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REVIEW ARTICLE

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Diagnosis and management of chronic thromboembolic pulmonary hypertension (CTEPH) in sickle cell disease: A review

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Abstract

Pulmonary hypertension in sickle cell disease (SCD) is a complex phenomenon resulting from multiple overlapping etiologies, including pulmonary vasoconstriction in the setting of chronic hemolytic anemia, diastolic dysfunction, and chronic thromboembolic disease. The presence of pulmonary hypertension of any cause in SCD confers a significant increase in mortality risk. Evidence to guide the management of patients with sickle cell disease and chronic thromboembolic pulmonary hypertension (CTEPH) is scant and largely the realm of case reports and small case series. Centered on a discussion of a complex young patient with hemoglobin hemoglobin SC who ultimately underwent treatment with pulmonary thromboendarterectomy, we review the available literature to guide management and discuss and overview of treatment of CTEPH in SCD, considering the unique considerations and challenges facing patients suffering from this multisystem disease.

KEYWORDS
balloon pulmonary angioplasty, hemolytic anemia, pulmonary thromboendarterectomy

INTRODUCTION

Pulmonary hypertension (PH) is a known complication of sickle cell disease (SCD), with a prevalence of 6%–10% in adults, and is associated with significant morbidity and mortality.[1–3] The release of free hemoglobin into the plasma during hemolysis results in endothelial dysfunction, inflammation, proliferative vasculopathy, and hypercoagulability.[4] In addition, SCD is associated with an increased risk of thromboembolic disease, specifically

pulmonary embolism, resulting in an increased risk of chronic thromboembolic pulmonary hypertension (CTEPH). While the cumulative incidence of venous thromboembolism (VTE) in SCD is reported to be 7.4% by age 30% and 11.3% by age 40, the incidence of PE is twofold higher than isolated DVT.[5] Pulmonary thromboendarterectomy (PTE) is a well-established curative treatment for operable CTEPH. However, due to increased operative risk in this patient population with prolonged cardiopulmonary bypass (CPB), there are relatively few reported cases of PTE in SCD-associated CTEPH. Herein, we report a case of a patient with hemoglobin SC disease and CTEPH who underwent a successful PTE and discuss the available evidence to guide the management of CTEPH in patients with SCD.

CASE EXAMPLE

Our case is a 30-year-old female with hemoglobin SC disease complicated by recurrent episodes of vaso-occlusive crisis and pulmonary embolism (PE). She was initially diagnosed with PE 18 months before admission to our hospital, when she presented to an outside hospital with chest pain and underwent ventilation-perfusion lung scintigraphy (V/Q) showing multiple perfusion defects in the right lobe (Figure 1). No acute deep venous thrombosis (DVT) was identified on lower extremity Doppler imaging. Computed tomography pulmonary angiography (CTPA) revealed bilateral lower lobe subsegmental pulmonary emboli (Figure 2). She was discharged on apixaban. Fifteen months later, she was admitted for progressive dyspnea and lower extremity edema. Transthoracic echocardiogram (TTE, Figure 3) showed preserved left ventricular function but severe right ventricular dilation and an estimated right ventricular systolic pressure (RVSP) of 87 mmHg for which she was treated with intravenous loop diuretics.

Shortly after, she was admitted to a local hospital for chest and lower extremity pain and dyspnea, underwent red blood cell exchange, and was transferred to a tertiary care center for management of acute decompensated right heart failure. TTE showed a severely dilated RV with moderately reduced systolic function, severe tricuspid regurgitation (TR) with an estimated RVSP of 97 mmHg, and a new moderate pericardial effusion without evidence of RV diastolic collapse. Right heart catheterization (RHC) revealed severe precapillary PH, with pulmonary artery

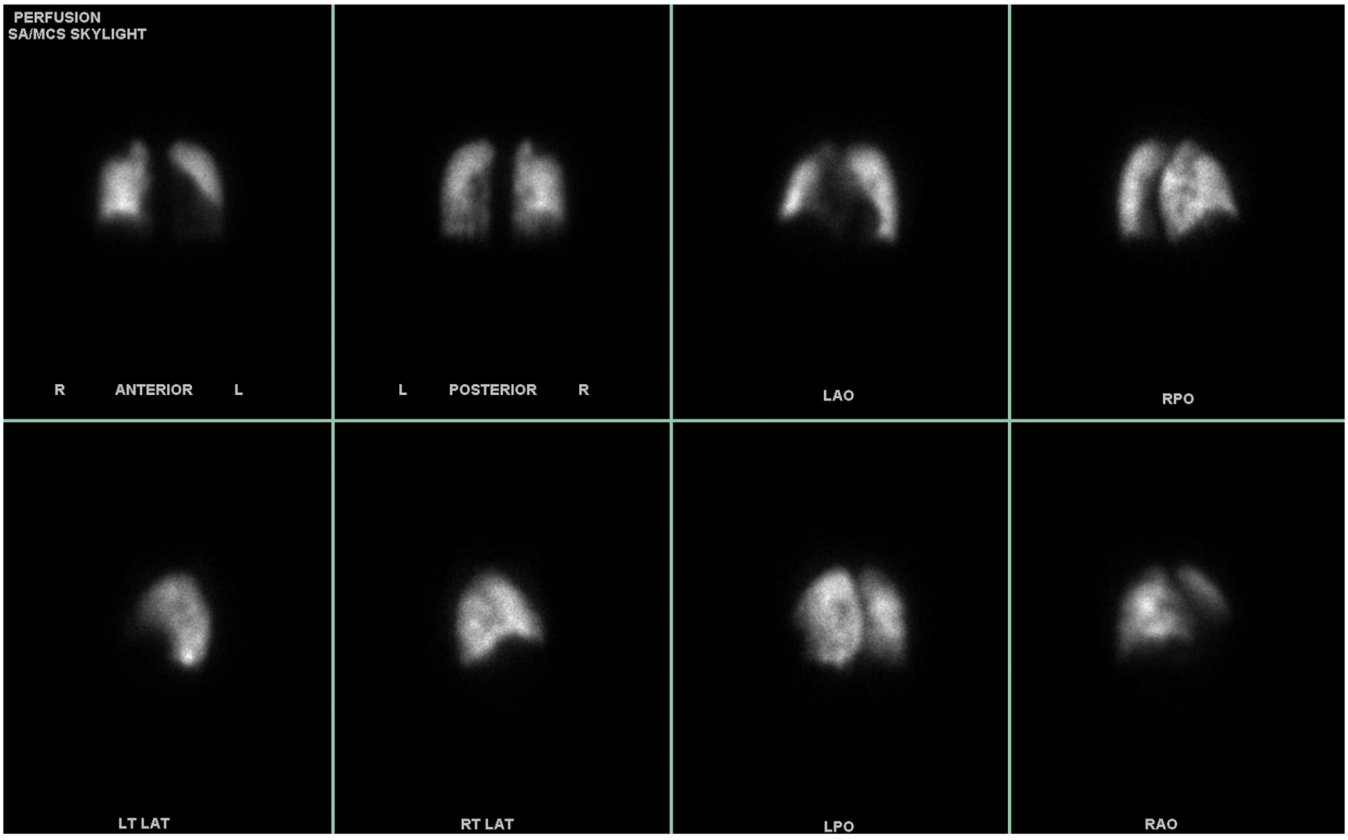

FIGURE 1 Nuclear perfusion scan of the lungs performed before pulmonary thromboendarterectomy surgery. Note subtle perfusion defects, particularly in the right lower lobe.

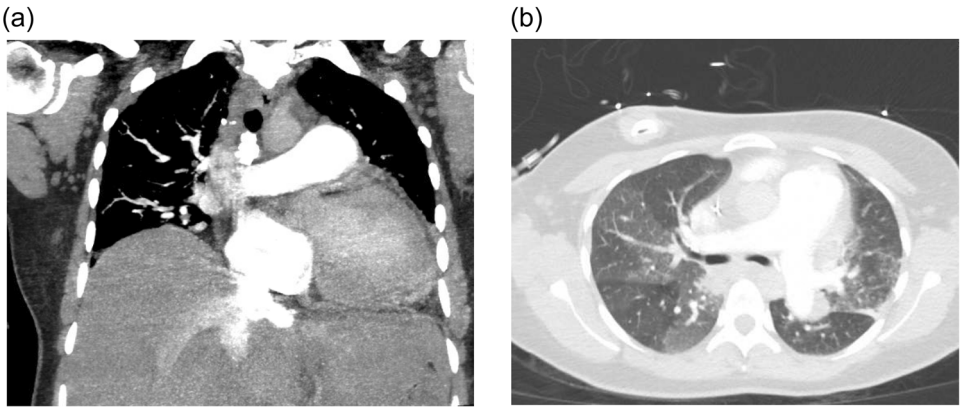

FIGURE 2 Representative images of computed tomography angiography of the chest. (a) Right middle and right lower perfusion defect in coronal view; reflux of contrast into the hepatic circulation is also apparent. (b) Bilateral mosaic attenuations and enlargement of the pulmonary trunk.

pressures of 53/30 (mean 40), pulmonary capillary wedge pressure of 6, pulmonary vascular resistance (PVR) of 8.5 Wood units (WU), and thermodilution cardiac index of 1.82 L/min/m^2. She was treated with intravenous diuresis and inotropic support for cardiogenic shock; intravenous treprostinil and riociguat were started as procedural options were considered. Once stable, she was referred to a high-volume PTE center due to suspicion for CTEPH, where invasive pulmonary angiography revealed occlusion of several proximal segmental vessels of the right upper and lower lobes and left lower lobe (Figure 4). She received an exchange transfusion before surgery and underwent a successful PTE with tricuspid valve repair (Figure 5). Hemodynamics about 3 months after PTE were improved, with PA pressures of 40/20 mmHg (mean 30), PCWP of 12 mmHg, PVR of 3 WU, and Fick cardiac index of 3.1 L/min/m^2.

OVERVIEW OF PH ETIOLOGIES IN SCD

SCD encompasses a number of autosomal recessive genetic disorders marked by a single-point substitution mutation in the β-globin gene. The two most common genotypes of SCD are the homozygous form HbSS (sickle cell anemia) and the double heterozygous HbSC (hemoglobin SC disease). In HbS, a single point mutation in the sixth codon of the β-globin gene leads to the replacement of glutamic acid by valine, while in HbC the mutation results in a substitution of glutamic acid for lysine. In HbC, there is an increase in the potassium-chloride cotransporter activity resulting in red blood cell dehydration and increased viscosity. While HbSS and HbSC share common features of hemolysis, painful vaso-occlusive crisis (VOC), acute coronary syndrome, and multiorgan failure, there are significant differences in the degree of anemia, hemolysis, and coagulopathy. HbSS is associated with more profound anemia and complications of hemolysis, whereas HbSC is characterized by less hemolysis and milder anemia but is associated with more coagulopathy. In an autopsy study of 44 patients with HbSC, PE was reported as the second most common cause of death.[6] HbSC patients also have more frequent proliferative retinopathy compared to HbSS due to increased blood viscosity. Both HbSS and HbSC are associated with PH. In our clinical experience, patients with HbSC who present with severe PH are usually found to have CTEPH as the underlying cause.

The mechanism of PH in SCD is multifactorial and can result from sequelae of chronic hemolysis, thromboembolic disease, and left heart disease/heart failure with preserved ejection fraction (HFpEF), the latter induced by left ventricular dilation and diastolic dysfunction from chronic anemia. Therefore, PH in SCD can be precapillary, postcapillary, or combined pre- and postcapillary (CpcPH). Due to the complex nature of its pathobiology, PH in SCD is categorized within Group V in the World Health Organization's classification system for PH.[7] Studies of hemodynamic assessment of PH in SCD have suggested the prevalence of PH on right heart catheterization to be 6%, with one study showing a nearly even split between pre- and post-capillary disease.[1,8] Differentiating PH phenotypes in SCD allows for targeting the underlying pathobiology, as patients diagnosed in these categories may be responsive to class-specific therapy. Contributors to PH in SCD frequently overlap, but regardless of the predominant mechanism, the presence of PH substantially increases morbidity and mortality.[9,10]

Chronic hemolysis and recurrent vaso-occlusive crises characterize SCD. While the exact mechanism

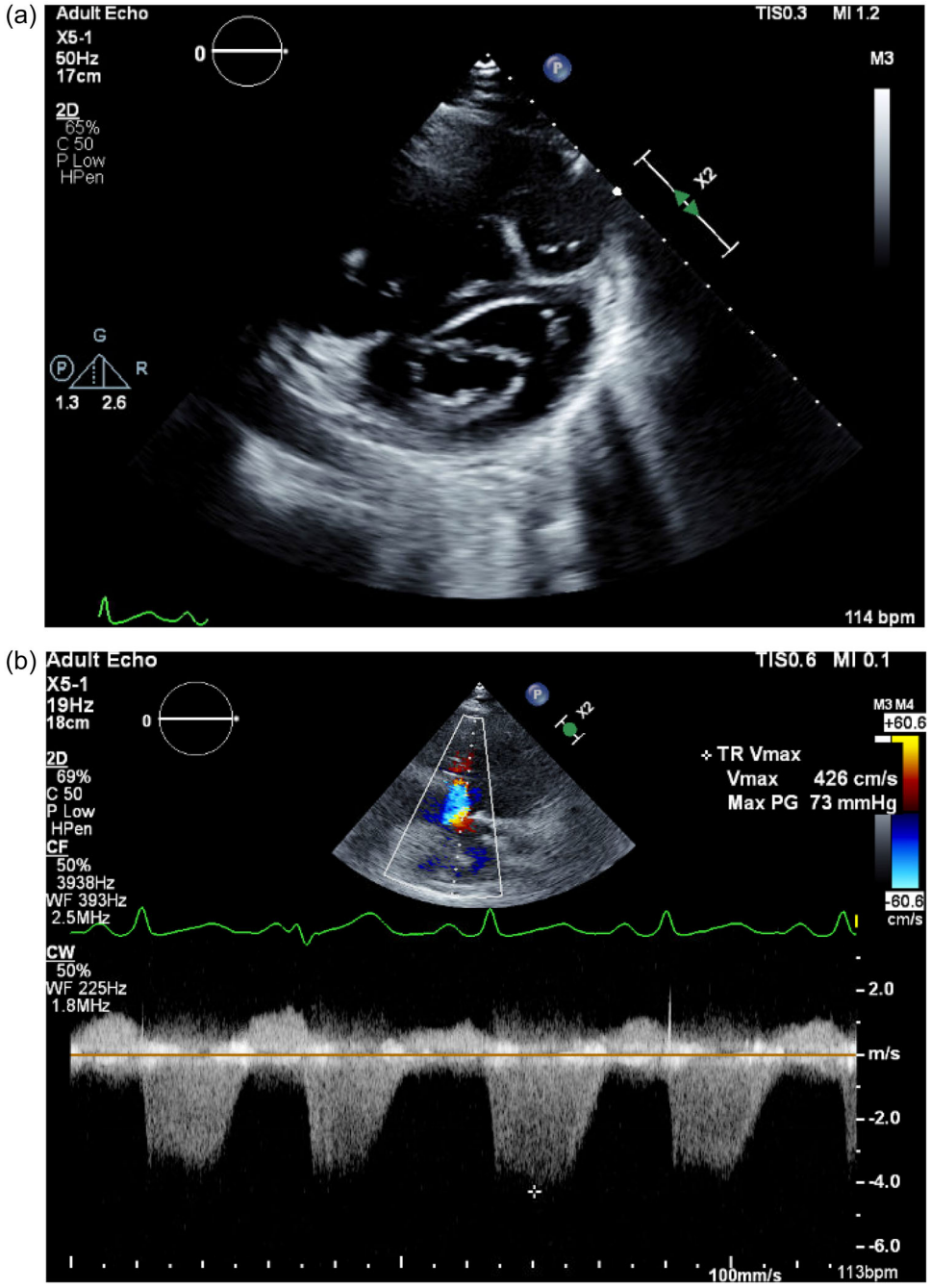

FIGURE 3 Images of transthoracic echocardiography before pulmonary thromboendarterectomy surgery. (a) Parasternal short axis view demonstrating severe right ventricular dilation and interventricular septal flattening. (b) Continuous wave Doppler measurement of tricuspid regurgitation (TR) illustrating markedly elevated TR velocity at over 4 m/s.

remains unknown, intravascular hemolysis appears to play a role in both the hypercoagulable state and the proliferative vasculopathy associated with pre-capillary PH in patients with SCD. The release of free hemoglobin into the plasma during hemolysis results in increased superoxide, which is known to scavenge nitric oxide (NO), resulting in decreased NO bio-availability and endothelial dysfunction. There is a demonstrable correlation between the rate of hemolysis and levels of platelet activation and procoagulants.[4] Markers of hemolysis, such as low hemoglobin, high lactate dehydrogenase (LDH), and low transferrin levels have been shown to be independent predictors of PH in SCD.[9] Furthermore, in the Walk-PHaSST study, in addition to tricuspid regurgitant velocity (TRV) ≥ 3 m/s, markers of hemolysis were identified as independent predictors of mortality.[11]

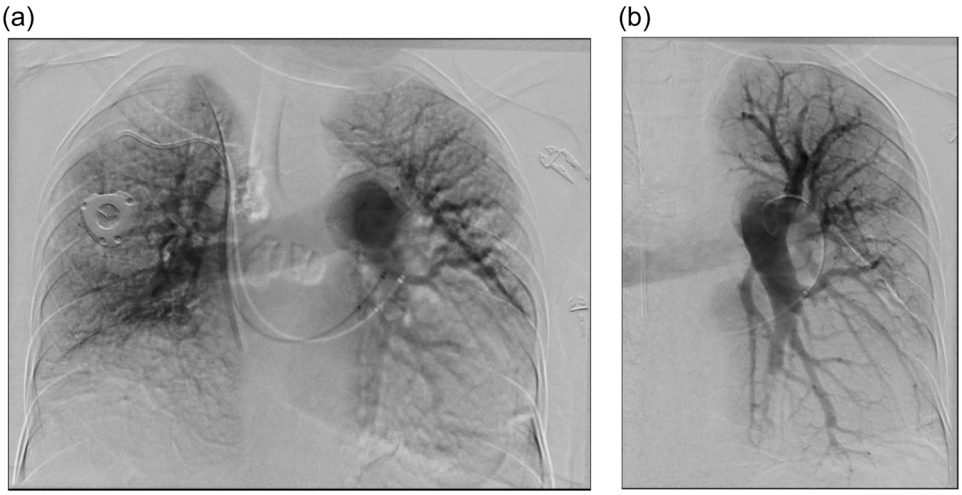

FIGURE 4 Digital subtraction pulmonary angiography of the patient before pulmonary thromboendarterectomy surgery. Findings included multifocal distal pulmonary arterial pruning and peripheral wedge-shaped perfusion defects especially involving the right apex and right lateral middle/right lateral basal segments. (a) Frontal angiographic view of both lungs. (b) View of the left pulmonary arterial bed showing evidence of pruning.

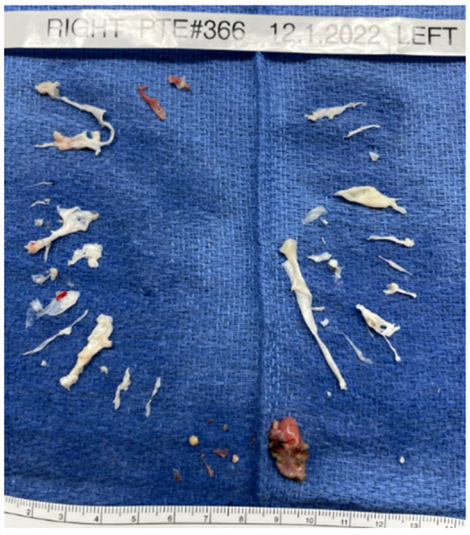

FIGURE 5 Specimens taken from pulmonary thromboendarterectomy surgery.

DIAGNOSIS OF PH IN SCD

Given the significant morbidity and mortality associated with PH in SCD, early screening would allow for timely identification of those at increased risk of PH in general. However, data at present does not show a clear benefit in screening asymptomatic patients. As such, the 2019 American Society of Hematology (ASH) guidelines advise against echocardiogram screening for PH in asymptomatic patients but suggests comprehensive assessment with history and physical examination for signs and symptoms of PH.[12] The American Thoracic Society (ATS) 2014 guidelines recommend a one-time screening echocardiogram in children 8–18 years of age.[13] In adults 18 years or older, the ATS recommends screening with echocardiogram every 1–3 years, with a shorter screening time recommended in those with symptoms or TRV ≥ 2.5 m/s.[13] While TRV ≥ 2.5 m/s is a good predictor of those at increased risk of mortality, it can miss a significant number of patients with PH, while targeting a higher cut off would increase the positive predictive value.[14] The TRV estimate of PH can be significantly discrepant from invasive hemodynamic findings, with both underestimation and overestimation reported.[15] The use of other echocardiogram parameters such as right ventricular dilation, hypertrophy, and septal flattening in addition to TRV would increase the likelihood of identifying an at-risk group. Additionally, further risk stratification with 6-min walk distance (6 MWD) < 330 m, N-terminal pro b-type natriuretic peptide (NT-proBNP) > 164 pg/mL, and markers of hemolysis such as LDH can increase the predictive value of TRV.[14] Right heart catheterization is recommended for further evaluation and confirmation of the diagnosis in patients with high suspicion for PH on echocardiography.

COAGULATION, THROMBOEMBOLISM, AND CTEPH IN SCD

SCD is a hypercoagulable state, with patients experiencing VTE at a four-fold higher rate than individuals without SCD.[16] Both recurrence and progression of PE can lead to the development of CTEPH. In one case

series by Anthi et al, CTEPH was reported in about 12% of V/Q studies completed in patients with SCD and PH.[8] In a recent study of 142 patients with SCD, Mehari et al. observed V/Q mismatch in 45.8% of patients, which was associated with the presence of PH and higher mortality.[17] Another study of 58 patients with SCD and precapillary PH found a high frequency of V/Q mismatch, especially in those with HbSC genotype, where 85% had mismatched segmental perfusion defects.[18] Additionally, a subgroup analysis of the Walk-PHaSST trial identified a cohort of 31 patients with a reported history of PE and found a 0.3 m/s average TRV increase in this group, with a significantly higher proportion of these patients having a TRV ≥ 3 m/s.[19]

The overlap between the development of pulmonary emboli and vaso-occlusive events because of SCD itself can present diagnostic challenges. Repeated vaso-occlusive events are thought to cause extensive damage to the pulmonary vascular bed, which in a small minority of SCD patients leads to an ill-defined sickle cell chronic lung disease.[20] This is characterized by hypoxemia, restrictive defect on pulmonary function testing, and imaging abnormalities frequently visible on chest imaging. It is conceivable that the repeated vaso-occlusive events resulting in chronic lung disease may produce permanent vascular damage, resembling in some respects the persistent vessel occlusion observed in chronic thromboembolic disease.

Established guidelines continue to recommend the use of ventilation-perfusion scanning (V/Q) as the preferred modality to screen for CTEPH.[7] CT pulmonary angiography and conventional digital subtraction angiography are typically used as complementary testing to confirm the presence of thromboembolic disease or provide anatomical data that could be used to justify operative management.

Abnormal V/Q findings are relatively common in patients with SCD, but the rate of concordance in the detection of PE with other forms of imaging, such as CTPA, differs between studies.[17]

A 2018 study of 245 adults with SCD for whom there was suspicion for PE found comparable performance between CTPA and V/Q for PE detection.[21] A later study of 142 stable adults with SCD revealed that 45.8% had abnormal V/Q scans.[17] Positive findings were associated with worsened hemodynamics in those patients who had right heart catheterization data as well as higher mortality and lower functional status. Interestingly, there was only slight concordance between V/Q and CTPA ($\kappa = 0.13$, $p = 0.065$), though the study was limited by significantly fewer patients having undergone CTPA scans.

There is also evidence that SCD patients with acute chest syndrome (ACS), itself a vaso-occlusive phenomenon that could conceivably affect perfusion to an affected region, may produce positive V/Q scans in the absence of PE.[22] A small retrospective study suggested a significant relationship between positive V/Q scan and a clinical diagnosis of ACS. Separating a perfusion defect due to ACS alone versus one due to PE, itself thought to be a possible trigger of ACS, is likely difficult or impossible in the acute setting. Within our center, this has repeatedly represented a challenge for patient management, as the decision to start anticoagulation for an SCD patient with only a positive V/Q scan and no clear evidence of VTE by history or other imaging modality is not straightforward.

Patients with CTEPH require indefinite anticoagulation (AC) to prevent the recurrence of VTE. While vitamin K antagonists (VKA) remain the standard of care in CTEPH, direct oral anticoagulants (DOACs) are now increasingly used based on their efficacy in VTE. Data on the efficacy of DOACs in CTEPH are lacking. A retrospective study examining outcomes after PTE in those treated with VKA versus DOAC found no survival difference between the two groups, 0.67/person-year with VKA and 0.68/person-year with DOAC.[23] However, higher VTE recurrence rates were seen in the DOAC group (4.62/person-year) compared to VKA group (0.76/person-year). Anticoagulation guidelines in SCD-CTEPH are similar to guidelines in the general population.

DISEASE-MODIFYING THERAPIES AND CONNECTIONS TO VTE

The hallmark of SCD is recurrent hemolysis resulting in painful VOC, endothelial inflammation, increased oxidative stress, and a prothrombotic state, and a major risk factor for VTE in SCD is three or more hospitalizations for VOC.[24] Therefore, addressing the risk factors contributing to thrombosis is paramount in preventing VTEs and subsequent complications. The principal maintenance treatment for SCD is hydroxyurea (HU), which acts to increase the production of fetal hemoglobin F as well as to increase nitric oxide by reducing free circulating hemoglobin and direct mediation of intracellular NO production.[25] Hydroxyurea use has been proven to reduce vaso-occlusive crisis pain and frequency of acute chest syndrome and is associated with reductions in serum markers of hypercoagulability.[26,27] Hydroxyurea has also been shown to reduce the risk of arterial thrombosis compared to non-HU users.[28]

In addition to HU, there are currently three US Food and Drug Administration approved disease-modifying therapies: crizanlizumab, L-glutamine, and volexotor.

Crizanlizumab targets p-selectin, a surface adhesion molecule that is upregulated with endothelial inflammation and has been shown to be associated with PH in SCD.[29] It has also been shown to reduce the incidence of VOC and may reduce thrombotic events.[30] L-glutamine targets oxidative stress by upregulating nicotinamide adenine dinucleotide (NAD) in sickled cells and has been shown to reduce VOC and hemolysis in a Phase 3 trial.[31] Volexotor, which binds to the HbS surface to increase oxygen affinity and reduce HbS polymerization, increased hemoglobin levels, and reduced markers of hemolysis in a Phase 3 trial.[32] Early introduction of these disease-modifying therapies in those that cannot tolerate HU or in addition to HU is essential to mitigate the risk of VTE, which in turn may credibly lower the risk of subsequent CTEPH development. There are limited data to directly suggest changes in rates of PH with the use of disease-modifying therapies in SCD; studies thus far have not effectively demonstrated an effect on HU in reducing PH, but are limited by methodology, particularly the use of echocardiography as the primary diagnostic tool.[33]

OPERATIVE AND PERIOPERATIVE MANAGEMENT OF CTEPH IN SCD

Pulmonary thromboendarectomy (PTE) is the first-line treatment for anatomically operable cases of CTEPH without prohibitive comorbidities, and results in substantial improvements in hemodynamics and functional outcomes.[34] However, it is a major surgery with significant potential for complications. Patients with SCD are at increased risk of sickling from prolonged cardiopulmonary bypass, arrest time, hypothermia, and acidosis, all of which are expected conditions during PTE surgery and the peri-operative period. Furthermore, patients with SCD are at an increased risk of post-operative complications, including acute chest syndrome, vaso-occlusive pain crisis, stroke, or acute thrombosis.[35] Recurrence of PH in this patient population is high due to the persistent risk of chronic hemolysis and in situ thrombosis.

Despite these risks, there are documented cases of successful PTE in this patient population, as in our case. All such cases utilized preoperative exchange transfusion to reduce the risk of sickling. While there is no definitive cutoff for HbS, the consensus opinion is to reduce HbS to <30% for major surgeries—either with simple transfusion if Hb is <9 g/dL or with exchange transfusion when Hb is >9 g/dL. A retrospective study of 19 patients with hemoglobinopathies or hemolytic anemia found that reducing the HbS level to ≤20% with exchange transfusion preoperatively and in the immediate postoperative period resulted in favorable outcomes in PVR reduction, functional classification, and 6-min walk distance.[36] In our case, preoperative HbS was 34.6%, after which exchange transfusion was performed before surgery, resulting in a repeat HbS of 13.1%. There were no intra or postoperative complications, and there was significant improvement in hemodynamics (Table 1). Similar strategies were utilized in the other case reports of SCD-CTEPH with successful PTE (Table 2). Other measures to minimize the risk of sickling including correction of intraoperative acidemia and avoidance of hypoxia and hypovolemia.

TABLE 1 Case study hemodynamic data.

Right heart cath parameters	One month before PTE	Immediately before PTE	Immediately post-PTE (closing)	3 weeks post-PTE	3.5 months post-PTE
PAP s/d/m (mmHg)	53/30 (40)	50/23 (33)	40/20	40/17 (28)	48/22 (30)
PAWP (mmHg)	6	10	Not performed	9	12
RAP (mmHg)	22	16	11 (CVP)	13	9
CO (L/min/m^2) by Fick	3.23	4.9	4.7	6.14	6.3
CI (L/min/m^2) by Fick	1.57	3.4	2.3	2.9	3.1
PA sat (%)	34	54	Not provided	60	68
PVR (Wood units)	9.9	5.14	3	2.99	2.8
Pulmonary vasodilators	None	Treprostinil 32 ng/kg/min; riociguat 1.5 mg q8h	None	Riociguat 1 mg q8h	Riociguat 2 mg q8h

Abbreviations: CI, cardiac input; CO, cardiac output; PA sat, pulmonary artery saturation; PAP, pulmonary artery pressure; PAWP, pulmonary arterial wedge pressure; PTE, pulmonary thromboendarterectomy; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

TABLE 2 Case reports of sickle cell disease-associated CTEPH treated with PTE.

Reference	Patients	Perioperative management	Hemodynamics	Abbreviated course
Yung et al.[37]	One HbS/β+ One HbSS	7 units of exchange transfusion (1 day preoperative) Pre: 54.9% HbS, 27.8% HbF, 13.7% HbA, 3.6% HbA_2	Pre: PA 70/35 Post: PA 30/17	Complicated by right intercostal artery bleeding, reperfusion injury Discharged POD 19 on 4 LPM oxygen
		8 units of exchange transfusion (1 day preoperative) Pre: 88.5% HbS, 5.9% HbF	Pre: PA 70/20 Post: PA 39/13	Complicated by postoperative pleuritis responsive to prednisone Discharged POD 9 on 2 LPM oxygen
Jerath et al.[38]	One HbSC	20 units of exchange (4 days preoperative) Pre: HbS 51%, HbC 46%, HbA_2 3% Post: HbS 14%, HbC 13%, HbA 71%	Pre: PA 61/34 (41) Post: PA 25/8 (16)	Extubated POD 1 Discharged POD 6 NYHA Class I symptoms 15 months after PTE
Marques et al.[39]	One HbSS	8 units of exchange preoperative, 4 units of intraoperative Pre: HbS 27%, HbA 71% Post: HbS 9%, HbA 91%	Pre: PA 62/36 Post: PA 45/20	Discharged POD 6 Exercise tolerance reportedly improved
Freeman and Ataga[40]	Two HbSS	Exchange transfusion performed; details not provided Hb electrophoresis not provided	Pre: mPAP 41 Pre: mPAP 40	Improvement from NYHA Class IV to Class II at 1 year Improvement from NYHA Class IV to Class III at 6 months postoperative
Mahesh et al.[36]	19 with hemoglobinopathies including two HbSC	Patient 1: HbS 45.5% Patient 2: HbS 47.4% Both required 8–9 units of exchange preoperatively to reduce HbS to <20%	Pre: mPAP 52 Post not reported Pre: mPAP 28 Post: mPAP 22	No specific follow-up information provided
Agrawal et al.[41]	One HbSS	Unclear if exchange transfusion performed	Pre: PA 70/27 (44) Post not provided	Improvement in oxygenation and 6 MWD Residual PH at 2 months postoperative; started on riociguat
De Sousa et al.[42]	One HbSS One HbSC	6 units of exchange transfusion HbSS patient: Pre: HbS 68.1% Post: HbS 36%	HbSS patient: Pre: 70/28 (42) Post, 3 months: 46/13 (24)	Both patients asymptomatic at 3-month follow-up Improvement from NYHA Class IV to Class I
		4 units of exchange transfusion HbSC patient: Pre: HbS 46.3% Post: HbS 16.6%	HbSC patient: Pre: 100/25 (50) Post, 3 months: 38/15 (22)	
Spencer et al.[43]	One HbSS (pediatric case of an 11-year-old)	Exchange transfusion not reported	Pre: PA 80/35 (52) Post: not reported	Asymptomatic at 6 months postoperative with normal TTE findings

TABLE 2 (Continued)

Reference	Patients	Perioperative management	Hemodynamics	Abbreviated course
		Hgb electrophoresis not provided		

Abbreviations: CTEPH, chronic thromboembolic pulmonary hypertension; LPM, liters per minute; mPAP, mean pulmonary arterial pressure; MWD, minute walk distance; NYHA, New York Heart Association; PA, pulmonary artery; POD, postoperative day; PTE, pulmonary thromboendarterectomy; TTE, transthoracic echocardiogram.

Balloon pulmonary angioplasty (BPA) carries a class I recommendation for inoperable CTEPH and results in superior hemodynamic improvements when compared to medical therapy alone.[7] The RACE trial investigated the efficacy and safety of BPA versus medical therapy in treatment naïve patients with inoperable CTEPH. At 26 weeks, PVR was reduced to 39.9% (95% CI: 36.2–44.0) and 66.7% (60.5–73.8) of previous baseline in the BPA and riociguat groups, respectively.[44] However, treatment-related adverse events were more common with the BPA group. Pretreatment with riociguat decreased severe treatment-related events with BPA, suggesting the benefit of combination therapy.[44] Reports of BPA use in SCD patients with CTEPH are extremely few and limited largely to small case series.[45,46] In a retrospective study assessing the outcomes of precapillary PH in 58 SCD patients, Savale et al. included three patients with inoperable CTEPH treated with BPA with resultant improvement in hemodynamics.[18] Karyofyllis et al. reported a case of SCD with precapillary PH secondary to CTEPH deemed high risk for PTE treated with medical therapy, followed by BPA with improvement in hemodynamic and functional class.[45] Similarly, Sianos et al. reported a case of SCD with CTEPH who underwent staged BPA without complications.[46]

The decision to proceed with PTE versus BPA can be complex and should include assessment of comorbidities, anatomic considerations, and degree of hemodynamic compromise, amongst other considerations. Anatomically, proximal obstruction is generally considered surgical whereas more distal disease may be surgically inaccessible and best suited for BPA. The definition of "distal" varies based on PTE center experience, with even segmental resection considered feasible in the most experienced CTEPH centers.[47] Those with the most severe hemodynamic impairments are more likely to benefit from PTE. Though our patient primarily had segmental CTEPH, given her severely impaired hemodynamics and lack of other high-risk comorbidities, PTE was determined to be the best therapeutic approach.

PULMONARY VASODILATORS IN CTEPH AND SCD

Currently, the lone approved medical therapy for inoperable, persistent, or recurrent CTEPH after PTE is the oral soluble guanylate cyclase (sGC) stimulator riociguat. The CHEST-1 study, a randomized, double-blind, placebo-controlled study of riociguat in inoperable CTEPH, showed an improvement in PVR, 6-min walk distance, WHO functional class, and NT-proBNP after 16 weeks.[48] In the open-label extension trial (CHEST-2), there was persistence of efficacy for up to 1 year.[49] While riociguat is a well-established medical therapy for inoperable CTEPH in the general population, there are a lack of RCTs in SCD-associated CTEPH. Most of the available data on riociguat in SCD with CTEPH is from small case series, though a Phase 2 randomized clinical trial of the drug in high-risk SCD patients (NCT02633397) has been completed and is awaiting results. A retrospective case series of 6 patients with SCD, including one HbSC patient, examined the use of riociguat in CTEPH and SCD.[50] The drug was well-tolerated in four of six patients, with an increase in VOC in one patient not concurrently on hydroxyurea. Improvement was observed in NT-proBNP, functional class, and RVSP, though follow-up right heart catheterization data was not available. Additional single case report suggests good tolerance and functional improvement with riociguat.[51] In another case series of 11 SCD patients, seven of whom had CTEPH based on V/Q, treatment with parenteral prostacyclins resulted in significant improvements in right ventricular systolic pressure and a trend towards improvement in 6-min walk distance. Nearly all patients were taking hydroxyurea and were on combination therapy with an endothelin-receptor antagonist, a phosphodiesterase-5 inhibitor, or both.[52] It should be noted that phosphodiesterase-5 inhibitor use is generally avoided in SCD due to findings from the Walk-PHaSST trial suggesting an increase in vaso-occlusive crises.[11]

Studies to support the use of PH therapies preoperatively in patients who are candidates for PTE with severe hemodynamic compromise are lacking, and at least one study has shown that the use of preoperative

pulmonary vasodilators delayed definitive therapy.[53] In one small RCT of 13 patients, the use of bosentan as a bridge to PTE showed improvement in PVR and mPAP; no difference in postoperative outcomes was observed, but the study was likely not powered to show this.[54] There is a need for more RCTs to assess which patients would benefit from preoperative PH therapies.

CONCLUSIONS

Patients with SCD are at an increased risk of CTEPH, especially those with HbSC genotype which is associated with higher baseline hemoglobin, lower rates of hemolysis, and higher rates of VTE compared to HbSS. Regardless of the genotype CTEPH is associated with significant morbidity and mortality and these patients require a nuanced approach to identify those who would benefit from PTE. While SCD patients are considered a high-risk surgical group, every effort should be made to offer these individuals a potentially curative surgery. Reducing the HbS with exchange transfusion in addition to avoidance of acidosis, hypercapnia, and aiming for euvolemia can mitigate the risk of sickling. Managing these patients should be a multidisciplinary approach that includes specialists in PH, cardiothoracic surgery, hematology, and pain management. Our case highlights the complexity of the management of underlying PH in SCD and illustrates the idea that SCD-CTEPH can be safely managed with PTE.

AUTHOR CONTRIBUTIONS

All authors have read and approved the submitted work and participated in writing the manuscript. As corresponding author, Dr. Steven J. Cassady takes full responsibility for the contents of the article and the data presented herein.

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CONFLICT OF INTEREST STATEMENT

Dr. Gautam V. Ramani has served as a consultant for Merck and as a principal investigator for pharmaceutical studies with Janssen Pharmaceuticals and United Therapeutics. Dr. Mark T. Gladwin's work is supported by National Heart, Lung, and Blood Institute (NHLBI) Grant R01098032. Dr. Mark T. Gladwin is a coinventor of patents and patent applications directed to the use of recombinant neuroglobin and heme-based molecules as antidotes for carbon monoxide poisoning, which have been licensed by Globin Solutions, Inc. Dr. Mark T. Gladwin is a shareholder, advisor, and director in Globin Solutions, Inc. Dr. Mark T. Gladwin is also coinventor on patents directed to the use of nitrite salts in cardiovascular diseases, which were previously licensed to United Therapeutics, and is now licensed to Globin Solutions and Hope Pharmaceuticals. Dr. Mark T. Gladwin was a principal investigator in a research collaboration with Bayer Pharmaceuticals to evaluate riociguate as a treatment for patients with sickle cell disease. Dr. Mark T. Gladwin is textbook author and receives royalties from MedMaster Inc. and is a textbook editor and receives royalties from McGraw-Hill. Dr. Mark T. Gladwin is a paid consultant for Third Pole Therapeutics. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

The authors have nothing to report.

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