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## Cardiovascular Abnormalities in Sickle Cell Disease

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### Abstract

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 leg 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 which has also been a strong independent predictor of mortality 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.

### Keywords

Sickle; Cell; Disease

### Background

Sickle cell disease is an autosomal recessive Mendelian disease affecting approximately 1/500 African Americans and 1/1200 Hispanic Americans.(1–4) It is estimated that 72,000 Americans have sickle cell disease. A single point mutation in the beta globin gene results in a substitution of a glutamic acid residue with a valine at position six (beta G6V), with the mutant hemoglobin referred to as hemoglobin S. The hemoglobin functions normally except

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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 sickle cell disease, resulting in an average of 2 admissions or emergency room visits a year.(10) However, this is only the tip of the proverbial ice-berg, as most patients experience daily pain but avoid medical evaluation in the hospital setting.(11) In fact, only about a third of patients frequently go to the emergency room for evaluation and therapy.(12)

While in Sub-Saharan Africa babies born to sickle cell disease rarely live beyond two years of age, in the U.S. and Europe patient survival has steadily increased over the last decade.(4) This improved longevity is likely related to reduced infectious co-morbidities 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 U.S. 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 Cooperative Study of patients with Sickle Cell Disease (CSSCD), 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 and men to 42,(10) however it is now apparent that many patients have the potential to live well into the 7<sup>th</sup> 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 dysfunction, iron overload, and thrombosis.(3,15,18,20)

## **Pulmonary Hypertension**

### **Mechanisms of disease and clinical risk factors**

Pulmonary hypertension 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 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 6–10 microM 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, thrombo-embolism, lung fibrosis and hypoxemia, increases in other vasoactive mediators such as placental growth factor and endothelin-1, renal insufficiency and genetic factors (summarized in Figure 2).(18,26–28)

In SCD, a number of the chronic complications appear to be related to hemolytic anemia while 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 are 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, pulmonary hypertension, cutaneous leg ulceration, proteinuria, renal dysfunction, systolic systemic hypertension, risk of death and possibly stroke may 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)

While this hypothesis for subphenotypes has been challenged in editorial forums,(33,34) most studies have supported this hypothesis over the last 7 years using 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 NIH-PH cohort,(18) the Duke cohort,(37) the UNC cohort,(27) the Muti-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 classic cooperative study of sickle cell disease (CSSCD) cohort revealed that an abnormally high NT-proBNP level 160 pg/ml, a biomarker for pulmonary hypertension in patients with sickle cell disease(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 (RR 6.24, 95% CI 2.9–13.3,  $P < 0.0001$ ). The recently published analysis of screening patients in the Walk-PHASST cohort confirms similar strong associations between indices 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, pulmonary hypertension, leg ulceration and risk of death have now been confirmed in two PH screening studies based on right heart catheterization (discussed in more detail below).(26,43)

### Screening for PH: TRV and NT-proBNP as risk markers in SCD

Echocardiography is a useful non-invasive screening tool for PH, but diagnosis requires right heart catheterization. Using the Bernoulli equation, the tricuspid regurgitation velocity (TRV) provides a calculated estimate of right ventricular and pulmonary artery systolic pressures ( $PASP \approx 4 * TRV^2$ ) 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 National Institutes of Health (NIH),(18) Duke University, (37) and the University of North Carolina Chapel Hill (UNC).(27) In all of these studies Doppler-echocardiography was performed on sickle cell disease patients in steady state, not during hospitalization with vaso-occlusive pain crisis. A tricuspid regurgitation velocity (TRV) of 2.5 m/s or above was prospectively chosen as a cut-off for high risk patients, and the percentage of patients with a value  $\geq 3.0$  m/s, a more conventional cut-off for PH screening, was also reported. Approximately 30% of patients had a TRV  $\geq 2.5$  m/s and 10% had a value  $\geq 3.0$  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 (mean  $\pm$  SD  $2.8\pm 0.1$ ) and 11% had a TRV value  $\geq 3.0$  m/s ( $3.4\pm 0.4$ ).(42)

In all epidemiological studies conducted to date, a mild-to-moderate elevation in Doppler-estimated right ventricular systolic pressure (TRV  $\geq 2.5$  m/s) was common in adults with SCD and was associated with a 9.24–15.9 risk ratio for early death.(18,27,37) In the 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 ( $P<0.000006$ ).

While non-invasive estimates of PH require confirmatory right heart catheterization, from a screening standpoint the data suggest that a TRV value less than 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  $\geq 3$  m/s is three standard deviations 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) Based on these data, for patients with TRV  $\geq 3$  m/s, standard of care should include clinical evaluation with right heart catheterization and evaluation for PH risk factors, including left ventricular 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 2.5–2.9 m/s, which is 1–2 SDs above the mean) remains a source of controversy. However, in adults with SCD this group overall also appears 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 2.5–2.9 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 using right heart catheterization as 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 based on elevated TRV underwent right heart catheterization and of these, fifty-six patients (10.5% of the 533 patients evaluated) were diagnosed with PH defined by mean pulmonary artery pressure (mPAP)  $\geq 25$  mm Hg, which is the consensus definition of PH. Approximately 50% had pulmonary venous hypertension (PVH) and 50% pulmonary arterial hypertension (PAH), based on 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 (20/56 deaths, 36%) than the general sickle cell group with normal Doppler-

echocardiographic estimates of pulmonary pressures (50/477 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, mean pulmonary artery pressure, transpulmonary gradient, and pulmonary vascular resistance.

Parent and colleagues also published a large screening study of pulmonary hypertension in 398 sickle cell disease patients in France.(26) In this study, they performed right heart catheterization in all patients with Doppler-determined TRV  $\geq 2.5$  m/s. They found that 25% of patients with a TRV  $\geq 2.5$  m/s had a mPAP  $\geq 25$  mm Hg diagnosed by right heart catheterization (perhaps not surprising considering values of 2-SD versus 3-SD above the normal mean). In patients with a TRV of  $\geq 2.9$  meters/sec or a TRV between 2.5 and 2.8 meters/sec per AND either an NT-proBNP level  $\geq 164.5$  pg/ml or a 6-minute walk distance of  $< 333$  meters, the positive predictive value was 62%, and the false negative rate was reduced to 7%. Similar to other studies, they found an association between PH and high prevalence of cutaneous leg ulcers, low exercise capacity, and increased risk of death (12.5% in PH group versus 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 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 may 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 less than 30 ml/min, an abnormal prothrombin time (international normalized ratio greater than 1.7), and chronic restrictive lung disease defined by a total lung capacity (TLC) of less than 70 percent of predicted.(26) It is not clear why these complications were defined as severe, as hemodialysis was not required in the definition and the threshold of TLC 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 considering the fact that 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 Hb SS patients had a creatinine clearance  $<30$  ml/min estimated by the Cockcroft-Gault formula. Of these, 22 (91.7%) had a TRV  $\geq 2.5$  meters/sec and 13 (54.2%) had a TRV  $\geq 3.0$  meters/sec, indicating the likely high prevalence of PH in these excluded patients.

While it is clear that the echocardiogram represents a screening test that must be confirmed using right heart catheterization, the estimates of positive predictive value by Parent and colleagues are greatly influenced by baseline prevalence. By exclusion of 9% of the population at high risk for PH the investigators may have biased their results to lower sensitivity. However, the use of NT-BNP and walk distance to increase the positive predictive value of borderline Doppler-echocardiographic findings (TRV 2.5–2.9 meters/sec) 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 and colleagues 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  $\geq$  25 mm Hg.(43) This study also confirmed associations with hemolytic anemia, renal insufficiency, exercise intolerance and high associated mortality.

### Treatment options for PH in SCD

Based on the high associated mortality for PH in SCD, it has been recommended that the underlying sickle cell disease be aggressively controlled.(4) The pulmonary pressures may rise during episodes of vaso-occlusive pain crisis and the acute chest syndrome, and right heart failure may develop at high pulmonary pressures.(49,50) If patients are not on 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 pulmonary hypertension, a regular simple or exchange transfusion program should be initiated targeting a hemoglobin S level of less than 20% after transfusions. Patients should be evaluated for iron overload and chelation therapy initiated. Resting, nocturnal and exercise desaturation should be managed with supplemental oxygen. Patients should be evaluated for thrombo-embolic disease, sleep apnea, HIV 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  $\geq$  25 mm Hg, PCWP  $<$  15 mm Hg and an elevated transpulmonary gradient  $\geq$  10–12 mm Hg) therapy with PAH specific therapies can be considered. While PAH represents a common complication in patients with sickle cell disease, with a high associated morbidity and mortality, there exist no large randomized placebo-controlled trials to guide therapy decisions. A trial of bosentan, an endothelin A and B receptor blocker, was stopped early based on 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 on therapy and a trend towards 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 six-minute walk distance, suggesting improvement in pulmonary hypertension.(54) There was also a trend towards improved Borg Dyspnea Score and NYHA classification. Based on the lower risk of hepatocellular dysfunction on ambrisentan, and the fact that many patients with SCD have co-morbid 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, as these agents appear to be effective in both PAH and PVH related to diastolic dysfunction.(55,56) A small open label study of sildenafil in patients with SCD that were on maximal hydroxyurea therapy or transfusions revealed significant reductions in TRV and NT-proBNP and increases in six minute walk distance.(57) However, a large multi-center trial of sildenafil was discontinued early based on an unexpected increase in hospitalization for pain (45 % of sildenafil, 22% placebo,  $p=0.022$ ). (42) Consistent with these observations, the use of phosphodiesterase 5 inhibitors in other PAH patient populations, and in large clinical trials of patients with erectile dysfunction, have 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. Based on the results of the Walk-PHASST sildenafil treatment study, therapy with PD5

inhibitors should only be used in SCD patients that are extremely well-controlled on hydroxyurea and transfusion therapy, and should not be considered a first-line therapy.

## Left Ventricular 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 sickle cell disease 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 left ventricle (61) and the degree of LV dilation is closely linked to the degree of anemia (62). The dilated left ventricle 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 left ventricle 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 dilatation leads to increased wall stress and an increase in LV mass. Early studies of sickle cell disease 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 pulmonary hypertension 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. While 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 sickle cell disease 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 controls, 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 left ventricular filling pressures (71)

Invasive right heart catheterization measurements of patients with pulmonary hypertension (mean PAP greater than or equal to 25mmHg) show evidence of diastolic dysfunction in approximately 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 non-invasive 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 non-invasive predictor of diastolic dysfunction. This ratio has not been prospectively validated in the different hemodynamic circumstances of sickle cell disease. Nonetheless, a retrospective review of the NIH cohort patients undergoing echocardiography and cardiac catheterization within 72 hours suggested that the  $E/e'$  ratio is useful to predict a pulmonary capillary wedge pressure  $> 15$ mmHg. ROC analysis showed that a cut-off value of 8.2 had a sensitivity of

78%, specificity of 71% (PPV 65%, NPV 82%, area under the curve 0.72) for predicting an elevated wedge pressure (Figure 3)(75). Prospective studies using simultaneous echo and catheterization measurements are needed to further validate this finding in SCD.

### **LV Systolic Dysfunction**

While “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 indices of contractility since 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 controls. 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, while Lamers et al (81) used a slightly different method as well as matched controls and found a significant decrease in contractility in SCD patients.

### **Right ventricular dysfunction**

Imaging studies of SCD patients at steady state without pulmonary hypertension have shown dilated right heart chambers without significant RV 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  $\geq 3$ 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 pulmonary hypertension and/or evidence of RV dysfunction are the ones most likely to develop acute right heart failure (Figure 4). Acute pressure overload on top of a chronic pulmonary vasculopathy is felt to be the reason for acute RV decompensation.

### **Myocardial Infarction**

Myocardial ischemia and infarction have been reported to occur in SCD, but in almost all cases evaluated in the literature 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), MRI 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 procoagulant state, and the systemic vasculopathy described above. 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-minute 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 pulmonary hypertension.(48) Despite mild increases in pulmonary pressures and pulmonary vascular resistance, studies of SCD patients have shown more severely reduced 6-minute walk distances compared with patients with primary PAH (92). In the Walk-Phasst study, the mean  $\pm$  SD distance walked in 6-minutes was 458 $\pm$ 91 m, 438 $\pm$ 98 m and 409 $\pm$ 96 m in patients with TRV values of <2.7 meters/sec, 2.7 to <3.0 meters/sec and 3.0 meters/sec, respectively (P=0.001)(42). In this study, a reduction in 6-minute walk distance was independently associated with echocardiographic measures of PH (the TRV value) and with measures of diastolic dysfunction, suggesting two major independent determinants of cardiac dysfunction with exercise (71). Although limitations in 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), MRI 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 may 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 left ventricular hypertrophy in their series. Maisel et al (87) studied 30 SCD patients with 24-hour electrocardiographic monitoring during acute crisis and found significant arrhythmias in 80% of patients with over half the patients having ventricular arrhythmias. A subgroup of these patients underwent gated nuclear studies and there was a trend towards more arrhythmias in patients with ventricular dysfunction. Further evaluation of electrocardiographic findings and arrhythmias is needed in order 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 sickle cell disease population.(3,18,49,94,101–104) This occurs in the setting of hospitalization with sepsis or multi-organ failure, during recovery from a routine vaso-occlusive event, or at home. While 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, Mancini et al (102) found that death was sudden and unexpected in 40% of patients and was usually associated with acute events. While 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/pulmonary hypertension 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 pulmonary hypertension and diastolic left ventricular 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 severe multi-organ dysfunction.

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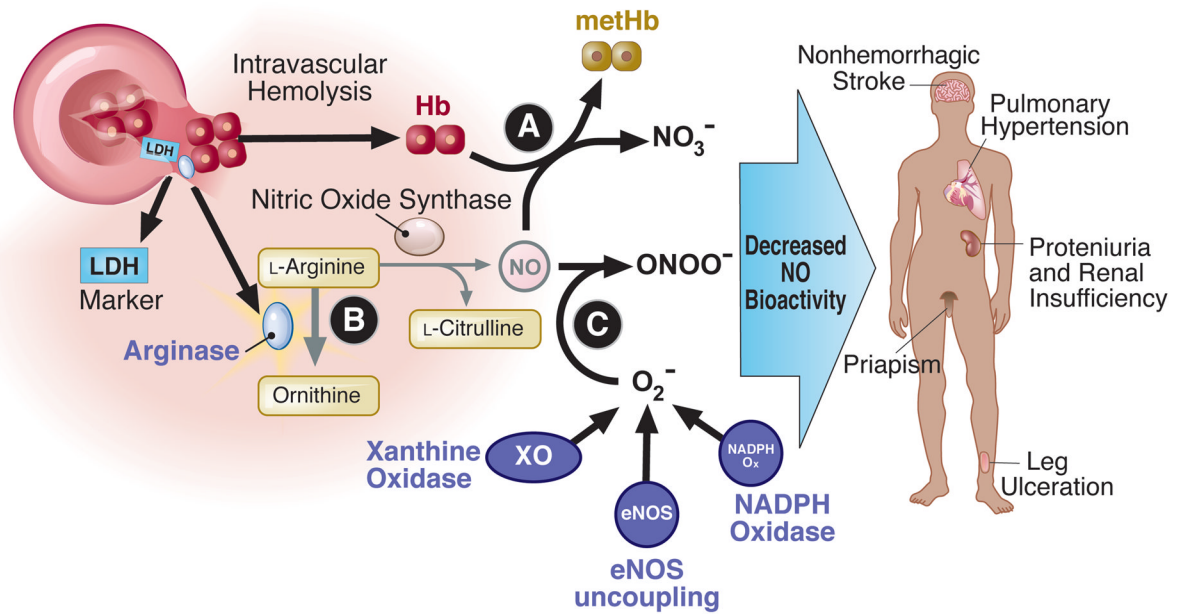
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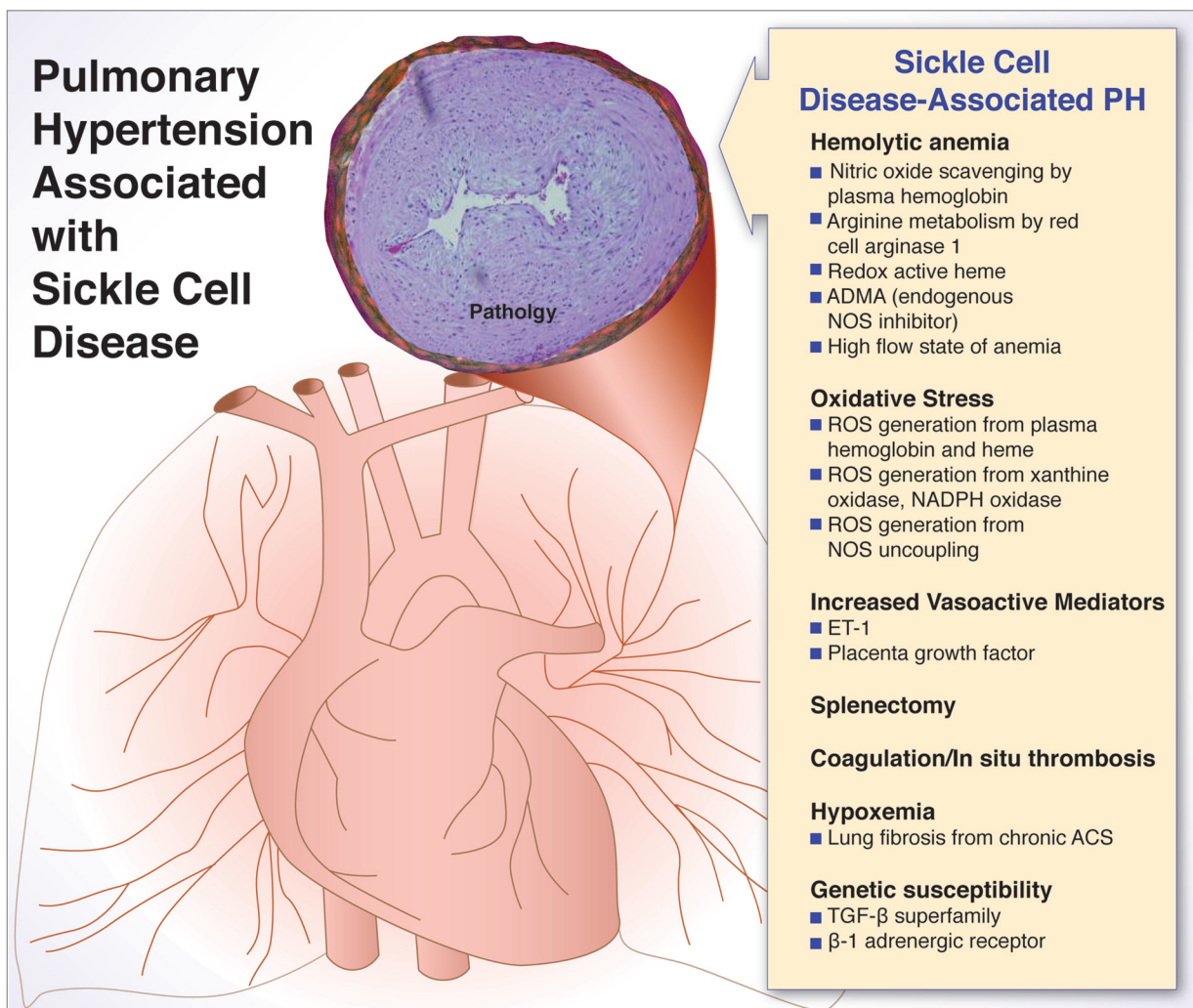
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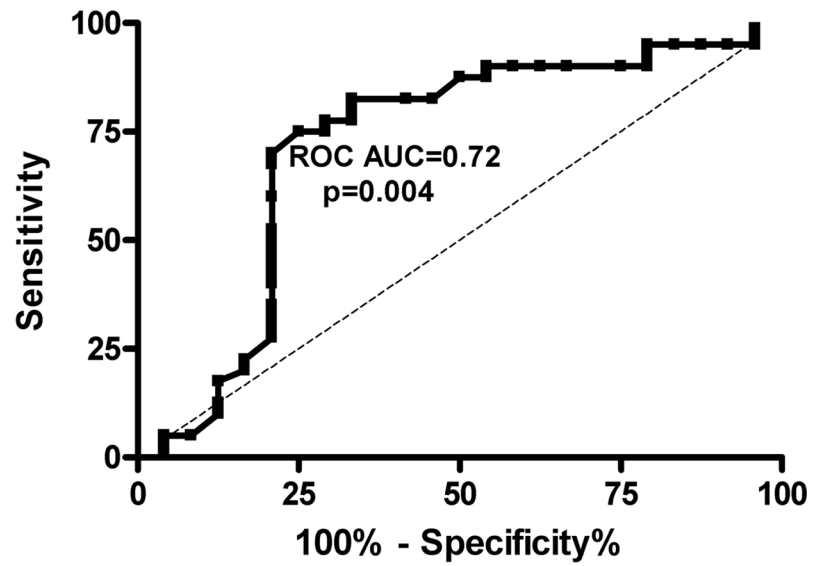
**Figure 1. Mechanisms of hemolytic anemia in reducing NO bioavailability and association with vasculopathic sub-phenotypes of sickle cell disease**

Hemolysis releases cell-free plasma hemoglobin and arginase 1 into plasma, which catabolize NO and L-arginine. Activation of vascular oxidases, such as xanthine oxidase, NADPH oxidase and uncoupled eNOS, generate superoxide which scavenges NO. Hemolytic anemia and reduced NO bioavailability are associated with vasculopathic clinical complications in SCD patients.



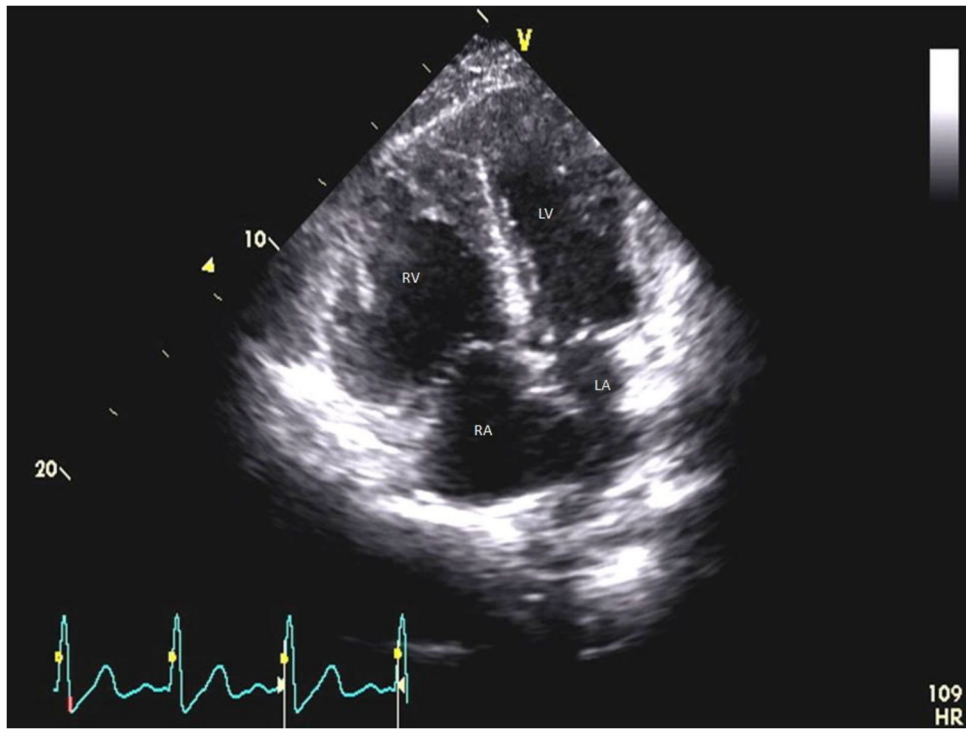
**Figure 2. Mechanisms of pulmonary hypertension in SCD patients**

A pulmonary vessel with severe intimal and smooth muscle proliferation is shown from a 35 year old patient with SCD who died suddenly with known PAH. Mechanisms that contribute to the development of PH identified in animal and human studies are summarized.



**Figure 3. Sensitivity and specificity analysis of diastolic dysfunction measures in SCD patients**  
Receiver operating characteristic curve for tissue Doppler lateral  $E/e'$  ratio to predict a pulmonary capillary wedge pressure  $>15$ mmHg by cardiac catheterization within 72 hours in SCD patients.





**Figure 4.** This echocardiographic image (apical 4-chamber view) from a SCD patient admitted with acute chest syndrome shows a dilated, dysfunctional right ventricle. A movie image of this patient's echocardiogram is available on-line.

Table 1

Summary of SCD Right Heart Catheterization Studies  
Hemodynamic values from right heart catheterization studies in SCD.

First Author (Ref.#)	Number of Subjects Screened	Exclusions	Criteria for RHC	Number of RHCs	Number of Subjects with PH <sup>#</sup>	% of RHC with PH	% of Screened Subjects with PH	Mean Age of PH Subjects	mPAP (mmHg)	PVR (dyne · sec/cm <sup>5</sup> )	CO (Liters/min)	6MWD (m)	Duration of Follow-up (yrs)	Mortality in PH group
Mehari et al.(100)	533	none	TRV < 2.8m/s 6MWD < 500m unexplained dyspnea or desaturation	86	56	65	11	41	36 ± 9	229 ± 149	8 ± 3	358 ± 113	4.4	36%
Parent et al. (85)	445	renal insufficiency restrictive lung disease liver disease	TRV < 2.5m/s	96	24	25	5	45	30 ± 6	138 ± 58	9 ± 2	404 ± 94	2.2	13%
Fonseca et al (84)	80	none	TRV < 2.5m/s	26	8	31	10	46	33 ± 9	179 ± 120 <sup>§</sup>	5 ± 2 <sup>£</sup>	460 ± 152	2.8 <sup>¤</sup>	38%

\* Pulmonary hypertension defined as mean PAP > 25mmHg

<sup>#</sup> Median (interquartile range)

<sup>§</sup> converted mean value: PVR measured in Woods units as 2.24 ± 1.5

<sup>£</sup> Cardiac index (L/min/m<sup>2</sup>)

<sup>¤</sup> Estimated from figure in epub