Cardiovascular Abnormalities in Sickle Cell Disease

Mark T. Gladwin, MD,*† Vandana Sachdev, MD‡

Pittsburgh, Pennsylvania; and Bethesda, Maryland

Sickle cell disease is characterized by recurrent episodes of ischemia-reperfusion injury to multiple vital organ systems and a chronic hemolytic anemia, both contributing to progressive organ dysfunction. The introduction of treatments that induce protective fetal hemoglobin and reduce infectious complications has greatly prolonged survival. However, with increased longevity, cardiovascular complications are increasingly evident, with the notable development of a progressive proliferative systemic vasculopathy, pulmonary hypertension (PH), and left ventricular diastolic dysfunction. Pulmonary hypertension is reported in autopsy studies, and numerous clinical studies have shown that increased pulmonary pressures are an important risk marker for mortality in these patients. In epidemiological studies, the development of PH is associated with intravascular hemolysis, cutaneous ulceration, renal insufficiency, iron overload, and liver dysfunction. Chronic anemia in sickle cell disease results in cardiac chamber dilation and a compensatory increase in left ventricular mass. This is often accompanied by left ventricular diastolic dysfunction that has also been a strong independent predictor of mortality in patients with sickle cell disease. Both PH and diastolic dysfunction are associated with marked abnormalities in exercise capacity in these patients. Sudden death is an increasingly recognized problem, and further cardiac investigations are necessary to recognize and treat high-risk patients.

From the *Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania; †Vascular Medicine Institute, University of Pittsburgh; and the ‡Cardiovascular and Pulmonary Branch, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland. This work was supported in part by the Intramural Research Program of the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services. Dr. Gladwin receives research support from NIH grants RO1HL089032, RO1HL096973, and PO1HL103455, the Institute for Transfusion Medicine and the Hemophilia Center of Western Pennsylvania. Dr. Sachdev has reported that she has no relationships relevant to the contents of this paper to disclose.

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Sickle cell disease (SCD) is an autosomal recessive Mendelian disease affecting approximately 1 of 500 African Americans and 1 of 1,200 Hispanic Americans (1–4). It is estimated that 72,000 Americans have SCD. A single point mutation in the beta globin gene results in a substitution of a glutamic acid residue with a valine at position 6 (beta G6V), with the mutant hemoglobin referred to as hemoglobin S. The hemoglobin functions normally except when deoxygenated. This exposes a hydrophobic area around the valine that produces interactions between beta chains on neighboring hemoglobin tetramers, ultimately resulting in arrangement into a polymer nucleus and then a long polymer bundle. The polymerization process is accelerated by the extent of hemoglobin S deoxygenation and hemoglobin S concentration and modulated by the presence of fetal hemoglobin, which interferes with polymerization. Polymerization of deoxygenated hemoglobin S within the erythrocyte ultimately reduces its flexibility and distorts its shape, reducing membrane fluidity and altering its rheological properties in flowing blood. Both physical entrapment and red blood cell-leukocyte-endothelial adhesive interactions driven by secondary inflammation result in obstruction of the microvasculature (4–8). This produces ischemia-reperfusion injury to vital organs, further amplifying inflammatory and oxidative stress, activation of the innate immune response, and driving infarction of all critical organs, such as the spleen, kidneys, liver, muscle, brain, lung, and bone (3,6,9). Infarction of the bone marrow results in edema and necrosis, producing episodes of severe bone pain that characterize the vaso-occlusive painful crisis. This is the most common complication of SCD, resulting in an average of 2 admissions or emergency room visits/year (10). However, this is only the tip of the proverbial iceberg, because most patients experience daily pain but avoid medical evaluation in the hospital setting (11). In fact, only approximately one-third of patients frequently go to the emergency room for evaluation and therapy (12).

Although in Sub-Saharan Africa babies born to SCD rarely live beyond 2 years of age, in the United States and Europe, patient survival has steadily increased over the last decade (4). This improved longevity is likely related to reduced infectious comorbidities related to sanitation and penicillin prophylaxis, improvements in the quality and availability of red cell transfusions, and use of the fetal hemoglobin-inducing therapy hydroxyurea. In the United States, early mortality from sepsis, severe vaso-occlusive crisis, the acute chest syndrome, and childhood stroke have been significantly reduced with...
transfusion and hydroxyurea therapy (13–17). The CSSCD (Cooperative Study of patients with Sickle Cell Disease), a large pediatric and adult registry study performed before the advent of hydroxyurea or prophylactic transfusions to prevent strokes in children at risk, indicated that women survived to a median age of 48 years and men to 42 years (10); however, it is now apparent that many patients have the potential to live well into the seventh decade. This “good news” is tempered by the appreciation that, as patients survive to adulthood and old age, they are accumulating end-organ injury and failure and a progressive systemic and pulmonary vasculopathy (4,18,19).

The development of this vasculopathy is driven primarily by chronic hemolytic anemia but compounded by other comorbidities such as renal and liver failure, systemic hypertension, diastolic left ventricular (LV) dysfunction, iron overload, and thrombosis (3,15,18,20).

**Pulmonary Hypertension**

**Mechanisms of disease and clinical risk factors.** Pulmonary hypertension (PH) represents one of the major emerging vasculopathic complications of SCD as this patient population ages. Hemolytic anemia has been proposed as an important mechanism leading to pulmonary vasculopathy. As shown in Figure 1, hemoglobin, when decompartmentalized from the red cell, will react with nitric oxide (NO) at the near diffusion limit, to oxidize the NO to nitrate (21,22). This reaction is so fast and irreversible that even levels of cell-free plasma hemoglobin of only 6 to 10 µm are sufficient to inhibit all NO signaling and produce vasoconstriction (23,24). In addition to cell-free hemoglobin, hemolysis releases other red cell enzymes that have the potential to inhibit NO signaling. Arginase 1 is present in abundance in red cells and metabolizes arginine to ornithine, reducing arginine availability for NO synthesis (25). In addition, other independent factors that contribute to the development of PH in this population include surgical splenectomy and functional asplenia, thromboembolism, lung fibrosis and hypoxemia, increases in other vasoactive mediators such as placental growth factor and endothelin (ET)-1, renal insufficiency, and genetic factors (summarized in Fig. 2) (18,26–28).

In SCD, a number of the chronic complications seem to be related to hemolytic anemia, whereas other complications are related to inflammation and vaso-occlusion (classic “sickling” events) (29). Vaso-occlusive pain crisis and the acute chest syndrome are caused by vaso-occlusion by sickled and adhesive red cells and leukocytes; in epidemiological studies the risk of developing these clinical manifestations is related to high steady state hemoglobin levels (less hemolysis and higher viscosity), high white blood cell count (inflammation), and low levels of fetal hemoglobin (which inhibits hemoglobin S polymerization) (10). In contrast, other complications such as endothelial dysfunction, PH,

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**Abbreviations and Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>ET</td>
<td>endothelin</td>
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<tr>
<td>LV</td>
<td>left ventricle/ventricular</td>
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<tr>
<td>mPAP</td>
<td>mean pulmonary artery pressure</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>NT-proBNP</td>
<td>N-terminal pro-B-type natriuretic peptide</td>
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<td>PAH</td>
<td>pulmonary arterial hypertension</td>
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<tr>
<td>PH</td>
<td>pulmonary hypertension</td>
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<tr>
<td>SCD</td>
<td>sickle cell disease</td>
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<tr>
<td>TRV</td>
<td>tricuspid regurgitation velocity</td>
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**Figure 1** Mechanisms of Hemolytic Anemia in Reducing NO Bioavailability and Association With Vasculopathic Sub-Phenotypes of SCD

Hemolysis releases cell-free plasma hemoglobin (Hb) and arginase 1 into plasma, which catabolize nitric oxide (NO) and L-arginine. Activation of vascular oxidases—such as xanthine oxidase (XO), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and uncoupled endothelial nitric oxide synthase (eNOS)—generate superoxide, which scavenges NO. Hemolytic anemia and reduced NO bioavailability are associated with vasculopathic clinical complications in sickle cell disease (SCD) patients. LDH = lactate dehydrogenase; metHb = methemoglobin; NO$_3^-$ = nitrate; O$_2$ = oxygen; ONOO$^-$ = peroxynitrite. Figure modified and reproduced, with permission, from Kato et al. (29).
cutaneous leg ulceration, proteinuria, renal dysfunction, systolic systemic hypertension, risk of death, and possibly stroke might be in part mediated by chronic hemolytic anemia; epidemiological studies show that the risk of developing these complications is related to low steady state hemoglobin with weaker association with rates of painful crisis and acute chest syndrome (18,20,30–32).

Although this hypothesis for subphenotypes has been challenged in editorial forums (33,34), most studies have supported this hypothesis over the last 7 years with animal models, human vascular studies, and large epidemiological cohort studies. From an epidemiological standpoint, in patients with SCD a number of clinical vasculopathic complications are significantly associated with markers of hemolytic anemia, including PH, priapism, leg ulceration, and risk of death (18,30,35,36). Numerous cohort studies have consistently associated the severity of hemolytic anemia with increasing Doppler-estimated pulmonary artery systolic pressure and high risk of death, including the National Institutes of Health (NIH)-PH cohort (18), the Duke cohort (37), the University of North Carolina Chapel Hill cohort (27), the Multi-Centers Study of Hydroxyurea cohort (31), the Pediatric Hypoxic Response (PUSH) cohort (32,38,39), and a recently published Greek study (40). An analysis of banked plasma samples from the CSSCD cohort revealed that an abnormally high N-terminal pro-B-type natriuretic peptide (NT-proBNP) level ≥160 pg/ml, a biomarker for PH in patients with SCD (31), was present in 27.6% of adult SCD patients, and high levels were associated with markers of hemolytic anemia such as a low hemoglobin level (p < 0.001), high lactate dehydrogenase (p < 0.001), and high total bilirubin levels (p < 0.007) (41). An NT-proBNP level ≥160 pg/ml was a major and independent predictor of mortality (relative risk: 6.24, 95% confidence interval [CI]: 2.9 to 13.3, p < 0.0001). The recently published analysis of screening patients in the Walk-PHASST (Walk–Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy) cohort confirms similar strong associations between indexes of hemolytic anemia, high NT-proBNP, low walk distance, and increased Doppler-echocardiographic estimates of pulmonary artery systolic pressures (42). Similar associations between markers of hemolytic anemia, PH, leg ulceration, and risk of death have now been confirmed in 2 PH screening studies on the basis of right heart catheterization (discussed in more detail in the following text) (26,43).

Screening for PH: tricuspid regurgitation velocity and NT-proBNP as risk markers in SCD. Echocardiography is a useful noninvasive screening tool for PH, but diagnosis requires right heart catheterization. With the Bernoulli
equation, the tricuspid regurgitation velocity (TRV) provides a calculated estimate of right ventricular and pulmonary artery systolic pressures (pulmonary artery systolic pressure = approximately 4*TRV²) after adding an estimate of the central venous or right atrial pressure (44). In patients with SCD, echocardiographic estimates have been shown to correlate reasonably well with measured pulmonary artery systolic pressures by right heart catheterization (R = 0.77; p < 0.001) (18).

Three relatively large screening studies have been performed at the NIH (18), Duke University (37), and the University of North Carolina Chapel Hill (27). In all of these studies Doppler-echocardiography was performed on SCD patients in steady state, not during hospital stay with vaso-occlusive pain crisis. A TRV of 2.5 m/s or above was prospectively chosen as a cutoff for high-risk patients, and the percentage of patients with a value ≥3.0 m/s, a more conventional cutoff for PH screening, was also reported. Approximately 30% of patients had a TRV ≥2.5 m/s, and 10% had a value ≥3.0 m/s. In a recently completed large U.S. and U.K. screening study (called the Walk-PHASST screening study) that included 483 patients with homozygous SS disease, 26% of the subjects had a TRV of 2.7 to <3.0 m/s (2.8 ± 0.1) and 11% had a TRV value ≥3.0 m/s (3.4 ± 0.4) (42).

In all epidemiological studies conducted to date, a mild-to-moderate elevation in Doppler-estimated right ventricular systolic pressure (TRV ≥2.5 m/s) was common in adults with SCD and was associated with a 9.24 to 15.9 risk ratio for early death (18,27,37). In multi-center Walk-PHASST cohort, increases in estimated pulmonary artery systolic pressures have been shown to predict high NT-proBNP levels and decreased functional capacity (42,45), and our preliminary analysis of 2-year mortality data indicates a significantly increased risk of death in the patients with elevated TRV values (p < 0.000006).

Although noninvasive estimates of PH require confirmatory right heart catheterization, from a screening standpoint the data suggest that a TRV value <2.5 m/s or an NT-BNP <160 pg/ml are normal screening values and associated with a low risk of death for a patient with SCD (18,27,31,37). In contrast, a TRV ≥3 m/s is 3 SDs above the mean, is present in approximately 10% of SCD adults, and is associated with a risk ratio for death of 10.6 (95% CI: 3.3 to 33.6; p < 0.001) (3). On the basis of these data, for patients with TRV ≥3 m/s, standard of care should include clinical evaluation with right heart catheterization and evaluation for PH risk factors, including LV diastolic and/or systolic dysfunction, kidney and liver disease, iron overload, systemic hypertension, thromboembolism, and nocturnal or exercise hypoxemia.

The intermediate group (TRV value of 2.5 to 2.9 m/s, which is 1 to 2 SDs above the mean) remains a source of controversy. However, in adults with SCD this group overall also seems to have decreased exercise capacity and increased mortality, with a risk ratio for death of 4.4 (95% CI: 1.6 to 12.2; p < 0.001). The label applied to this intermediate risk group of SCD patients with TRV 2.5 to 2.9 m/s does not change its clinical implications for adults with SCD. Refinement of risk definition in this group in future studies will advance the field.

**Diagnosis and characterization of PH with right heart catheterization as the gold standard.** Three new studies have now been published with PH defined by definitive right heart catheterization. The hemodynamic values reported and samples sizes are summarized in Table 1. The NIH screening study, first published with 195 patients in 2004, has now been extended for 9 years of follow-up in 533 patients, with median follow-up of 4.4 years (46). In this study, 86 subjects with suspected PH on the basis of elevated TRV underwent right heart catheterization, and of these, 56 patients (10.5% of the 533 patients evaluated) were diagnosed with PH defined by mean pulmonary artery pressure (mPAP) ≥25 mm Hg, which is the consensus definition of PH. Approximately 50% had pulmonary venous hypertension, and 50% had pulmonary arterial hypertension (PAH), on the basis of a pulmonary artery occlusion pressure above or below 15 mm Hg, respectively.

This study has confirmed the high risk of death even with more moderate elevations of mPAP (median mPAP of 36 mm Hg). During a median follow-up of 4.4 years, mortality rate was significantly higher in the PH group (20 of 56 deaths, 36%) than the general sickle cell group with normal Doppler-echocardiographic estimates of pulmonary pres-

**Table 1: Hemodynamic Values From RHC Studies in SCD**

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>Number of Subjects Screened</th>
<th>Exclusions</th>
<th>TRV ≥2.5 m/s</th>
<th>Number of RHCs</th>
<th>Number of Subjects With PH*</th>
<th>% of RHC With PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehari et al. (46)</td>
<td>533</td>
<td>None</td>
<td>TRV ≥2.5 m/s</td>
<td>86</td>
<td>56</td>
<td>65</td>
</tr>
<tr>
<td>Parent et al. (26)</td>
<td>445</td>
<td>Renal Insufficiency, Restrictive Lung Disease, Liver disease</td>
<td>TRV ≥2.5 m/s</td>
<td>96</td>
<td>24</td>
<td>25</td>
</tr>
<tr>
<td>Fonseca et al. (84)</td>
<td>80</td>
<td>None</td>
<td>TRV ≥2.5 m/s</td>
<td>26</td>
<td>8</td>
<td>31</td>
</tr>
</tbody>
</table>

*Pulmonary hypertension (PH) defined as mean pulmonary artery pressure (mPAP) ≥25 mm Hg; †median (interquartile range); ‡converted mean value: pulmonary vascular resistance (PVR) measured in Woods units as 2.24; §cardiac index (l/min/m²); ‡converted mean value: pulmonary vascular resistance (PVR) measured in Woods units as 2.24.
sures (50 of 477 deaths, 13%, p < 0.0001). In multivariate analysis, most measures of pulmonary vascular disease were associated with risk of death, including systolic pulmonary arterial pressure, pulse pressure, mPAP, transpulmonary gradient, and pulmonary vascular resistance.

Parent et al. (26) also published a large screening study of PH in 398 SCD patients in France. In this study, they performed right heart catheterization in all patients with Doppler-determined TRV ≥2.5 m/s. They found that 25% of patients with a TRV ≥2.5 m/s had a mPAP ≥25 mm Hg diagnosed by right heart catheterization (perhaps not surprising, considering values of 2-SD vs. 3-SD above the normal mean). In patients with a TRV of ≥2.9 m/s or a TRV between 2.5 and 2.8 m/s AND either an NT-proBNP level ≥164.5 pg/ml or a 6-min walk distance of <333 m; the positive predictive value was 62%, and the false negative rate was reduced to 7%. They found, similar to other studies, an association between PH and high prevalence of cutaneous leg ulcers, low exercise capacity, and increased risk of death (12.5% in PH group vs. 0.3% in non-PH group; p = 0.002) and lack of association with vaso-occlusive pain crisis and the acute chest syndrome (26,47).

The Parent et al. (26) study also confirmed risk factors associated with PH from the NIH cohort, including renal insufficiency, markers of hemolysis (lactate dehydrogenase and aspartate aminotransferase released by red cells but not alanine aminotransferase, which is specific for hepatocytes) and markers of cholestatic liver dysfunction (increased alkaline phosphatase and direct bilirubin). These findings support the hypotheses that PH in SCD arises as a consequence of chronic hemolytic anemia and is associated with end-organ dysfunction (renal and liver) but is not a direct consequence of repeated episodes of vaso-occlusion and acute chest syndrome (3,18,26,47).

A number of differences in study design and analysis might have resulted in small differences in prevalence estimates and could also have biased sensitivity and specificity analysis of echocardiography. In terms of prevalence estimates, the Parent study excluded approximately 9% of patients, those with “severe” renal, liver, or lung disease, defined by a creatinine clearance of <30 ml/min, an abnormal prothrombin time (international normalized ratio >1.7), and chronic restrictive lung disease defined by a total lung capacity of <70% of predicted (26). It is not clear why these complications were defined as severe, because hemodialysis was not required in the definition and the threshold of total lung capacity used is classified by the ATS as a moderate reduction. It is also not clear why these patients would be excluded from a prevalence study of SCD-related PAH, especially because all of these complications represent significant published risk factors for SCD-related PH (18,42,48). For example, in the Walk-PHASST screening study (42), 24 of 375 (6.4%) adult hemoglobin SS patients had a creatinine clearance <30 ml/min estimated by the Cockcroft-Gault formula. Of these, 22 (91.7%) had a TRV ≥2.5 m/s, and 13 (54.2%) had a TRV ≥3.0 m/s, indicating the likely high prevalence of PH in these excluded patients.

Although it is clear that the echocardiogram represents a screening test that must be confirmed with right heart catheterization, the estimates of positive predictive value by Parent et al. are greatly influenced by baseline prevalence. The investigators might have biased their results to lower sensitivity, by exclusion of 9% of the population at high risk for PH. However, the use of NT-proBNP and walk distance to increase the positive predictive value of borderline Doppler-echocardiographic findings (TRV 2.5 to 2.9 m/s) represents a significant contribution by these investigators and an approach that can be advocated in clinical evaluations.

A third right heart catheterization screening study by Fonseca et al. (43) in SCD patients screened in Brazil has now been published. This study, with no exclusion criteria applied to screened patients, revealed a 10% prevalence of PH, defined also by mPAP ≥25 mm Hg. This study also confirmed associations with hemolytic anemia, renal insufficiency, exercise intolerance, and high associated mortality. 

Treatment options for PH in SCD. On the basis of the high associated mortality for PH in SCD, it has been recommended that the underlying SCD be aggressively controlled (4). The pulmonary pressures might rise during episodes of vaso-occlusive pain crisis and the acute chest syndrome, and right heart failure might develop at high pulmonary pressures (49,50). If patients are not taking hydroxyurea, this therapy should be started and titrated to a maximally tolerated dose to increase fetal hemoglobin levels.
(recently reviewed) (51,52). For subjects not responding or tolerating hydroxyurea as well as those with more significant PH, a regular simple or exchange transfusion program should be initiated targeting a hemoglobin S level of <20% after transfusions. Patients should be evaluated for iron overload, and chelation therapy should be initiated. Resting, nocturnal, and exercise desaturation should be managed with supplemental oxygen. Patients should be evaluated for thrombo-embolic disease, sleep apnea, human immunodeficiency virus infection, liver disease, renal insufficiency, and other conditions that could contribute to the development or evolution of PH.

In patients with PAH defined by right heart catheterization (mPAP ≥25 mm Hg, pulmonary capillary wedge pressure <15 mm Hg, and an elevated transpulmonary gradient ≥10 to 12 mm Hg), therapy with PAH-specific therapies can be considered. Although PAH represents a common complication in patients with SCD, with a high associated morbidity and mortality, there exist no large randomized placebo-controlled trials to guide therapy decisions. A trial of bosentan, an ET A and B receptor blocker, was stopped early on the basis of a decision by the sponsor, with only approximately 15 sites activated and 27 subjects enrolled. An underpowered analysis of these subjects showed no evident increase in adverse events in subjects receiving therapy and a trend toward an increase in cardiac output but no significant changes in pulmonary pressures (53). In a case series of 17 SCD patients with PH, open label treatment with either bosentan (ET A and B receptor blocker) or ambrisentan (a selective ET A receptor blocker) resulted in lower NT-proBNP levels, lower TRV measurements, and higher 6-min walk distance, suggesting improvement in PH (54). There was also a trend toward improved Borg Dyspnea Score and New York Heart Association functional classification. Because of the lower risk of hepatocellular dysfunction on ambrisentan and because many patients with SCD have comorbid iron overload or liver disease, this drug is likely the best selection as a first-line agent, with simultaneous diuresis to prevent edema and a rise in filling pressures.

Phosphodiesterase 5 inhibitor (PD5) therapy was considered one of the most promising approaches to SCD-associated PH, because these agents seem to be effective in both PAH and pulmonary venous hypertension related to diastolic dysfunction (55,56). A small open label study of sildenafil in patients with SCD who were taking maximal hydroxyurea therapy or transfusions revealed significant reductions in TRV and NT-proBNP and increases in 6-min walk distance (57). However, a large multi center trial of sildenafil was discontinued early on the basis of an unexpected increase in hospital stay for pain (45% of sildenafil, 22% placebo, p = 0.022) (42). Consistent with these observations, the use of PD5s in other PAH patient populations and in large clinical trials of patients with erectile dysfunction has been associated with an increase in the incidence of myalgias and back pain that could have contributed to the increase in the pain reported in the current study (58–60). It is increasingly evident that back pain and myalgias represent a class effect of PD5 inhibitors. Therapy with PD5 inhibitors should only be used, on the basis of the results of the Walk-PHASST sildenafil treatment study, in SCD patients that are extremely well-controlled on hydroxyurea and transfusion therapy and should not be considered a first-line therapy.

LV Dysfunction

LV dilation. Cardiac complications are a common feature of SCD and are felt to be an important cause of the morbidity and mortality associated with this disease. The chronic anemia of SCD results in an increase in cardiac output with only a minimal increase in heart rate. Left ventricular stroke volume increases with significant dilation of the LV (61), and the degree of LV dilation is closely linked to the degree of anemia (62). The dilated LV adapts to the increased wall stress by developing eccentric hypertrophy (63) in which wall thickening is increased and myofibers are elongated. Eccentric hypertrophy allows the LV to adapt to chronic volume overload by initially preserving diastolic compliance and maintaining normal filling pressures.

Increased LV mass and diastolic dysfunction. Over time, progressive dilation leads to increased wall stress and an increase in LV mass. Early studies of SCD found evidence of increasing LV mass with increasing age (62,64) as well as impaired LV filling (65). The presence of increased mass in both children and adults has been confirmed in the majority of imaging studies. Recent studies using standard Doppler parameters and tissue Doppler have shown that diastolic dysfunction is common in children (66–68), and in adults it was found to be an independent risk factor for mortality with a risk ratio of 4.8 (95% CI: 1.9 to 12.1, p < 0.001) (69). Importantly, the combination of diastolic dysfunction measures and PH increases this mortality risk ratio to above 13.

As expected, diastolic abnormalities are associated with older age, increases in blood pressure, increased LV mass, and higher creatinine levels. Although the association of increased LV mass and diastolic dysfunction is clearly linked to systemic hypertension in the general population, it is unclear whether these findings in SCD are due to a combination of compensatory hypertrophy secondary to anemia and LV dilation along with a systemic vasculopathy affecting afterload. Direct myocardial damage from microvascular disease and iron deposition have also been postulated as etiologies for the cardiac abnormalities. Systemic blood pressure in SCD is known to be lower than in control subjects, but the presence of relative systemic hypertension has been linked with renal dysfunction and adverse outcomes (70). In addition, there are significant associations between systolic blood pressure and both increased pulmonary pressures and LV filling pressures (71).
Invasive right heart catheterization measurements of patients with PH (mean PAP ≥25 mm Hg) show evidence of diastolic dysfunction in approximately one-half of the patients (48,72). Screening echocardiography studies show a significant variation in the prevalence of diastolic dysfunction, due to the well-known difficulty in the noninvasive diagnosis of diastolic dysfunction. Although a tissue Doppler-derived E/e’ ratio >15 is accepted as a predictor of high LV filling pressure in the setting of LV dysfunction, the application of this in patients with preserved systolic function has been difficult (73). Kasner et al. (74) studied patients with heart failure and normal ejection fraction and found that an increased E/e’ ratio above 8 was a useful noninvasive predictor of diastolic dysfunction. This ratio has not been prospectively validated in the different hemodynamic circumstances of SCD. Nonetheless, a retrospective review of the NIH cohort patients undergoing echocardiography and cardiac catheterization within 72 h suggested that the E/e’ ratio is useful to predict a pulmonary capillary wedge pressure >15 mm Hg. Receiver-operating characteristic analysis showed that a cutoff value of 8.2 had a sensitivity of 78% and specificity of 71% (positive predictive value 65%, negative predictive value 82%, area under the curve 0.72) for predicting an elevated wedge pressure (Fig. 3) (75). Prospective studies using simultaneous echo and catheterization measurements are needed to further validate this finding in SCD.

LV systolic dysfunction. Although “heart disease” and “heart failure” have traditionally been considered common in adult SCD patients, recent large screening echocardiographic studies indicate that LV systolic function is preserved in the majority of SCD patients studied in a resting state (69,76,77), and the presence of segmental wall motion abnormalities is rare. When LV dysfunction is present, it has been seen particularly in older patients and those with associated conditions such as hypertension and renal disease (78). Most studies have used parameters such as ejection fraction, velocity of circumferential shortening, shortening fraction, and systolic time intervals to assess LV systolic function. It is important to note that none of these parameters are true indexes of contractility, because they are known to be affected by heart rate, preload, and afterload. In an early study using a more load-independent measure, the end-systolic stress volume index, Denenberg et al. (79) showed that there was significant LV contractile dysfunction in SCD patients, compared with control subjects. More recent evaluations using the end-systolic wall stress to velocity of circumferential shortening relationship have shown mixed results in children. Batra et al. (80) found systolic function and contractility to be preserved, whereas Lamers et al. (81) used a slightly different method as well as matched control subjects and found a significant decrease in contractility in SCD patients.

Right Ventricular Dysfunction

Imaging studies of SCD patients at steady state without PH have shown dilated right heart chambers without significant right ventricular dysfunction in most cases (69,76). During acute chest syndrome, pulmonary pressures increase, and in a series of 84 consecutive hospital admissions, cor pulmonale was seen in 13% of patients (50). All of these patients had a TRV ≥3 m/s during the acute event, and they were at particularly high risk for multi-organ failure and sudden death. Our clinical experience suggests that those patients with resting PH and/or evidence of right ventricular dysfunction are the ones most likely to develop acute right heart
failure (Fig. 4). Acute pressure overload on top of a chronic pulmonary vasculopathy is felt to be the reason for acute right ventricular decompensation.

Myocardial Infarction

Myocardial ischemia and infarction have been reported to occur in SCD, but in almost all cases evaluated in the published data and in our practice at the National Institutes of Health, coronary angiography reveals normal coronary arteries (82–86). Case reports of patients presenting with acute crisis have shown ECG abnormalities (87), nuclear perfusion defects (88,89), magnetic resonance imaging abnormalities (84), and troponin elevations (86) suggestive of acute myocardial infarction. These findings have been attributed to acute and chronic microvascular occlusion in the setting of chronic endothelial damage, a pro-coagulant state, and the systemic vasculopathy previously described. Reversal of the cardiac abnormalities has been seen after exchange transfusion and aggressive supportive care for the ischemia (85,90); however, evidence-based guidelines for treatment with antiplatelet agents, anticoagulation, and thrombolytics are lacking.

Functional Capacity

Marked abnormalities in exercise capacity have consistently been seen in SCD patients. In addition to possible cardiac filling abnormalities, suggested mechanisms for this limitation in patients studied with cardiopulmonary testing include the anemia itself, pulmonary vascular disease, peripheral vascular disease, and/or a myopathy (91). The 6-min walk test is a useful measure of functional capacity in this population, and the walk distance correlates directly with peak oxygen consumption and indirectly with the severity of the PH (48). Despite mild increases in pulmonary pressures and pulmonary vascular resistance, studies of SCD patients have shown more severely reduced 6-min walk distances compared with patients with primary PAH (92). In the Walk-PHASST study, the mean ± SD distance walked in 6 min was 458 ± 91 m, 438 ± 98 m, and 409 ± 96 m in patients with TRV values of <2.7 m/s, 2.7 to <3.0 m/s, and ≥3.0 m/s, respectively (p = 0.001) (42). In this study, a reduction in the 6-min walk distance was independently associated with echocardiographic measures of PH (the TRV value) and with measures of diastolic dysfunction, suggesting 2 major independent determinants of cardiac dysfunction with exercise (71). Although limitations in the 6-min walk distance are known to predict morbidity and mortality in heart failure, severe lung disease, and PAH (93), long-term mortality analysis from SCD cohorts is not yet available.

Cardiac Iron Overload

Myocardial iron deposition has been considered as one etiology for the cardiac abnormalities seen in SCD. Although autopsy studies have documented myocardial iron deposition (94), magnetic resonance imaging studies using T2* measurements suggest that this finding is rare even in the presence of a significant transfusion history, systemic iron overload, and/or hepatic iron overload (95,96). The rate of transfusional iron overload in the liver is lower for sickle cell patients than for myelodysplastic syndromes or thalassemia major (97), perhaps due to the intermittent nature of the transfusions or the systemic inflammatory state that limits cellular iron accumulation. In SCD patients, ferritin levels have been found to be a univariate predictor of mortality (31). Myocardial T2* measurements are associated with LV dysfunction and cardiac arrhythmias in thalassemia (98), but this relationship has not been established in SCD, suggesting that other etiologies for myocardial dysfunction might be more prevalent.

Dysrhythmia

Electrocardiographic abnormalities, including QT prolongation, are not uncommon in SCD patients at rest (99). Liem et al. (100) reported a 38% prevalence of QT prolongation in children and young adults, but they did not find a correlation between the QT measurement and LV hypertrophy in their series. Maisel et al. (87) studied 30 SCD patients with 24-h electrocardiographic monitoring during acute crisis and found significant arrhythmias in 80% of the patients, with over one-half the patients having ventricular arrhythmias. A subgroup of these patients underwent gated nuclear studies, and there was a trend toward more arrhythmias in patients with ventricular dysfunction. Further evaluation of electrocardiographic findings and arrhythmias is needed to identify SCD patients at higher risk for sudden cardiac death.

Sudden Death

Sudden death is an increasingly recognized and reported mechanism of death in the aging SCD population (3,18,49,94,101–104). This occurs in the setting of hospital stay with sepsis or multi-organ failure, during recovery from a routine vaso-occlusive event, or at home. Although this was historically ascribed to narcotic “overdose,” it is now clear that this is a direct complication of pulmonary vascular and cardiac disease.

In a large autopsy series of 306 SCD patients, Manci et al. (102) found that death was sudden and unexpected in 40% of patients and was usually associated with acute events. Although clinical examination of these patients had reported underlying chronic organ injury in 25% of patients, they found pathologic evidence of chronic organ injury in 75% of patients, suggesting that the severity of the underlying disease was often underestimated by clinicians. More recent autopsy series (19,94) have shown that cardiopulmonary causes account for the majority of deaths, with sudden death/pulseless electrical activity, heart failure/myocardial
infarction, and pulmonary thromboembolism/PH being the most common findings at the time of death.

Conclusions

Despite a significant increase in longevity for SCD patients over the last several decades, the mortality rate from cardiovascular and pulmonary complications remains high. Multiple pathologic and clinical studies have shown that patients with PH and diastolic LV dysfunction represent a particularly high-risk subgroup. These cardiopulmonary complications contribute to a markedly low functional capacity and associated high risk of both sudden death and complications.

Reprint requests and correspondence: Dr. Mark T. Gladwin, Pulmonary, Allergy and Critical Care Medicine, University of Pittsburgh, 3459 Fifth Avenue, NW 628 Montefiore Hospital, Pittsburgh, Pennsylvania 15213. E-mail: gladwinmt@upmc.edu.

REFERENCES


Key Words: cell ● disease ● sickle.

APPENDIX

For the supplemental video, please see the online version of this article.