REVIEW ARTICLE

MECHANISMS OF DISEASE

Pulmonary Complications of Sickle Cell Disease

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The inheritance of two copies of a mutant β-globin gene, one from each parent, is the underlying cause of sickle cell disease. The mutation, GAG→GTG, substitutes valine for glutamic acid at position 6 in the β-globin chain of hemoglobin A, resulting in a hemoglobin called hemoglobin S.[1-3] Sickle cell disease is one of the most common autosomal recessive disorders in the world. Approximately 8% of black Americans are heterozygous and have the sickle cell trait, whereas approximately 1 in 600 is homozygous and has sickle cell disease. In certain areas of sub-Saharan Africa, an estimated 40 to 60% of the population is heterozygous, suggesting that 1 to 4% of babies born in this region have the disease.[4]

Hemoglobin S polymerizes on deoxygenation. The polymers make the erythrocyte rigid, distort its shape, and cause structural damage in the red-cell membrane, all of which alter the rheologic properties of the cell, impair blood flow through the microvasculature, and lead to hemolysis and vaso-occlusive episodes.[2,5] The extent of hemoglobin S polymerization is a primary determinant of the severity of sickle cell disease[6] and is proportional to the degree and duration of hemoglobin deoxygenation and to the concentration of intracellular hemoglobin S raised to approximately the 15th power.[2] The presence of fetal hemoglobin in the erythrocyte reduces the concentration of hemoglobin S and thereby inhibits its polymerization.[7]

The complications of sickle cell disease are myriad, but the two most common acute events are vaso-occlusive pain crisis, caused by physical and adhesive entrapment of red cells containing hemoglobin S in the microcirculation, and the acute chest syndrome, a lung injury syndrome.[8,9] In addition, affected adults are at risk for a progressive vasculopathy, characterized by systemic and pulmonary hypertension, endothelial dysfunction, and proliferative changes in the intima and smooth muscle of blood vessels.[10-16] With increasing age, chronic end-organ complications begin to appear. These include chronic renal failure, hemorrhagic and nonhemorrhagic stroke, avascular necrosis of bone, and pulmonary hypertension, which has a remarkably high prevalence among adults with sickle cell disease.[12,17] From a clinical perspective, pulmonary complications — namely, the acute chest syndrome and pulmonary hypertension — are the most common causes of death in patients with sickle cell disease.[8,9,12,18]

Advances in our understanding of the mechanism of vaso-occlusion and the sequelae of chronic intravascular hemolysis have led to insights into the highly variable clinical manifestations of sickle cell disease. We present a new formulation of sickle cell disease and propose that certain of its complications are driven by the vaso-occlusive process, whereas others result from the deleterious effects of intravascular hemolysis on endothelial-cell and vascular function.

PHENOTYPES OF SICKLE CELL DISEASE

All patients with sickle cell disease have the same GAG→GTG substitution, but the penetrance and severity of specific complications arising from the mutant hemoglobin S gene, as well as the risk factors for these complications and the age at which they occur, are highly variable. For example, the major laboratory risk factors for both vaso-occlusive pain crisis and the acute chest syndrome are high, steady-state leukocyte counts and high hemoglobin levels.[1,8,9] In contrast, cholelithiasis, cutaneous leg ulceration, priapism, and pulmonary hypertension are associated with low steady-state hemoglobin levels and an increased rate of intravascular hemolysis.[12,17,19-23] These latter complications also occur in other hemolytic diseases. For example, pulmonary hypertension is common in thalassemia even though the acute chest syndrome does not occur in that disorder, which is not caused by hemoglobin S.[24-28] Priapism and cutaneous leg ulceration also occur in other hemolytic disorders, although to a lesser extent than in sickle cell disease.[21,29-34]

Given the divergent clinical manifestations of and epidemiologic risk factors for vaso-occlusive pain crisis and the acute chest syndrome (as compared with other vasculopathic complications, such as sudden death, pulmonary hypertension, cutaneous leg ulceration, and priapism), sickle cell disease may be best understood as the interaction of two overlapping subphenotypes driven by two major mechanisms: vaso-occlusion and hemolytic anemia (Fig. 1).

VASO-OCCLUSION

Vaso-occlusive crises are recurrent episodes of severe pain in sickle cell disease. The cause of these events is microvascular entrapment of erythrocytes and leukocytes, which obstruct blood flow and bring about organ ischemia. In the microcirculation of transgenic mouse models of sickle cell disease, hypoxia or inflammatory agents, such as tumor necrosis factor α or lipopolysaccharide, increase adhesive interactions between endothelium, leukocytes, and erythrocytes in the postcapillary venules, thereby initiating vascular occlusion.[35-39] This model indicates that cycles of ischemia and reperfusion, in addition to intravascular hemolysis, cause oxidant stress, in which there is activation of vascular oxidases,[40-42] and inflammatory stress, which is characterized by the expression of endothelial-cell adhesion molecules and inflammatory cytokines and by leukocytosis.[35,37,43-45] Precapillary obstruction by rigid, deformed erythrocytes with a high content of hemoglobin S polymer probably also contributes to occlusion of the microcirculation (Fig. 1).[46]

Bone marrow and periosteal ischemia and reperfusion instigate cellular injury, infarction, tissue necrosis, edema, and inflammation. The clinical manifestations of these microvascular events are explosive episodes of pain and inflammation, often accompanied by fever and leukocytosis and sometimes by bone marrow necrosis, with pulmonary emboli consisting of necrotic marrow fat and cellular elements.[1,8,9] Epidemiologic studies of the frequency and severity of vaso-occlusive crises indicate an association with high concentrations of hemoglobin S, low concentrations of fetal hemoglobin, and high steady-state leukocyte counts and hemoglobin levels.[8] These epidemiologic data point to polymerized hemoglobin S, inflammation, and hyperviscosity as major determinants of the severity of erythrocyte vaso-occlusion.

THE ACUTE CHEST SYNDROME

The acute chest syndrome is a common form of lung injury in sickle cell disease. When severe, this syndrome is analogous to the acute respiratory distress syndrome. In a patient with sickle cell disease it is generally defined by the development of a new pulmonary infiltrate that is consistent with alveolar consolidation but not atelectasis, involving at least one complete lung segment. The radiographic abnormality is usually accompanied by chest pain, fever, tachypnea, wheezing, or cough.[8] The acute chest syndrome is the second most common cause of hospitalization among patients with sickle cell disease and the leading cause of admission to an intensive care unit and premature death in this patient population.[8]

CAUSES OF THE ACUTE CHEST SYNDROME

Three major causes of the acute chest syndrome have been proposed: pulmonary infection, embolization of bone marrow fat, and intravascular pulmonary sequestration of sickled eryth-

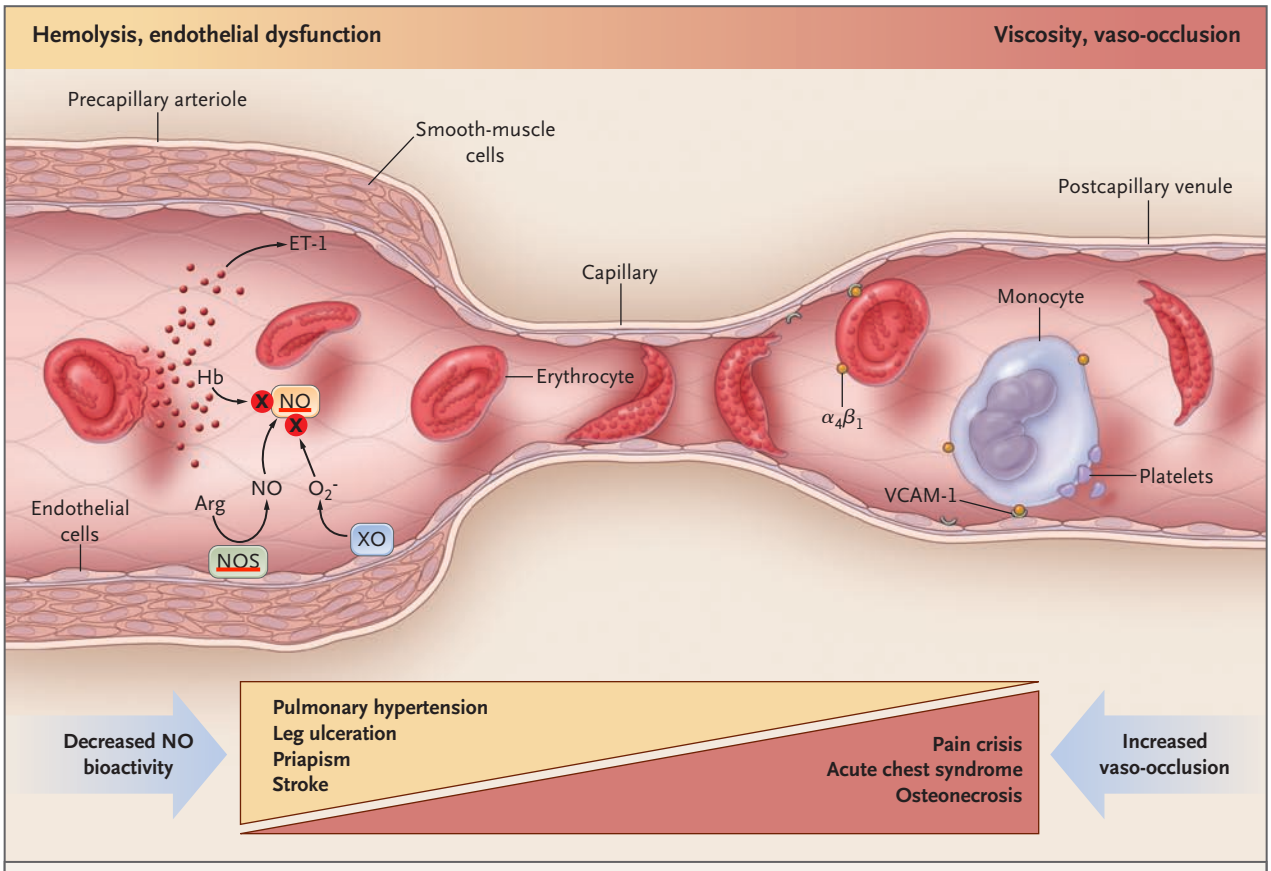

Figure 1. Hypothetical Mechanisms of Clinical Subphenotypes of Sickle Cell Disease.

It is hypothesized that many of the complications of sickle cell disease can be divided into two overlapping subtypes, each driven by distinct mechanisms. Cutaneous leg ulceration, priapism, pulmonary hypertension, sudden death, and stroke are associated with low steady-state hemoglobin (Hb) levels and an increased rate of intravascular hemolysis, shown on the left side of the figure. These vasculopathic complications probably result from endothelial dysfunction, mediated by both inactivation of nitric oxide (NO) by free-plasma hemoglobin and vascular reactive oxygen species as well as arginine (Arg) catabolism by plasma arginase. This process of hemolysis-associated endothelial dysfunction may also cause hemostatic activation and intimal and smooth-muscle proliferation. Such clinical complications as vaso-occlusive pain crisis, the acute chest syndrome, avascular necrosis of bones, and retinal vasculopathy are associated with high steady-state leukocyte counts and high hemoglobin levels. These complications are likely to result from obstruction of capillaries and postcapillary venules by erythrocytes containing polymerized hemoglobin S and by leukocytes (a monocyte is shown), as shown on the right side of the figure. ET-1 denotes endothelin 1, NOS nitric oxide synthase, O_2^- superoxide, VCAM-1 vascular-cell adhesion molecule 1, and XO xanthine oxidase.

rocytes, resulting in lung injury and infarction (Fig. 2).

Pulmonary Infection

The most common cause of the acute chest syndrome in children and adults is pulmonary infection by a community-acquired pathogen, which incites an excessive inflammatory response to what often should have been a mild upper respiratory infection. Studies have shown that transgenic mice that express human hemoglobin S are susceptible to inflammatory triggers such as lipopolysaccharide and episodic exposure to environmental hypoxia, with the development of lung injury at doses of endotoxin or degrees of hypoxia that do not adversely affect wild-type mice.[47,48]

The National Acute Chest Syndrome Study Group analyzed 671 episodes of the acute chest syndrome in 538 patients with sickle cell disease to determine the cause, outcome, and response to therapy.[9] Respiratory airway sputum and bronchoalveolar-lavage specimens were analyzed for viral and bacterial infections, and an infectious agent was identified in 54% of patients who

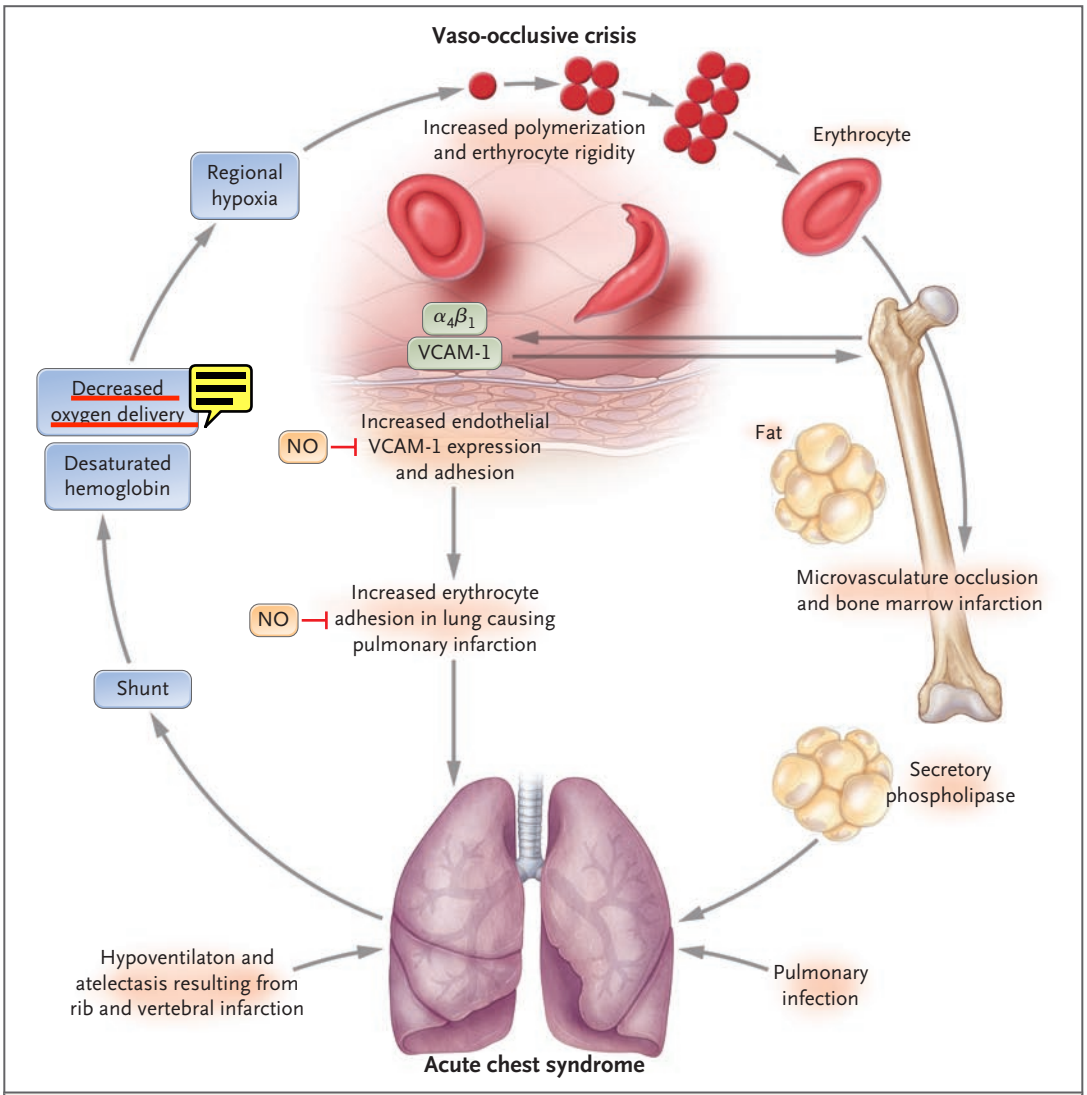

Figure 2. The Vicious Cycle of the Acute Chest Syndrome.

The acute chest syndrome is a lung injury syndrome initiated by three major triggers, all related to vaso-occlusion by sickle cells: infection, embolization of bone marrow fat, and intravascular sequestration of red cells, all of which cause lung injury and infarction. Lung injury results in ventilation–perfusion mismatch and hypoxemia, which leads to increased deoxygenation of hemoglobin S, followed by hemoglobin polymerization and erythrocyte vaso-occlusion, which in turn promote bone marrow infarction and pulmonary vaso-occlusion. NO denotes nitric oxide, and VCAM-1 vascular-cell adhesion molecule.

were admitted to a hospital. Most of the agents were atypical bacteria and viruses. Community-acquired encapsulated bacteria were isolated in less than 10% of cases, even though normal splenic phagocytic function is rare in sickle cell disease.

Fat Emboli

The second major cause of the acute chest syndrome is the fat emboli syndrome. It is associated with a severe vaso-occlusive pain crisis involving multiple bones, especially the pelvis and femur, which results in infarction and edema of the bone marrow. The bone marrow undergoes necrosis, and its contents, including fat, cells, and even bony spicules, are released into the bloodstream and travel to the lung, where they cause acute pulmonary hypertension, severe lung inflammation, and hypoxemia.[49-51] Secretory phospholipase A_2 is thought to convert bone marrow

phospholipids to free fatty acids, which initiate an inflammatory response and lung injury in a process analogous to that triggered by intravenous administration of oleic acid in mouse models of the acute respiratory distress syndrome.[52]

Oil red O staining of lipid accumulations within alveolar macrophages is diagnostic of the fat emboli syndrome, and the lipid accumulations can be identified in more than 16% of cases of the acute chest syndrome in adults and children.[9] A study compared induced sputum samples of alveolar macrophages with samples obtained using bronchoalveolar lavage and found a modest but significant correlation between the two methods ($r=0.65$).[53] In this study, patients with lipid-laden macrophages in induced sputum samples had significantly greater extrathoracic pain, more neurologic symptoms, lower platelet counts, and higher aminotransferase levels than patients without evidence of fat emboli. The acute chest syndrome can be part of the spectrum of disorders in the systemic fat emboli syndrome. This latter syndrome should be suspected in patients with abrupt multiorgan failure, rapid development of the acute respiratory distress syndrome, acute increases in pulmonary arterial pressures, evidence of hepatic injury, alterations in mental status, seizures, prominent thrombocytopenia, and in rare cases, coagulopathy.[54,55]

Pulmonary Infarction

Pulmonary infarction, or vaso-occlusion, may also contribute to the development of the acute chest syndrome. In a small number of patients, wedge-shaped lung infarction, sometimes followed by central cavitation, develops.[9,56]

CLINICAL ASPECTS OF THE ACUTE CHEST SYNDROME

In most adults with sickle cell anemia, the acute chest syndrome develops 24 to 72 hours after the onset of severe pain in the arms, legs, or chest. The acute chest syndrome is associated with marked systemic inflammation, with a mean peak temperature of 38.9°C and a mean white-cell count of 23,000 per cubic millimeter.[9] Although a high steady-state hemoglobin level (without pain crisis) is a major risk factor for the acute chest syndrome, in hospitalized patients with vaso-occlusive pain crisis, an abrupt drop in the hemoglobin level (a mean decrease of 0.78 g per deciliter from steady-state levels) and an increase in markers of hemolysis often precede the development of the acute chest syndrome. The platelet count also falls before the onset of the acute chest syndrome; a platelet level of 200,000 per cubic millimeter or less is an independent risk factor for severe manifestations of the syndrome and is associated with increased risks of neurologic complications and the need for mechanical ventilation.

The mean length of hospitalization for adults with the acute chest syndrome is 10.5 days, as compared with only 3 to 4 days for uncomplicated vaso-occlusive pain crisis. Mechanical ventilation is required in 13% of patients with the syndrome, and 3% die. The outcome for patients on mechanical ventilation is actually quite good, with a mortality rate of only 19%, as compared with the outcome for all patients with the acute chest syndrome, for whom the mortality rate is approximately 30%.[9] Rapid simple or exchange transfusion, ideally with antigen-matched blood, removes the trigger for acute lung injury — sickled erythrocytes — allowing rapid recovery in young patients.

Sickle cell disease is often accompanied by asthma. Reactive airway disease occurs in 13% or more of patients with the acute chest syndrome and in up to 53% of children between birth and the age of 9 years.[9,57] Although a number of studies suggest that asthma is a risk factor for the acute chest syndrome and stroke in patients with sickle cell disease,[58-60] it remains uncertain whether there is an increase in the prevalence of asthma among children with sickle cell disease in the steady state, as compared with matched controls.[59,61] During steady-state sickle cell disease, the major abnormality in pulmonary function is a restrictive ventilatory impairment, characterized by a mild reduction in total lung capacity, and reduced diffusion capacity for carbon monoxide.[62,63] These abnormalities worsen with age and are associated with increases in pulmonary-artery pressures.[63,64]

HEMOLYSIS, ENDOTHELIAL-CELL DYSFUNCTION, AND VASCULOPATHY

CATABOLISM OF HEMOGLOBIN

A complex biochemical and cellular system clears and detoxifies the hemoglobin that red cells release into the plasma during normal oxidative and

mechanical stress.[65] The hemoglobin dimer binds with an unusually high protein–protein affinity to haptoglobin.[66] The resulting complex exposes a neoepitope recognized by the hemoglobin scavenger protein CD163, a transmembrane glycoprotein that initiates the uptake of hemoglobin into macrophages and monocytes. The uptake of hemoglobin by these cells activates interleukin-10 and induces expression of heme oxygenase-1 and biliverdin reductase.[67-69] These enzymes catabolize heme and signal potent antiproliferative, antioxidant, and antiinflammatory reactions.[68-70] The downstream activities of these molecules take place in response to the oxidative and inflammatory effects of free heme, iron, and oxygen: the binding of haptoglobin to hemoglobin limits heme-mediated lipid peroxidation;[71] biliverdin reductase catalytically generates NADPH and reduces glutathione,[69] and heme oxygenase-1 generates carbon monoxide and biliverdin, both of which limit proliferative and thrombotic vascular injury.[68] New therapeutic approaches, such as haptoglobin infusions, inhaled carbon monoxide gas and carbon monoxide–releasing compounds, and genetic or pharmacologic induction of heme oxygenase are being studied in animal models for the treatment of vascular injury in sickle cell disease.[72]

HEMOLYSIS

Effect on Nitric Oxide

In sickle cell disease, the hemoglobin and heme scavenging systems are saturated and overwhelmed, even in the steady state.[73,74] Free plasma hemoglobin, in addition to generating reactive oxygen species, such as the hydroxyl and superoxide radicals (through the Fenton and peroxidase and auto-oxidation chemical reactions),[75,76] is also a potent scavenger of nitric oxide.[77] Nitric oxide, which is normally produced by the endothelium, regulates basal vasodilator tone; inhibits platelet and hemostatic activation; inhibits transcriptional expression of nuclear factor κB–dependent adhesion molecules, such as vascular-cell adhesion molecule 1, intercellular adhesion molecule 1, and the selectins; and reduces superoxide levels through radical–radical scavenging.[78-82] The half-life of nitric oxide in the blood is extremely short because of its rapid reaction with hemoglobin to form methemoglobin and nitrate.[83] Actually, the vasodilator activity of nitric oxide is possible only because most hemoglobin is normally compartmentalized within erythrocytes. Flowing blood produces a cell-free zone along the endothelium; this zone and an area of nonflowing blood around the outside of the erythrocyte (called the unstirred layer) constitute major diffusion barriers against nitric oxide entry into red cells.[84-86] These barriers reduce the rate at which nitric oxide reacts with intracellular hemoglobin by two to three orders of magnitude. The release of hemoglobin into plasma during hemolysis circumvents these diffusion barriers and serves as a potent inhibitor of all nitric oxide bioactivity, leading to a clinical state of endothelial-cell dysfunction and nitric oxide resistance.[14,74,77,87-92]

Effect on Arginine

Hemolysis also releases erythrocyte arginase 1 into plasma. Arginase metabolizes plasma arginine into ornithine, reducing the required substrate for nitric oxide synthesis and compounding the reduction in the bioavailability of nitric oxide in sickle cell disease (Fig. 1).[93] In one study, the plasma levels and enzymatic activity of arginase 1 were significantly increased in 228 patients with sickle cell disease as compared with black control subjects; moreover, arginase 1 modulated the metabolic profile of arginine by reducing arginine levels and increasing the production of ornithine relative to that of citrulline.[93] These abnormalities were associated with severe pulmonary hypertension and an increased risk of death. Intravascular hemolysis has also been shown to be associated with reduced availability of nitric oxide and arginine in animal models and in humans with severe falciparum malaria.[94,95] In the study of malaria, impairment of nitric oxide–dependent, flow-mediated vasodilatation developed and was associated with hemolysis and high levels of arginase and lactate dehydrogenase.[95]

THE HYPERCOAGULABLE STATE

Chronic depletion of nitric oxide and arginine may also contribute to the hypercoagulable state in hemolytic diseases. Since nitric oxide is a potent inhibitor of platelet activation, the depletion of nitric oxide and arginine (the substrate for nitric oxide synthesis) in sickle cell disease allows for platelet activation.[96] Arginine consumption is compounded by increased intracellular platelet expression of arginase.[97]

Recent studies of sickle cell disease showed

correlations between the intrinsic rate of hemolysis and the levels of procoagulant factors in blood.[98-100] In addition to the release of free hemoglobin, hemolysis is associated with the formation of red-cell microvesicles containing phosphatidylserine, an activator of tissue factor.[100,101] Patients with sickle cell disease who have functional asplenia and patients with thalassemia who have undergone surgical splenectomy have increased levels of plasma hemoglobin and red-cell microvesicles, which are potential mechanisms for the hypercoagulability associated with both diseases, with possible exacerbation by asplenia.[100]

Additional support for the idea that hemolysis impairs nitric oxide signaling comes from transgenic mouse models of sickle cell disease and spherocytosis and from mouse models of alloimmune hemolysis and malaria.[42,94,102] In these models, there is impaired vasodilatation in response to nitric oxide donors and endothelial-dependent vasodilators, and pulmonary hypertension and right heart failure develop.[42,102]

PULMONARY HYPERTENSION IN SICKLE CELL DISEASE

A major risk factor for pulmonary hypertension in sickle cell disease is the severity of hemolytic anemia, which can be determined by measuring steady-state hemoglobin levels and levels of lactate dehydrogenase, indirect bilirubin, and reticulocytes.[12,19,23,103,104] An association between the development of pulmonary hypertension and the intensity of hemolytic anemia has been observed in three prospective screening studies of adults with sickle cell disease[12,103,104] and in a growing number of pediatric studies.[105-108] Pulmonary hypertension is a reported complication of other forms of chronic hereditary or acquired hemolytic anemia, including thalassemia intermedia and thalassemia major, paroxysmal nocturnal hemoglobinuria, spherocytosis, stomatocytosis, pyruvate kinase deficiency, alloimmune hemolytic anemia, glucose-6-phosphate dehydrogenase deficiency, unstable hemoglobin variants, and the microangiopathic hemolytic anemias.[65,109] Although data from cohort screening studies are available only for sickle cell disease and thalassemia, there are growing numbers of case reports and case series involving pulmonary hypertension in other chronic hereditary and acquired hemolytic anemias.

ECHOCARDIOGRAPHY

Three prospective screening studies using echocardiography have shown that 20% of adults with sickle cell disease have borderline or mild pulmonary hypertension, defined by a pulmonary artery systolic pressure greater than 35 mm Hg; 10% of these adults have moderate to severe pulmonary hypertension, defined by a pressure greater than 45 mm Hg.[12,103,104] Despite pulmonary artery systolic pressures that are much lower than those in idiopathic or hereditary pulmonary hypertension, in sickle cell disease borderline or mild pulmonary hypertension is associated with an extremely high risk of death.[12,103,104,110-112] It remains to be determined whether elevations in pulmonary pressures are a marker for vasculopathy and a risk factor for cardiovascular death or whether the elevations contribute directly to death due to progressive or acute right heart failure. The implications of borderline elevations in pulmonary artery systolic pressure in the pediatric population remain unknown.

Adults with sickle cell disease should be screened for pulmonary hypertension with transthoracic Doppler echocardiography.[12] The thin body habitus of these adults, along with dilated and hyperdynamic heart chambers, allows easy detection of the regurgitation of blood backward across the tricuspid valve during right ventricular systole (Fig. 3). The tricuspid regurgitant jet velocity is used to estimate the right ventricular and pulmonary-artery systolic pressures (which are approximately four times the tricuspid regurgitant jet velocity squared) after the addition of an estimate of the central venous pressure. In sickle cell disease, these estimated pulmonary systolic pressures correlate well with measurements obtained by means of right heart catheterization.[12] A value of 2.5 m per second or more corresponds to an estimated pulmonary-artery systolic pressure of 35 mm Hg, which is approximately 2 SD above the normal mean value; for patients less than 40 years of age, the reference value for the mean pulmonary-artery systolic pressure, estimated with the use of Doppler echocardiography, is 27.5±14.2 mm Hg (95% confidence interval [CI], 19.3 to 35.5).[113] Although a more traditional definition of pulmonary hyper-

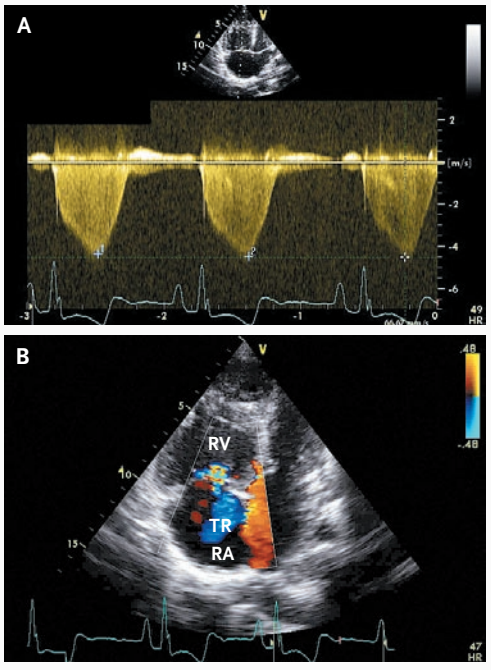

Figure 3. Doppler Echocardiogram Showing Increased Pulmonary-Artery Pressures (High Tricuspid Regurgitant Jet Velocity) and Right Heart Failure in a Patient with Sickle Cell Disease and Pulmonary Hypertension.

A Doppler echocardiographic tracing (Panel A) shows three measured regurgitant-jet-velocity envelopes across the tricuspid valve at values of 4.4, 4.5, and 4.5 m per second, which are consistent with a pressure gradient from ventricles to atria of approximately 80 mm Hg. A value of 2.5 m per second or more constitutes borderline or mild pulmonary-artery systolic hypertension and is a major risk factor for death among patients with sickle cell disease. A four-chamber view of the heart (Panel B) shows right ventricular (RV) and right atrial (RA) dilatation and tricuspid-valve regurgitation (TR) (blue), moving from RV to RA during ventricular systole. A video of this echocardiogram is available with the full text of this article at www.nejm.org. Echocardiogram and image cortesy of Vandana Sachdev, M.D., National Heart, Lung, and Blood Institute.

tension would be a tricuspid regurgitant jet velocity of 3.0 m per second or more, values between 2.5 and 2.9 m per second are associated with an increased risk of death among patients with sickle cell disease.[12,103,104] A follow-up analysis of the National Institutes of Health (NIH) pulmonary-hypertension screening cohort[12] showed that with a tricuspid regurgitant jet velocity of 2.5 to 2.9 m per second, as compared with a velocity of less than 2.5 m per second, the rate ratio for death was 4.4 (95% CI, 1.6 to 12.2; P<0.001), and with a velocity of 3.0 m per second or more, the rate ratio was 10.6 (95% CI, 3.3 to 33.6; P<0.001).

BRAIN NATRIURETIC PEPTIDE

Another screening method entails measurement of plasma levels of the N-terminal fragment of the brain natriuretic peptide, released from cardiomyocytes during pressure or volume stretch.[112] In pulmonary hypertension — both idiopathic and the type associated with sickle cell disease — the level of brain natriuretic peptide correlates with the degree of pulmonary vascular resistance and the risk of death (risk ratio, 5.1; 95% CI, 2.1 to 12.5; P<0.001).[112] Analysis of the levels of N-terminal brain natriuretic peptide at study entry for patients with sickle cell disease who were enrolled in the NIH pulmonary-hypertension screening study and those enrolled in the Multicenter Study of Hydroxyurea in Sickle Cell Anemia revealed that approximately 30% of patients with sickle cell disease in both cohorts had elevated brain natriuretic peptide values (>160 ng per milliliter) and, as compared with patients with lower values, had a significantly increased risk of death (2.87; 95% CI, 1.2 to 6.6; P=0.02).[112]

It is clear that pulmonary pressures rise acutely during vaso-occlusive crisis and even more so in the acute chest syndrome.[114] A recent study of 84 consecutively hospitalized patients with the syndrome showed that 13% of the patients had right heart failure. All five patients who required mechanical ventilation and all four patients who died during the study had jet velocity values of 3 m per second or greater.[115] These data suggest that acute pulmonary hypertension and right heart dysfunction are major coexisting conditions in the acute chest syndrome.

CARDIAC CATHETERIZATION

We suggest that patients with evidence of hemodynamically significant pulmonary hypertension (echocardiographic evidence of right heart dysfunction or a tricuspid regurgitant jet velocity of 3.0 m per second or more) should undergo right heart catheterization to confirm the diagnosis and rule out left heart disease (pulmonary venous hypertension). Right heart catheterization in patients with sickle cell disease and pulmonary hypertension reveals a hyperdynamic state similar to the hemodynamics characteristic of porto

pulmonary hypertension.[64,110] The mean pulmonary-artery pressure in patients with sickle cell disease and pulmonary-artery hypertension is approximately 40 mm Hg, and pulmonary vascular resistance is approximately 250 dyn·sec·cm^{-5}. The relatively low pulmonary vascular resistance is caused by the high cardiac output that is characteristic of anemia. Approximately 60% of catheterized patients with a tricuspid regurgitant jet velocity that is 3.0 m per second or more meet the definition of pulmonary-artery hypertension, indicating that vasculopathy primarily involves the pulmonary arterial system. In the other 40% of patients, the left ventricular end diastolic pressures are greater than 15 mm Hg, indicating a component of left ventricular diastolic dysfunction.[64] Patients with both pulmonary vascular disease and echocardiographic evidence of diastolic dysfunction are at particularly high risk for death (relative risk ratio, 12.0; 95% CI, 3.8 to 38.1; P<0.001).[116]

Table 1. Proposed Mechanisms Leading to Pulmonary Hypertension in Sickle Cell Disease.

Hemolytic anemia
Nitric oxide scavenging through reactions with cell-free plasma hemoglobin
Arginine catabolism to ornithine through reactions with arginase 1, released from red cells
Increased platelet activation by cell-free plasma hemoglobin
Increased levels of endothelin 1
Increased endogenous inhibition of nitric oxide synthase; increased production of methylated arginine and asymmetric dimethylarginine during hemolysis-related protein turnover
High cardiac output resulting from anemia
Hypoxia-inducible factors
Increased expression of hypoxia-inducible factor α mediated by tissue hypoxia
Increased levels of erythropoietin
Increased levels of endothelin 1
Increased levels of vascular endothelial growth factor
Anemia-related inhomogeneous ventilation–perfusion resulting from vascular instability
Perfusion dysregulation, altering ventilation–perfusion matching
Hypoxemia
Systemic factors
Oxidant stress mediated by iron-overload, free iron, and heme
Renal failure
Increased levels of uric acid
Asplenia (autoinfarction or surgical removal), leading to thrombosis as a result of increased circulating plasma hemoglobin and microparticles, thrombocytosis, and increased red-cell phosphatidylserine, which may activate tissue factor

OTHER MECHANISMS OF PULMONARY HYPERTENSION

There are mechanisms other than intravascular hemolysis that contribute to the development of pulmonary hypertension in patients with sickle cell disease, and they should be identified and treated (Table 1). Iron overload, hepatitis C, or nodular hepatic regenerative hyperplasia can cause liver dysfunction, which can lead to portopulmonary hypertension.[12] Chronic renal failure, a common complication of sickle cell disease, is an additional risk factor for the development of pulmonary hypertension.[12,103] In situ thrombosis and pulmonary emboli are often identified clinically and at autopsy.[15] These findings may be risk factors for death, particularly among patients with functional or surgical asplenia.[117] Chronic thromboembolic pulmonary hypertension occurs in approximately 5% of patients with sickle cell disease and severe pulmonary hypertension.[64,118] Although it is widely held that repeated episodes of the acute chest syndrome cause pulmonary hypertension, with resulting chronic lung disease, most retrospective and prospective studies show no association between pulmonary hypertension and rates of the acute chest syndrome.[12,103,104,107,112,119] This finding supports the view that clinical subphenotypes of sickle cell disease arise from divergent mechanisms.

ALTERNATIVE HYPOTHESES

We recognize that alternative hypotheses could explain the clinical phenotypes associated with hemolytic anemia. For example, patients with severe hemolytic anemia also have bone marrow expansion and leukocytosis, suggesting that hemolysis may be associated with inflammation or may merely represent an index of disease severity. It is difficult to divorce the effects of hemolysis from those of anemia and oxidant stress; both can contribute directly to disease pathogenesis, independently of any direct effects of cell-free hemoglobin on vascular function.

CONCLUSIONS

Pulmonary complications — namely, the acute chest syndrome and pulmonary hypertension —

are the leading complications associated with death in adults with sickle cell disease. In patients who die of the acute chest syndrome, abrupt increases in pulmonary pressures and right heart failure are common, indicating a major interaction between these clinical entities. The current treatment of these complications is based on limited evidence or expert opinion, highlighting the critical need for randomized clinical trials in this area. Identification, prevention, and expert management of these complications by hematologists and pulmonologists will be a challenge as the population of patients with sickle cell disease ages and increases worldwide.

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