Venous thromboembolism (VTE) is employed as a clinical template to heighten awareness of a common problem faced by all clinicians and to distinguish blood disorders which are unique to the venous and to the arterial circulatory systems. We also provide practical steps and general guidance for diagnostic testing and management in routine clinical care.

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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.[1] 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,[2] with a reported prevalence of antithrombin deficiency of 1 in 500 to 1 in 5000 in the overall population.[3] 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, mesenteric, 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).[4] Despite its clear relationship with VTE, beginning as early as the first decade of life, there is no clear evidence that antithrombin deficiency increases the risk for arterial thrombosis.[5,6]

Protein C Deficiency

Protein C is a Vitamin K-dependent glycoprotein synthesized by the liver. Thrombin complexed to endothelial cell-based thrombomodulin cleaves an arginine-leucine bond within protein C, causing its activation. In turn, activated protein C inactivates factors Va and XIIIa, thus affecting both contact activated and tissue factor mediated pathways of the coagulation pathway. Activated protein C also neutralizes plasminogen activator inhibitor I, thus enhancing fibrinolytic activity. More than 160 protein C gene mutations have been reported,[7] and congenital protein C deficiency is transmitted in an autosomal dominant pattern. The prevalence of asymptomatic protein C deficiency has been reported to be between 1 in 200 and 1 in 500 healthy individuals, whereas the prevalence of clinically significant protein C deficiency has been estimated at 1 in 20 000 patients.[8]

The clinical phenotype of simple heterozygous protein C deficiency can range from asymptomatic to severe VTE. An estimated 50% of carriers develop venous thrombosis by age 45.[9] A metaanalysis reported that protein C deficiency significantly increased the risk of first VTE (OR = 7.75, 95% CI 4.48-13.38), and recurrent VTE (OR = 2.53, 95% CI 1.30-4.92).[4] In addition to VTE, the patients with heterozygous protein C 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.[5] 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.[6] 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 cofactor 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.[10,11]

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.[12] 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).[4] 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).[13] 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

Diseases	Mutations	Prevalence	Manifestation		
			VTE	RVTE	AT
ATD	*SERPINC1* gene	1/500∼1/5000	+	+	–
PCD	Protein C gene	1/200∼1/500	+	+	+/–
PSD	*PROS1*	0.03%-2%	+	+	+/–
APC resistance	FV Leiden (A506G); FVR2 (H1299R); FV Cambridge (R306T) and FV Hong Kong (R306G)	4%-6%	+	+	–
Prothrombin G20210A	Prothrombin G20210A	2%-4%	+	+/–	–

–: 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.

before age 55 years.[14] However, there are also studies reporting no convincing evidence for a link between protein S deficiency and arterial thrombosis.[5,6]

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 VIIIa. 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[15] and is the most prevalent hereditary thrombophilia, occurring in 4% to 6% of the general population.[16] It is rare or absent in populations from Far East Asia, black Africans, and indigenous populations of America and Australia.[17] 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.[18] 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.[19]

Heterozygosity for FV Leiden yields a lifelong hypercoagulable state associated with an approximately 3- to 7-fold increased risk of venous thrombosis, and is also predictive of recurrent VTE.[4,16] 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).[20] FV Leiden is considered a modest risk factor for ischemic stroke and myocardial infarction before age 55 years, particularly among women who smoke. It is not considered to be a risk factor for peripheral arterial occlusive events, with the exception of some patients with advanced native disease and/or surgical graft disease.[5,6,16]

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 healthy individuals in southern Europe, which is twice as high as that in northern Europe. Like FV Leiden, it is rare in Far East Asian, African, and indigenous Australian and American populations. In the literature, the mutation is found in 6% to 8% of VTE patients.[21]

Prothrombin G20210A mutation is associated with a 2- to 3-fold increased risk of VTE,[4] and is also associated with recurrent VTE.[4,22] As with the FV Leiden gene mutation, homozygosity is associated with the greatest overall risk.[23] There has not been a consistent association of prothrombin G20210A with arterial thrombosis; however, a modestly increased risk is likely present among affected individuals younger than 55 years.[5]

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. Other less common causes include myeloproliferative disorders, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria; and iatrogenic etiologies, such as chemotherapy for cancer, hormonal treatment for infertility, and surgical procedures.

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.[24] 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.[25] Antiphospholipid syndrome patients have significantly worse cardiovascular outcomes.[26]

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-b2GP1 antibodies) on 2 separate occasions at least 12 weeks apart, in the setting of thrombosis or pregnancy complications.[27] 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 anticoagulation 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.

PREVENTION AND TREATMENT STRATEGIES FOR VENOUS AND ARTERIAL THROMBOSIS

Asymptomatic individuals: Long-term anticoagulant thromboprophylaxis is not recommended in asymptomatic patients with inherited thrombophilias because of the increased risk of hemorrhage.[26]

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.[28]

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.[28]

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.[29] 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.[30] HIT is characterized by thrombocytopenia and a strong propensity for paradoxical thrombosis, manifesting either arterial, microvascular, or VTE, the latter being more common.[31,32]

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),[33] 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.[34] Alternative anticoagulants include the direct thrombin inhibitors lepirudin, argatroban, and bivalirudin, and the anti-Xa agent fondaparinux.[34] The use of warfarin anticoagulation has been associated with the development of venous limb gangrene and should be avoided until the platelet count has improved. Furthermore, it should be initiated with concurrent nonheparin anticoagulation and without bolus dosing.[34] For patients with HIT who have not sustained a thromboembolic event, therapeutic anticoagulation should be continued until the platelet count has returned to a stable plateau.[34] HIT patients with a thromboembolic complication should receive a standard course of therapeutic anticoagulation for the specific clinical event.[34] 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.[34]

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.[35] 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.[36] The classic pentad of thrombocytopenia, hemolytic anemia, fever, renal dysfunction, and neurologic symptoms is present in only a minority of TTP patients.[37] A single-center study showed that 21% of TTP patients develop incident myocardial infarction.[38] Among cardiovascular patients, use of antiplatelet agents such as clopidogrel and ticlopidine has been rarely associated with drug-induced TTP. Clopidogrel-associated TTP often occurs within 2 weeks of drug initiation. The survival rate for patients with clopidogrel-associated TTP is approximately 71.2%.[39]

The clinical laboratory picture is similar to that of disseminated intravascular coagulation, although prothrombin time and activated partial thromboplastin time are rarely abnormal.[40] ADAMTS-13 activity assays have advanced the diagnosis of TTP, with sensitivities ranging from 89% to 100% and specificity greater than 91%.[41] 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.[42] On the other hand, some have suggested a role for the therapeutic use of antiplatelet agents in conjunction with plasma exchange despite significant thrombocytopenia.[42] 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.[43]

Immune Thrombocytopenia

Immune thrombocytopenia (ITP) is an acquired immune-mediated disorder characterized by isolated thrombocytopenia (platelet count 150×10^9/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.[44] 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 10^5 adults/year for adults.[45] 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.[46] The symptoms and signs are highly variable and range from the completely asymptomatic patient to 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 $<20 \times 10^9$/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 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 proposed and treatment should be individualized to minimize both bleeding and thrombosis risks. Nonetheless, several cases suggest the feasibility of percutaneous revascularization in selected patients with multivessel coronary disease and ITP.[47]

ABNORMALITIES OF RED BLOOD CELLS

Anemia

The World Health Organization defines anemia as a hemoglobin concentration <13 g/dL in men and <12 g/dL in postmenopausal women. Anemia is common among patients with cardiovascular disease. The prevalence of anemia in patients with congestive heart failure ranges between 4% and 61% (median 18%) depending on the studied population, with the majority of studies indicating prevalence $>20\%$.[50] Anemia appears to be more prevalent in patients with advanced age and in those with severe limitations in functional capacity and greater severity of co-morbid kidney disease.[50] Among patients with myocardial infarction, baseline anemia was present in 10.5% of patients[51] and the incidence of hospital-acquired anemia was high (range 33% to 69% depending on hospital).[52]

The etiologies of anemia are multifactorial, including blood loss in the context of antiplatelet or anticoagulant therapies, iron deficiencies, hemodilution, activation of the inflammatory cascade, urinary losses of erythropoietin, and associated renal insufficiency.[52,53] Anemia is a strong independent predictor of increased mortality, hospitalization, and bleeding risk in patients with cardiovascular disease.[51–53]

Treatment and management of anemia has centered on erythropoietin-stimulating agents and parenteral iron supplementation. Many studies show a positive effect of erythropoietin or its derivatives when administered in combination with oral or intravenous iron, showing improvements in left and right ventricular systolic and diastolic function, dilation and hypertrophy, and renal function.[54] There is a need for an 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 β-thalassemia (HbS–β-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)

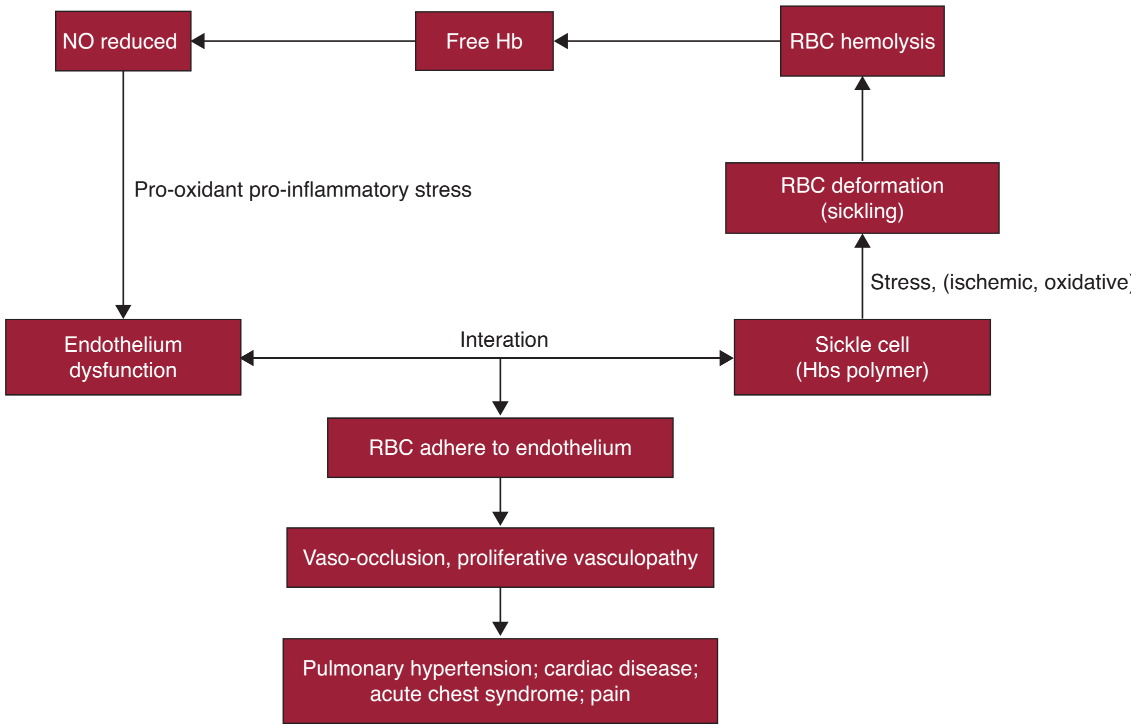

Figure 1. Cardiovascular pathologies of sickle cell disease. The sickle cells with hemoglobin S polymers are under ischemic, oxidative, or shear stress. These conditions cause deformations to red blood cells, called sickling and hemolysis. Free hemoglobin,released into plasma by hemolysis scavenges on nitric oxide, and leads to reduced nitric oxide bioavailability. The endothelial dysfunction characterized by reduced nitric oxide bioavailability, pro-oxidant and pro-inflammatory stress, and coagulopathy leads to enhanced erythrocyte-endothelial cell adhesion, results in vaso-occlusion and proliferative vascularopathy, and eventually produces a series of manifestations, such as pain, pulmonary hypertension, acute chest syndrome, stroke, and myocardial infarction.
Hb: hemoglobin; HbS: hemoglobin S; NO: nitric oxide; RBC: red blood cells.

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[61] (Fig. 1).

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.[62] 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.[63] 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%).[64]

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 is well tolerated, safe, and efficacious for most patients with SCD.[65] Novel therapeutic agents focusing on the NO pathway would be beneficial for complications. Results from studies that examined the effect of inhaled NO on different SCD subtypes appear to be promising despite the state of NO resistance observed in patients and in animal models.[66] Sildenafil, a phosphodiesterase type 5 inhibitor, has been shown to improve pulmonary hypertension in SCD patients.[67] Large trials are needed to confirm their efficacy and safety in the sickle cell population.

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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REFERENCES

1. Raskob GE, Silverstein R, Bratzler DW, Heit JA, White RH. Surveillance for deep vein thrombosis and pulmonary embolism: recommendations from a national workshop. Am J Prev Med. 2010;38:S502–9.
2. Stenson PD, Ball EV, Howells K, Phillips AD, Mort M, Cooper DN. The Human Gene Mutation Database: providing a comprehensive central mutation database for molecular diagnostics and personalized genomics. Hum Genomics. 2009;4:69–72.
3. Wells PS, Blajchman MA, Henderson P, Wells MJ, Demers C, Bourque R, et al. Prevalence of antithrombin deficiency in healthy blood donors: a cross-sectional study. Am J Hematol. 1994;45:321–4.
4. Young G, Albisetti M, Bonduel M, Brandao L, Chan A, Friedrichs F, et al. Impact of inherited thrombophilia on venous thromboembolism in children: a systematic review and meta-analysis of observational studies. Circulation. 2008;118: 1373–82.
5. Haywood S, Liesner R, Pindora S, Ganesan V. Thrombophilia and first arterial ischaemic stroke: a systematic review. Arch Dis Child. 2005;90:402–5.
6. Palareti G, Valdre L, Favaretto E, Bovina V, Cini M, Legnani C. No early signs of atherosclerotic alterations in carriers of inherited thrombophilia. Eur J Intern Med. 2010;21:273–7.
7. Alhenc-Gelas M, Gandrille S, Aubry ML, Aiach M. Thirty-three novel mutations in the protein C gene. French INSERM network on molecular abnormalities responsible for protein C and protein S. Thromb Haemost. 2000;83:86–92.
8. Dahlback B. The protein C anticoagulant system: inherited defects as basis for venous thrombosis. Thromb Res. 1995;77:1–43.
9. Allaart CF, Poort SR, Rosendaal FR, Reitsma PH, Bertina RM, Briet E. Increased risk of venous thrombosis in carriers of hereditary protein C deficiency defect. Lancet. 1993;341:134–8.
10. Gandrille S, Borgel D, Sala N, Espinosa-Parrilla Y, Simmonds R, Rezende S, et al. Scientific and Standardization Committee Communication: Protein S Deficiency: A Database of Mutations - FIRST UPDATE. Available at: http://www.isth.org/default/assets/File/proteinstext.pdf
11. Institute of Medical Genetics, Cardiff. Human Gene Mutation Database. Available at: http://www.hgmd.cf.ac.uk/ac/
12. Seligsohn U, Lubetsky A. Genetic susceptibility to venous thrombosis. N Engl J Med. 2001;344:1222–31.
13. Brouwer JL, Lijfering WM, Ten Kate MK, Kluin-Nelemans HC, Veeger NJ, Van der Meer J. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. Thromb Haemost. 2009;101:93–9.
14. Mahmoodi BK, Brouwer JL, Veeger NJ, Van der Meer J. Hereditary deficiency of protein C or protein S confers increased risk of arterial thromboembolic events at a young age: results from a large family cohort study. Circulation. 2008;118:1659–67.
15. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, De Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. Nature. 1994;369:64–7.
16. Ridker PM, Hennekens CH, Lindpaintner K, Stampfer MJ, Eisenberg PR, Miletich JP. Mutation in the gene coding for coagulation factor V and the risk of myocardial infarction, stroke, and venous thrombosis in apparently healthy men. N Engl J Med. 1995;332:912–7.
17. Rees DC, Cox M, Clegg JB. World distribution of factor V Leiden. Lancet. 1995;346:1133–4.
18. Castoldi E, Brugge JM, Nicolaes GA, Girelli D, Tans G, Rosing J. Impaired APC cofactor activity of factor V plays a major role in the APC resistance associated with the factor V Leiden (R506Q) and R2 (H1299R) mutations. Blood. 2004; 103:4173–9.
19. Norstrom E, Thorelli E, Dahlback B. Functional characterization of recombinant FV Hong Kong and FV Cambridge. Blood. 2002;100:524–30.
20. Dentali F, Crowther M, Ageno W. Thrombophilic abnormalities, oral contraceptives, and risk of cerebral vein thrombosis: a meta-analysis. Blood. 2006;107:2766–73.
21. Rosendaal FR, Doggen CJ, Zivelin A, Arruda VR, Aiach M, Siscovick DS, et al. Geographic distribution of the 20210 G to A prothrombin variant. Thromb Haemost. 1998;79:706–8.
22. Ho WK, Hankey GJ, Quinlan DJ, Eikelboom JW. Risk of recurrent venous thromboembolism in patients with common thrombophilia: a systematic review. Arch Intern Med. 2006;166:729–36.
23. Marchiori A, Mosena L, Prins MH, Prandoni P. The risk of recurrent venous thromboembolism among heterozygous carriers of factor V Leiden or prothrombin G20210A mutation. A systematic review of prospective studies. Haematologica. 2007;92:1107–14.
24. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood. 2003;101: 1827–32.
25. Long BR, Leya F. The role of antiphospholipid syndrome in cardiovascular disease. Hematol Oncol Clin North Am. 2008;22:79–94. vi-vii.
26. Maksimowicz-McKinnon K, Selzer F, Manzi S, Kip KE, Mulukutla SR, Marroquin OC, et al. Poor 1-year outcomes after percutaneous coronary interventions in systemic lupus erythematosus: report from the National Heart, Lung, and Blood Institute Dynamic Registry. Circ Cardiovasc Interv. 2008; 1:201–8.
27. Khor B, Van Cott EM. Laboratory evaluation of hypercoagulability. Clin Lab Med. 2009;29:339–66.
28. Bates SM, Greer IA, Pabinger I, Sofaer S, Hirsh J. Venous thromboembolism, thrombophilia, antithrombotic therapy, and pregnancy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. Chest. 2008;133:S844–86.
29. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. JAMA. 2006;295:1050–7.
30. Chang JJ, Parikh CR. When heparin causes thrombosis: significance, recognition, and management of heparin-induced thrombocytopenia in dialysis patients. Semin Dial. 2006;19:297–304.
31. Levine RL, McCollum D, Hursting M. How frequently is venous thromboembolism in heparin-treated patients associated with heparin-induced thrombocytopenia? Chest. 2006;130:681–7.
32. Nand S, Wong W, Yuen B, Yetter A, Schmulbach E, Gross Fisher S. Heparin-induced thrombocytopenia with thrombosis: incidence, analysis of risk factors, and clinical outcomes in 108 consecutive patients treated at a single institution. Am J Hematol. 1997;56:12–6.
33. Warkentin TE, Sheppard JA, Moore JC, Cook RJ, Kelton JG. Studies of the immune response in heparin-induced thrombocytopenia. Blood. 2009;113: 4963–9.
34. Warkentin TE, Greinacher A, Koster A, Lincoff AM. Treatment and prevention of heparin-induced thrombocytopenia: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. 8th ed. Chest. 2008;133: S340–80.
35. Tsai HM. Pathophysiology of thrombotic thrombocytopenic purpura. Int J Hematol. 2010;91:1–19.
36. Terrell DR, Vesely SK, Hovinga JA, Lammle B, George JN. Different disparities of gender and race among the thrombotic thrombocytopenic purpura and hemolytic-uremic syndromes. Am J Hematol. 2010;85:844–7.
37. Marques MB. Thrombotic thrombocytopenic purpura and heparin-induced thrombocytopenia: two unique causes of life-threatening thrombocytopenia. Clin Lab Med. 2009;29:321–38.
38. Gandhi K, Aronow WS, Desai H, Amin H, Sharma M, Lai HM, et al. Cardiovascular manifestations in patients with thrombotic thrombocytopenic purpura: a single-center experience. Clin Cardiol. 2010;33:213–6.
39. Zakarija A, Bandarenko N, Pandey DK, Auerbach A, Raisch DW, Kim B, et al. Clopidogrel-associated TTP. an update of pharmacovigilance efforts conducted by independent researchers, pharmaceutical suppliers, and the Food and Drug Administration. Stroke. 2004;35:533–7.
40. Park YA, Waldrum MR, Marques MB. Platelet count and prothrombin time help distinguish thrombotic thrombocytopenic purpura-hemolytic uremic syndrome from disseminated intravascular coagulation in adults. Am J Clin Pathol. 2010;133:460–5.
41. Scully M, Yarranton H, Liesner R, Cavenagh J, Hunt B, Benjamin S, et al. Regional UK TTP registry: correlation with laboratory ADAMTS 13 analysis and clinical features. Br J Haematol. 2008;142:819–26.
42. Kiss JE, Thrombotic thrombocytopenic purpura: recognition management. Int J Hematol. 2010;91:36–45.
43. Swisher KK, Terrell DR, Vesely SK, Kremer Hovinga JA, Lammle B, George JN. Clinical outcomes after platelet transfusions in patients with thrombotic thrombocytopenic purpura. Transfusion. 2009;49:873–87.
44. Thachil J. Nitric oxide in immune thrombocytopenic purpura. Hematology. 2009;14:59–62.
45. Terrell DR, Beebe LA, Vesely SK, Neas BR, Segal JB, George JN. The incidence of immune thrombocytopenic purpura in children and adults: A critical review of published reports. Am J Hematol. 2010;85:174–80.
46. Feudjo-Tepie MA, Robinson NJ, Bennett D. Prevalence of diagnosed chronic immune thrombocytopenic purpura in the US: analysis of a large US claim database: a rebuttal. J Thromb Haemost. 2008;6:711–2. author reply 3.
47. Neskovic AN, Stankovic I, Milicevic P, Aleksic A, Vlahovic-Stipac A, Calija B, et al. Primary PCI for acute myocardial infarction in a patient with idiopathic thrombocytopenic purpura. A case report and review of the literature. Herz. 2010;35:43–9.
48. De Mattia D, Del Vecchio GC, Russo G, De Santis A, Ramenghi U, Notarangelo L, et al. Management of chronic childhood immune thrombocytopenic purpura: AIEOP consensus guidelines. Acta Haematol. 2010;123:96–109.
49. Arnold DM, Nazi I, Kelton JG. New treatments for idiopathic thrombocytopenic purpura: rethinking old hypotheses. Expert Opin Investig Drugs. 2009;18: 805–19.
50. Tang YD, Katz SD. The prevalence of anemia in chronic heart failure and its impact on the clinical outcomes. Heart Fail Rev. 2008;13:387–92.
51. Tsujita K, Nikolsky E, Lansky AJ, Dangas G, Fahy M, Brodie BR, et al. Impact of anemia on clinical outcomes of patients with ST-segment elevation myocardial infarction in relation to gender and adjunctive antithrombotic therapy (from the HORIZONS-AMI trial). Am J Cardiol. 2010;105:1385–94.
52. Salisbury AC, Alexander KP, Reid KJ, Masoudi FA, Rathore SS, Wang TY, et al. Incidence, correlates, and outcomes of acute, hospital-acquired anemia in patients with acute myocardial infarction. Circ Cardiovasc Qual Outcomes. 2010;3:337–46.

53. Terrovitis JV, Anastasiou-Nana M, Kaldara E, Drakos SG, Nanas SN, Nanas JN. Anemia in heart failure: pathophysiologic insights and treatment options. Future Cardiol. 2009;5:71–81.
54. Anand IS. Anemia and chronic heart failure implications and treatment options. J Am Coll Cardiol. 2008;52:501–11.
55. Ghali JK, Anand IS, Abraham WT, Fonarow GC, Greenberg B, Krum H, et al. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. Circulation. 2008;117:526–35.
56. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, De Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019–32.
57. McMurray JJ, Anand IS, Diaz R, Maggioni AP, O'Connor C, Pfeffer MA, et al. Design of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF): a Phase III, anaemia correction, morbidity-mortality trial. Eur J Heart Fail. 2009;11:795–801.
58. Little to REVEAL: Adding EPO after PCI does not reduce infarct size. Available at: http://www.theheart.org/article/1151621.do
59. Rao SV, Jollis JG, Harrington RA, Granger CB, Newby LK, Armstrong PW, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA. 2004;292:1555–62.
60. Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med. 2010;38:S512–21.
61. Kaul DK, Finnegan E, Barabino GA. Sickle red cell-endothelium interactions. Microcirculation. 2009;16:97–111.
62. Haywood LJ. Cardiovascular function and dysfunction in sickle cell anemia. J Natl Med Assoc. 2009;101:24–30.
63. Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. N Engl J Med. 2008;359:2254–65.
64. Fitzhugh CD, Lauder N, Jonassaint JC, Telen MJ, Zhao X, Wright EC, et al. Cardiopulmonary complications leading to premature deaths in adult patients with sickle cell disease. Am J Hematol. 2010;85:36–40.
65. Steinberg MH, McCarthy WF, Castro O, Ballas SK, Armstrong FD, Smith W, et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. Am J Hematol. 2010;85:403–8.
66. Head CA, Swerdlow P, McDade WA, Joshi RM, Ikuta T, Cooper ML, et al. Beneficial effects of nitric oxide breathing in adult patients with sickle cell crisis. Am J Hematol. 2010;85:800–2.
67. Machado RF, Martyr S, Kato GJ, Barst RJ, Anthi A, Robinson MR, et al. Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension. Br J Haematol. 2005;130:445–53.