Current Pediatrics Reports (2019) 7:33–44
https://doi.org/10.1007/s40124-019-00188-3

CARDIOLOGY (W ZUCKERMAN AND E SILVER, SECTION EDITORS)

Pulmonary Hypertension in Children with Sickle Cell Disease: a Review of the Current Literature

Jamie K. Harrington[1] · Usha S. Krishnan[2]

Published online: 17 April 2019

Abstract

Purpose of Review Pulmonary hypertension (PH) is a well-recognized complication of sickle cell disease (SCD) and is one of the strongest predictors of increased morbidity and mortality in adult patients. There is evidence that PH can develop in children with SCD and the clinical implications of this finding are an area of active research. We review the current literature examining the association of SCD and PH in childhood.

Recent Findings The recent literature has focused on elucidating the multifactorial mechanisms for the development of PH in SCD with the goal of developing targeted therapies. In addition, there has been a focus on understanding the significance of echocardiographic evidence of PH in children with SCD, a finding that has recently been associated with adverse clinical factors. While still based on limited evidence, the increased understanding of the important prognostic implications of echocardiographic evidence of PH has led to the development of guidelines that recommend screening echocardiograms beginning in childhood in children with SCD.

Summary PH can develop in children with SCD and, while the exact clinical implications of this finding are still being elucidated, current guidelines and research are aimed at early identification and treatment to improve outcomes.

Keywords Sickle cell disease · pulmonary hypertension · pediatric · tricuspid regurgitant jet velocity

Introduction

Sickle cell disease (SCD) is a genetic erythrocyte disorder caused by an amino acid substitution on the β-globin chain resulting in structurally abnormal hemoglobin that can polymerize causing erythrocytes to form a sickle shape [1]. This makes them prone to vaso-occlusion and hemolysis leading to multisystem disease and severe end-organ complications [1, 2]. Pulmonary hypertension (PH) is one of the well-established comorbidities in SCD that has been shown to have a significant impact on morbidity, and is associated with increased mortality in adults [3–12].

✉ Usha S. Krishnan
usk1@cumc.columbia.edu

[1] Department of Cardiology, Boston Children's Hospital; and Department of Pediatrics, Harvard Medical School, Boston, MA, USA

[2] Division of Pediatric Cardiology, Department of Pediatrics, College of Physicians and Surgeons, Columbia University Medical Center, 3959 Broadway, CHN 2-255, New York, NY 10032, USA

While PH can only be definitively diagnosed by a hemodynamic assessment obtained on right heart catheterization (RHC), an elevated tricuspid regurgitant jet velocity (TRV) on echocardiography is frequently used as a noninvasive screening tool to estimate elevated pulmonary artery pressure (PAP) [13, 14]. An elevated TRV has been associated with increased morbidity and mortality in multiple adult studies [7, 11, 15]. In children with SCD, the prevalence of an elevated TRV has been shown to be substantial [16–20]. Yet, the clinical implications of this finding are not well defined. An association with mortality has not been shown. However, it has been associated with markers of increased hemolysis, hypoxia, and decline in the 6 minute walk test (6MWT), indicating that the onset of PH in childhood could be a harbinger of adverse outcomes in adulthood. These findings have led to the development of recent guidelines and consensus recommendations using the TRV to risk stratify and identify patients that should be considered for invasive hemodynamic testing and potential escalation in therapy [21••, 22•, 23–25].

In addition, enhanced understanding of the multifactorial etiologies of PH in SCD has led to better delineation of the complex molecular pathways contributing to its development.

It is the hope that further research in this area will lead to better therapies to treat and/or prevent PH in SCD, potentially starting in childhood [3, 26, 27].

This review will summarize the current literature on PH in children with SCD with a focus on the enhanced understanding of the pathophysiology, new potential therapeutic targets, the current understanding of the clinical implications of echocardiographic indicators of PH, and the existing recommendations for screening and management.

Defining Pulmonary Hypertension

Classification

The World Symposium of Pulmonary Hypertension (WSPH), endorsed by the World Health Organization, is composed of an international group of experts in PH who have developed a clinical classification system with the goal of creating categories of PH that share similar pathophysiology and therapeutic approaches [28, 29]. In 2008, at the 4th WSPH, PH in chronic hemolytic anemia was classified in group 1, pulmonary arterial hypertension (PAH) [28]. However, since then, it has become clear that the cause of PH in chronic hemolytic anemia is multifactorial and not completely understood, leading to its recent re-classification in 2013 at the 5th WSPH into group 5, PH with unclear multifactorial mechanisms [30]. This classification was maintained at the 6th WSPH in 2018 [31]. The re-classification is based on evidence that PH in SCD can occur due to both precapillary (PAH) and postcapillary (pulmonary venous hypertension) mechanisms, and that PAH in SCD has different pathology [32–34], hemodynamics [10, 35–37], and therapeutic responses [38, 39] than other causes of PAH.

Definition

Hemodynamic studies performed during cardiac catheterization are considered the gold standard for diagnosis of PH. PH in SCD can be divided into two broad categories, precapillary and postcapillary. Precapillary PH, or pulmonary arterial hypertension (PAH), has historically been defined by a mean pulmonary artery pressure (mPAP) of 25 mmHg or greater with a mean pulmonary artery wedge pressure (mPAWP) or left ventricular end-diastolic pressure (LVEDP) of 15 mmHg or less [24]. Recently, the 6th WSPH has proposed to modify the definition in adults as a mPAP of ≥ 20 mmHg [31, 40]. In order to stay consistent, the Pediatric Task Force chose to follow the adult definition, but encouraged more study of these patients [31]. An elevated pulmonary vascular resistance (PVR) would also be expected in PAH in SCD [21••]. However, the baseline PVR in SCD is lower than in non-anemic patients due to an increased cardiac output associated with chronic anemia and a lower blood viscosity. Therefore, many clinicians accept a lower PVR as elevated in SCD (> 2–3 Wood units) [24, 41]. In children, PVR is indexed to body surface area (PVRi), and a PVRi > 3 Wood units × m^2 is generally considered elevated [21••]. Postcapillary PH, or pulmonary venous hypertension, is defined as a mPAP ≥ 20–25 mmHg and a mPAWP or LVEDP ≥ 15 mmHg, without an elevated PVR [14, 24, 42]. However, due to the multifactorial nature of PH in SCD, many patients will have hemodynamic features of both pre- and post-capillary PH.

Echocardiographic Estimation of Pulmonary Artery Pressure

In children, invasive hemodynamic testing is infrequently performed and many clinicians have come to define PH based on the TRV derived from echocardiography. The TRV estimates the pressure gradient between the right ventricle (RV) and right atrium during systole by utilizing the modified Bernoulli equation (pressure gradient = $4v^2$; v = TRV) [43]. Therefore, the TRV estimates the RV systolic pressure (RVSP) and pulmonary artery systolic pressure (PASP), in the absence of pulmonary stenosis (RVSP = PASP = TR max pressure gradient + right atrial pressure; where the right atrial pressure is often estimated to be 3–5 mmHg or ignored) [43]. A TRV ≥ 2.5 m/s (25 mmHg) has been most commonly used to define elevated PAP [44]. This may be impacted by the newly proposed definition of PH which lowers the diagnosis of an elevated mPAP to 20 mmHg [31]. This requires evaluation in SCD patients, both adults and children. Since the current literature assessing PH in SCD, including the SCD-specific guidelines for the diagnosis of PH, has used the historic definition of 25 mmHg to define PH, this has been used to guide the recommendations in this review. However, it is important to realize that this may evolve as more evidence becomes available.

Pathophysiology

Hemolysis

The most fundamental mechanism for the development of PH in SCD is that chronic hemolysis leads to maladaptive changes, including nitric oxide (NO) dysregulation, endothelial damage, vasoconstriction, inflammation, hypercoagulability, and free radical generation, culminating in the development of PH [27, 45–51]. NO plays an important role in vasodilation through activation of cGMP-dependent protein kinases in smooth muscle cells. Dysregulated NO metabolism results in chronically increased vasoconstriction, decreased inhibition of vascular smooth muscle proliferation, and platelet aggregation [26]. Cell-free hemoglobin released during hemolysis scavenges NO resulting in dysregulation of the NO signaling

pathways [52, 53]. In addition, other products are released that inhibit the synthesis of NO. For example, arginase-1 destroys arginine, a necessary substrate of NO synthase [54], and asymmetric dimethylarginine is an inhibitor of NO synthase [55].

Many other products released during hemolysis are being discovered that also contribute to the pathophysiology of PH. Placenta growth factor, an angiogenic growth factor, has been shown to regulate the expression of genes involved in inflammation [56]. Purine nucleoside phosphorylase and adenosine deaminase result in accelerated metabolism of adenosine, inosine, and guanine, abolishing their vasoprotective effects, resulting in an angio-proliferative PH in rats [57]. Red cell microparticles produced during hemolysis and cell-free heme released from hemoglobin induce inflammatory pathways and lead to reactive oxygen species formation [49, 58–60]. Red cell microparticles have been shown to concentrate heme, and these complexes have been shown to cause toxic damage to endothelial cells [61], and to induce rapid vaso-occlusion in mice [62]. Some groups have begun to refer to these products as red cell damage-associated molecular patterns or DAMPs, and it is hypothesized that they play a pivotal role in activating and amplifying inflammation leading to endothelial damage and vaso-occlusion [63–65]. The cascade of events that is triggered by the multitude of products released during intravascular hemolysis culminates in chronic vasoconstriction, inflammation, endothelial damage, hypercoagulability, and thrombosis contributing to the development of PH over time. Research in this area is rapidly expanding and many of these pathways represent new potential therapeutic targets.

Left Heart Dysfunction

Another major pathophysiologic mechanism for the development of postcapillary PH involves left ventricular (LV) diastolic dysfunction leading to secondary pulmonary venous hypertension. In adults, this accounts for nearly half of the PH cases in SCD [27]. Recently, Niss et al. described a unique form of cardiomyopathy in children with SCD consisting of a restrictive physiology superimposed on a hyperdynamic physiology [66]. In a cohort of 134 SCD children, they found a significant number demonstrated left atrial enlargement (62%), as well as other echocardiographic findings of diastolic dysfunction. All children had normal systolic function. This is similar to other forms of restrictive cardiomyopathy, defined by diastolic dysfunction and left atrial dilation with preserved LV systolic function and size. However, unlike classic restrictive cardiomyopathy, in SCD, LV enlargement is almost universal secondary to the hyperdynamic circulation related to chronic anemia, and this represents a unique form of cardiomyopathy where there is restrictive and hyperdynamic physiology. Importantly, the study by Niss et al. brings attention to the fact that patients with restrictive cardiomyopathy can experience sudden death despite normal or only mildly elevated PAP [66]. The etiology of the restrictive physiology is not completely understood, but there is some evidence that it is related to myocardial fibrosis which can be seen in SCD due to dysregulated pro-fibrotic pathways and iron deposition [67–69]. While still an area of active research, it is increasingly recognized that despite preserved systolic function, patients develop diastolic dysfunction, resulting in PH.

Genetic Predisposition

The recent literature has also drawn attention to a genetic predisposition for the development of PH in SCD [70, 71]. There is remarkable clinical variability in SCD, even among individuals with identical genotypes. There are likely significant genetic variants contributing to this heterogeneity that could be potential therapeutic targets [72]. The phenotypic heterogeneity explained by the genetic variability of fetal hemoglobin and alpha-thalassemia is well recognized [73, 74]. However, many new genetic modulators are being discovered, such as polymorphisms in Endothelin-1 [75], TGF-beta, and other genes linked to vascular function and NO signaling [71], that may be associated with the development of PH. While many of these genetic variants are unvalidated, it has been shown that PH can cluster in families [76]. This is an area of increasing investigation.

Prevalence

The true prevalence of PH in SCD as defined by invasive cardiac hemodynamics is less than that defined by an elevated TRV [35, 36]. Adult studies report a prevalence of 20–40% by the TRV [7], whereas invasive testing reveals a prevalence of 10% or less [35, 36]. The prevalence of PH in children with SCD as defined by an elevated TRV, given the paucity of studies that have performed invasive assessment, ranges from < 10% to a similar prevalence seen in adults [16–20, 77–85].

Part of this variability may depend on the number and age of the children in each study cohort. The number of children with an elevated TRV increases with age [20, 79, 85]. Our group recently performed a large longitudinal analysis of echocardiographic abnormalities in children with SCD that supports this finding [79]. Since participation in the Cooperative Study of Sickle Cell Disease in the early 1990s, our institutional policy has been to perform echocardiograms beginning around 5 years of age as part of routine health maintenance for pediatric SCD patients. A longitudinal analysis of these echocardiograms showed that not only did the expected findings of LV dilation begin early in childhood and increase with age, but that the prevalence of an elevated TRV increased from 3% by 7 years of age to 15% by 13 years of age. Other groups have supported this finding. Hebson et al.

[85] showed that the prevalence in children younger than 10 years of age was < 10%, but increased to 30%, similar to adults, by 19–20 years of age.

In order to try to more accurately characterize the prevalence of an elevated TRV in children with SCD, two recent large meta-analyses were published [19, 20]. Musa et al. included 29 studies (5358 individuals) and found an elevated TRV in 21% of children and 24% of adults [19]. Caughey et al. conducted a random effects meta-analysis including 45 studies (6109 individuals) that found an elevated TRV in 21% of children and 30% of adults [20]. Based on these findings, the prevalence of an elevated TRV is around 20% in children with SCD and increases throughout childhood.

The prevalence of PH in children with SCD as defined by invasive cardiac hemodynamics has not been adequately assessed.

Clinical Associations

Hemolysis and Anemia

It has been well documented that an elevated TRV is associated with the severity of hemolysis and anemia [17, 78, 79, 82, 83, 86, 87]. In adults, a hemolysis score incorporating several different markers of hemolysis has been shown to be strongly associated with greater TRV values, and in a 2-year follow-up analysis was associated with an increased risk of death [88]. In children, elevated lactate dehydrogenase (LDH), bilirubin and reticulocyte levels, and decreased hemoglobin and hematocrit levels have been associated with an elevated TRV [17, 79, 82, 86].

Pulmonary Comorbidities

Sleep and waking oxygen saturation levels have been negatively correlated with the TRV [83, 89, 90]. In addition, a high prevalence of nocturnal hypoxia and sleep disordered breathing has been documented in children with SCD, and these findings have been associated with an elevated TRV [89, 91]. Asthma is also common in children with SCD and is associated with the development of PH [92, 93]. Children with SCD should be screened for asthma, obstructive sleep apnea, and sleep disordered breathing, and it is important to monitor routine pulmonary function tests.

Age

The prevalence of an elevated TRV in children with SCD increases with age [79, 85]. Kato et al. proposed a hypothetical model in which the duration and severity of the hemolysis-associated sequelae on the pulmonary vasculature leads to chronic vasoconstriction and vascular remodeling leading to worsening PH over time (Fig. 1) [87]. It is proposed that these changes may be reversible early on, but with time become fixed, providing impetus for early identification and intervention in childhood.

Generalized Vasculopathy

In adults, there is evidence of a generalized vasculopathy with vascular comorbidities in multiple organ systems. Vascular complications such as venous thromboembolism, proliferative retinopathy, nephropathy, and leg ulcers have been associated with elevated PAP [94–97]. While these complications are not usually seen in childhood, a recent study showed that proteinuria in children with SCD is associated with a TRV ≥ 2.5 m/s [98].

While less documented in children, the associations of an elevated TRV with the degree of anemia, the duration of exposure to the adverse effects of chronic hemolysis, and the association with other comorbidities and multi-organ system effects, are increasingly being appreciated to develop in childhood.

Association with Outcomes

In adults, elevated PAP detected on RHC and elevated TRV have been shown to be strong predictors of mortality (rate ratio, 10.1; 95% CI, 2.2 to 47.0; $P < 0.001$) [7] and to carry important prognostic implications [7–12, 15, 95, 99–101]. In children, an association with mortality has not been shown. However, an elevated TRV in children has been associated with indicators of adverse functional status [102–105].

Six-Minute Walk Test

As part of the Walk-PHaSST study (treatment of Pulmonary Hypertension and Sickle cell disease with Sildenafil Therapy), Sachdev et al. showed the 6MWT distance correlated inversely with the TRV, a finding which remained significant in multivariate analysis [100]. A similar association was demonstrated by Gordeuk et al. in a prospective, longitudinal, multi-center study in children with SCD [103]. In this study, an elevated TRV was associated with an estimated 4.4-fold increase in the odds of decline in age-standardized 6MWT distance ($P = 0.015$).

Other Markers of Adverse Functional Status

The literature is not as definitive in regards to the association of an elevated TRV with other markers of functional status in children with SCD. Dham et al. found that the TRV was associated with a history of acute chest syndrome (ACS), stroke, and transfusions, in addition to the 6MWT distance [104]. In the PUSH study (Pulmonary Hypertension and the Hypoxic Response in SCD), a higher steady-state TRV was associated with a history of acute pulmonary events [102]. However,

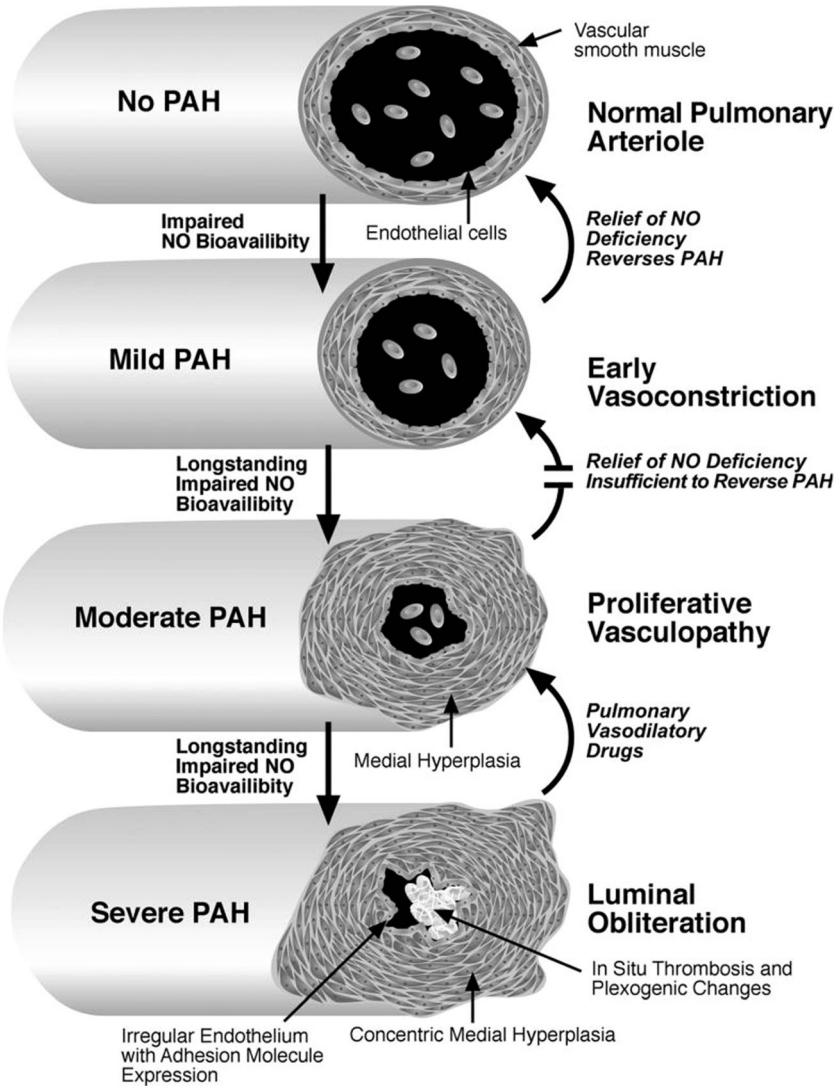

Fig. 1 Reproduced with permission from Kato et al. [87]. Proposed model for the development of pulmonary hypertension in sickle cell disease. Pulmonary hypertension results from the chronic exposure of the pulmonary vasculature to the adverse hemolysis associated sequelae of vasoconstriction and vascular remodeling. It is proposed that changes in the pulmonary vasculature may be reversible early on, but as the duration of exposure increases, the changes become irreversible. Definition of abbreviations: NO = nitric oxide; PAH = pulmonary arterial hypertension

more recently, it has been shown that SCD children with an elevated TRV did not differ from age-matched SCD controls in the incidence of ACS, hospitalization, or stroke [85]. More studies are needed to elucidate these associations.

Clinical Presentation

The most common symptoms of PH include fatigue, dyspnea on exertion, dizziness, syncope, chest pain, and palpitations. These symptoms can be seen in children with SCD secondary to anemia, pain crises, ACS, and other SCD-associated comorbidities making the presentation of PH difficult to discern. Physical exam findings can include a prominent second heart sound due to accentuated closure of the pulmonary valve in the setting of elevated PAP, as well as a holosystolic murmur from tricuspid regurgitation, and a right ventricular heave. Jugular venous distention, edema, and hepatomegaly may also be present. Chest radiography may demonstrate cardiomegaly and prominence of the proximal pulmonary vasculature with decreased vascularity peripherally. Electrocardiogram may show right axis deviation, prominent right-sided forces, and evidence of right ventricular hypertrophy; however, SCD patients may also have evidence of left heart dilation which may mask the right-sided changes to some degree. In most cases, children may not have clinically symptomatic PH and many of the presenting symptoms and exam findings may be absent, and thus, many providers send these children for screening echocardiography.

Screening Echocardiography

Tricuspid Regurgitant Jet Velocity

To help improve the diagnosis of PH, screening echocardiography is recommended; most commonly using an elevated

TRV as a surrogate marker for elevated PAP. However, in the last several years, the appropriateness of using the TRV as a screening tool in SCD patients has been debated and warrants discussion here.

In adults, it has been shown that using a TRV of ≥ 2.5 m/s has a poor positive predictive value for predicting PH by RHC [35]. Parent et al. showed that the positive predictive value of a TRV ≥ 2.5 m/s for detecting PH by RHC was only 25% [35]. Concerns regarding the use of an elevated TRV in children stem from the lack of reproducibility and the lack of a strong association with increased morbidity and mortality [85, 106].

The supporting argument for utilizing the TRV is nicely described by Kato et al. through an analogous comparison between using the transcranial Doppler (TCD) velocity to estimate the risk of stroke and using the TRV to estimate the risk of PH [26, 107•]. The argument draws attention to the fact that TCD has a similar specificity for predicting stroke, but is a widely accepted and recommended screening tool in SCD and therefore, recommends using the TRV as a physiological biomarker [107•].

Even though there is a low specificity of using the TRV to predict true PH by RHC, many experts believe that the strong association of an elevated TRV with morbidity and mortality in adults, and the increasing associations with morbidity being found in children, make it an important marker to follow in SCD [107•].

Other Echocardiographic Findings

If the TRV is inadequate to estimate the PAP, other echocardiographic markers can be used such as the pulmonary regurgitant jet velocity (if present) or the geometry of the interventricular septum; however, these have not been well evaluated in SCD.

In addition, a diastolic function assessment is also important given the increased understanding that a restrictive physiology can develop in childhood and may portend the development of pulmonary venous hypertension [66]. In adults, LV diastolic dysfunction has been associated with PH, increased mortality [108], and decreased functional status [100]. This is an active area of research in children.

Guidelines

Given the important clinical implications of PH in SCD, adult guidelines for screening echocardiography have been developed to help increase early identification of PH with the hope of early treatment and risk modification [24]. Currently, even though screening echocardiograms are recommended in children, guidelines are not well established.

In 2014, the American Thoracic Society (ATS) proposed an algorithm to evaluate PH in adults with SCD using screening echocardiography and TRV elevation [24]. This algorithm provides mortality risk stratification based on the degree of TRV elevation and provides recommendations for when to proceed to invasive testing with RHC. A TRV ≤ 2.5 m/s is considered low risk and continued routine screening is recommended. A TRV between 2.5 and 2.9 m/s is considered intermediate risk and consideration should be given to increased frequency of screening and optimization of SCD-specific therapy. If there are symptoms of PH, a decreased 6MWT distance, or elevated NT-pro-BNP, RHC is recommended. A TRV ≥ 3.0 is considered high risk and RHC is recommended. The addition of the 6MWT and NT-pro-BNP to the algorithm was based on evidence that they improve the positive predictive value for true PH on RHC [10, 35]. The committee makes a point to indicate that these recommendations will require frequent reassessment and updating as new evidence becomes available.

In 2015, the American Heart Association and ATS published joint guidelines for pediatric pulmonary hypertension which included some specific recommendations for PH in children with SCD [21••, 22•, 23]. The guidelines recommend that children should start having screening echocardiograms by 8 years of age, or sooner in those with frequent cardiorespiratory symptoms. Children with evidence of PH by echocardiography should undergo further cardiopulmonary evaluation (polysomnography, pulmonary function testing, evaluation for thromboembolic disease, assessment of oxygenation) with the aim of identifying predisposing factors that could be addressed. The indications of who should undergo invasive RHC are not clear, but it is clear that prior to initiation of PH-specific drug therapy RHC should be performed.

In order to accurately identify the TRV cutoff that should be used to indicate the need for RHC in children, Lilje et al. recommended a modified noninvasive screening protocol to better define this subgroup [109]. They divided a population of children with SCD into risk categories based primarily on the TRV. Using a cutoff of ≥ 2.5 m/s, 20.9% would qualify for elevated PH risk. However, if the cutoff is adjusted to ≥ 2.9 m/s, only 4.4% would qualify, and they recommend that invasive evaluation may be reserved for this subgroup. This recommendation is in line with ATS guidelines for adults; however, this has not been validated by invasive testing in children.

It is important to remember that all screening echocardiograms should be performed at steady state (at least 4 weeks after hospitalization from ACS and 2 weeks after a pain crisis or blood transfusion).

Table 1 provides a summary of recommendations from the current literature, and personal experience, regarding recommendations to guide screening echocardiography in children with SCD.

Serum Markers

In addition to screening echocardiography, several recent publications are investigating serum markers that may indicate an

Table 1 Summary of recommendations to guide echocardiography screening for pulmonary hypertension in children with sickle cell disease

	Recommendation
Timing of initial screening echocardiography	• Initiate around 8 years of age (sooner in children with frequent cardiopulmonary symptoms).
Frequency of screening echocardiography	• Adult guidelines recommend every 1–3 years.
	• The frequency can be adjusted based on severity of hemolysis, age, pulmonary comorbidities, and frequency of cardiopulmonary events.
Management of TRV < 2.5 m/s	• Low risk for PH.
	• Continue routine 1–3 yearly screening.
Management of TRV 2.5–2.8 m/s	• Borderline risk for PH.
	• Consider additional noninvasive testing (6MWT, NT-proBNP, polysomnography, pulmonary function testing etc).
	• Consider RHC is above additional testing is abnormal.
	• Increase screening echocardiography frequency to yearly.
	• Optimize SCD-directed therapy.
Management of TRV ≥ 2.9 m/s	• Moderate risk for PH.
	• Consider RHC (especially if persistent on serial evaluation).
	• More frequent echocardiographic evaluations.
Initial therapy	• Optimization of SCD-directed therapy (HU, chronic transfusions).
	• Minimize pulmonary comorbidities (supplemental oxygen for nocturnal hypoxia, evaluation of OSA, asthma management).
PH-directed therapy	• Consider only after RHC.
	• Only recommended for elevated PVR with a normal PCWP.

Adapted from Klings et al. [110] Abman et al. [111] Lilje et al. [112]

6MWT 6-min walk test, *HU* hydroxyurea, *NT-proBNP* N-terminal pro b-type natriuretic peptide, *OSA* obstructive sleep apnea, *PCWP* pulmonary capillary wedge pressure, *PH* pulmonary hypertension, *RHC* right heart catheterization, *SCD* sickle cell disease, *TRV* tricuspid regurgitant velocity

increased risk of PH and improve the positive predictive value of an elevated TRV. In adults, an elevated NT-proBNP (≥ 160 pg/mL) has been consistently shown to be a strong indicator of PH and predictor of mortality and is recommended as part of the screening algorithm [38, 113–115]. This has not been well assessed in children, but it is recommended when Doppler echocardiography is unclear or unavailable [21••]. Newer markers include apelin, Fas and its ligand (Fas/FasL), asymmetric dimethylarginine (ADMA), von Willebrand factor (vWF), and CD163, among others [110–112, 116, 117]. As research in this area continues to expand, it is likely that serum markers will be incorporated into screening algorithms to help improve the positive predictive value of echocardiography.

Treatment

There are two broad categories for treatment of PH in SCD. The first is treatment of the underlying sickle cell disease process, specifically the chronic hemolysis and anemia. The second is PH-targeted therapy.

Hemolysis Directed Therapy

The first line therapy for any patient with SCD that is identified to be at risk for PH involves more aggressive treatment of SCD-directed therapy [21••, 24]. This may include hydroxyurea (HU), blood transfusion, or supplemental oxygen [25, 118]. HU is felt to be beneficial in SCD because it increases levels of fetal hemoglobin and leads to reduced sickling, but it also may have beneficial anti-inflammatory effects by inhibiting hemolysis-induced inflammation [119]. The evidence that HU improves or prevents PH is scarce. In adults, it has been shown to reduce TRV in a small number of patients [120]. Anecdotal evidence comes from studies which have shown higher levels of fetal hemoglobin are associated with less PH [101]. In children, there is no direct evidence that HU prevents or improves PH [76, 85, 121]. There is some evidence in adults that chronic transfusion therapy may be associated with TRV. Detterich et al. found that the TRV was lower in chronically transfused patients with SCD [122]. Another SCD-therapy is hematopoietic stem cell transplant which may protect children with SCD from developing PH and may reduce TRV elevation [18, 123, 124]. Novel therapies,

such as infusions of haptoglobin, a hemoglobin binding protein that may preserve NO signaling by scavenging cell-free heme, are also being investigated [125–127].

Pulmonary Hypertension Directed Therapy

Therapy for SCD-associated pediatric PH has not been well evaluated. PH-targeted therapy is only recommended after PH has been documented by RHC and the etiology has been defined [21••]. Even when PH is confirmed by RHC, PH-targeted therapy is reserved for children with an elevated PVR in the setting of normal left-sided filling pressures [21••]. In these patients, an endothelin-receptor antagonist (ERA) or prostacyclin analog is recommended over a phosphodiesterase type 5 inhibitor (PDEi5) (sildenafil) (due to an association of treatment with PDE5i and increased mortality in some studies) [21••, 128].

A few studies have assessed PH-targeted therapies in adults with SCD. A randomized placebo-controlled trial aimed at determining if sildenafil could improve exercise capacity in SCD adults with elevated TRV was stopped early due to increased serious adverse events in the sildenafil arm [38]. ERAs have been shown to be well tolerated and there is some preliminary evidence for functional improvement and improvement of PH [39, 129, 130]. More evidence is required to make stronger recommendations in both children and adults with SCD-associated PH.

Future Research

Future investigations should be aimed at improving noninvasive screening guidelines to help clinicians identify children at risk for PH. Longitudinal studies are required to better define the sequelae of an elevated TRV in childhood and the potential for risk amelioration with early intervention. The impact of both SCD-directed and PH-directed therapies on preventing and treating PH in children needs to be understood to help strengthen therapy-directed recommendations.

Conclusions

The development of PH in SCD is complex and multifactorial. PH is associated with increased mortality in adults with SCD. There is significant interest in identifying children at risk of PH with the potential for early intervention and risk amelioration. This is an area of active research and many questions remain unanswered. However, some specific statements can be made based on the current literature:

1. SCD-associated PH is multifactorial in etiology and it can develop in childhood.
2. The TRV can be used to estimate the PAP, but a true diagnosis of PH can only be made by RHC.
3. The significance of an elevated TRV in childhood is still debated, but there is increasing evidence that it is associated with worse functional status (shorter 6MWT distance), and given the strong association with morbidity and mortality in adults, assessment with screening Doppler echocardiography in childhood is recommended.
4. Screening echocardiography beginning by 8 years of age is reasonable. Earlier evaluation should be considered in children with frequent cardiopulmonary symptoms. Echocardiography should be performed at steady state.
5. A TRV < 2.5 m/s indicates a low risk of PH. A value between 2.5 and 2.8 m/s is associated with an intermediate risk and consideration should be given to additional testing (NT-proBNP, 6MWT, polysomnography, oxygen assessment, pulmonary function testing). A value ≥ 2.9 m/s is associated with mild PH and RHC should be considered, especially if the TRV remains elevated on serial evaluation or if there are associated abnormalities (elevated NT-proBNP, abnormal 6MWT, frequent cardiopulmonary complications).
6. Escalation of SCD-directed therapies (HU and transfusion therapy) and reduction in pulmonary comorbidities (asthma, OSA, nocturnal hypoxia, etc.) should be considered in any child deemed at risk for PH (TRV ≥ 2.5 m/s, NT-proBNP ≥ 160 pg/mL, mPAP ≥ 25 mmHg on RHC).
7. RHC should be performed prior to initiation of targeted PH-therapy.
8. These recommendations are subject to frequent re-evaluation and modification as new evidence becomes available.

Compliance with Ethical Standards

Conflict of Interest Jamie K. Harrington and Usha S. Krishnan declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Prim . 2018;4:18010.
2. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010 ;376:2018–31.

3. Miller AC, Gladwin MT. Pulmonary Complications of Sickle Cell Disease. Am J Respir Crit Care Med. 2012;185:1154–65.
4. Gladwin MT, Sachdev V. Cardiovascular Abnormalities in Sickle Cell Disease. J Am Coll Cardiol. 2012;59:1123–33.
5. Gladwin MT. Cardiovascular complications in patients with sickle cell disease. Hematol Am Soc Hematol Educ Progr. 2017;2017: 423–30.
6. Gladwin MT. Cardiovascular complications and risk of death in sickle-cell disease. Lancet. 2016;387:2565–74.
7. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary Hypertension as a Risk Factor for Death in Patients with Sickle Cell Disease. N Engl J Med. 2004;350:886–95.
8. Gladwin MT, Barst RJ, Gibbs JSR, Hildesheim M, Sachdev V, Nouraie M, et al. Risk factors for death in 632 patients with sickle cell disease in the United States and United Kingdom. West J, editor. PLoS One. 2014;9:e99489.
9. Mehari A, Gladwin MT, Tian X, Machado RF, Kato GJ. Mortality in Adults With Sickle Cell Disease and Pulmonary Hypertension. JAMA. 2012;307:1254.
10. Mehari A, Alam S, Tian X, Cuttica MJ, Barnett CF, Miles G, et al. Hemodynamic Predictors of Mortality in Adults with Sickle Cell Disease. Am J Respir Crit Care Med. 2013;187:840–7.
11. Damy T, Bodez D, Habibi A, Guellich A, Rappeneau S, Inamo J, et al. Haematological determinants of cardiac involvement in adults with sickle cell disease†. Eur Heart J. 2015;37:1158–67.
12. Castro O, Minniti CP, Nouraie M. Pulmonary Hypertension in Sickle Cell Disease. N Engl J Med. 2011;365:1645–9.
13. McLaughlin V V., Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. J Am Coll Cardiol [Internet]. Journal of the American College of Cardiology. 2009;53:1573–619.
14. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2016;37:67–119.
15. Upadhya B, Stacey RB, Ntim W, Knovich MA, Pu M. Echocardiography-Derived Tricuspid Regurgitant Jet Velocity Is an Important Marker for the Progression of Sickle-Cell Disease. Acta Haematol. 2014;132:152–8.
16. Pashankar FD, Carbonella J, Bazzy-Asaad A, Friedman A. Prevalence and risk factors of elevated pulmonary artery pressures in children with sickle cell disease. Pediatrics. 2008;121:777–82.
17. Ambrusko SJ, Gunawardena S, Sakara A, Windsor B, Lanford L, Michelson P, et al. Elevation of tricuspid regurgitant jet velocity, a marker for pulmonary hypertension in children with sickle cell disease. Pediatr Blood Cancer. 2006;47:907–13.
18. Colombatti R, Maschietto N, Varotto E, Grison A, Grazzina N, Meneghello L, et al. Pulmonary hypertension in sickle cell disease children under 10 years of age. Br J Haematol. 2010;150:601–9.
19. Musa BM, Galadanci NA, Coker M, Bussell S, Aliyu MH. The global burden of pulmonary hypertension in sickle cell disease: a systematic review and meta-analysis. Ann Hematol. 2016;95: 1757–64.
20. Caughey MC, Poole C, Ataga KI, Hinderliter AL. Estimated pulmonary artery systolic pressure and sickle cell disease: a meta-analysis and systematic review. Br J Haematol. 2015;170:416–24.
21.•• Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric Pulmonary Hypertension: Guidelines From the American Heart Association and American Thoracic Society. Circulation. 2015;132:2037–99. **This is an executive summary from a committee of experienced clinicians from the American Heart Association and American Thoracic Society summarizing and appraising the relevant literature, and providing evidence-based recommendations for diagnosis and management of pulmonary hypertension in children, including in sickle cell disease.**
22.• Abman SH, Ivy DD, Archer SL, Wilson K, AHA/ATS Joint Guidelines for Pediatric Pulmonary Hypertension Committee. Executive Summary of the American Heart Association and American Thoracic Society Joint Guidelines for Pediatric Pulmonary Hypertension. Am J Respir Crit Care Med. 2016;194:898–906. **This is an executive summary of the longer official guidelines, reference 21, from the American Heart Association and American Thoracic Society joint committee on recommendations for diagnosis and management of pediatric pulmonary hypertension highlighting the key recommendations.**
23. Abman SH. New guidelines for managing pulmonary hypertension. Curr Opin Pediatr. 2016;28:597–606.
24. Klings ES, Machado RF, Barst RJ, Morris CR, Mubarak KK, Gordeuk VR, et al. An official American Thoracic Society clinical practice guideline: diagnosis, risk stratification, and management of pulmonary hypertension of sickle cell disease. Am J Respir Crit Care Med. 2014;189:727–40.
25. Yawn BP, Buchanan GR, Afenyi-Annan AN, Ballas SK, Hassell KL, James AH, et al. Management of Sickle Cell Disease. JAMA. 2014;312:1033.
26. Kato GJ, Steinberg MH, Gladwin MT. Intravascular hemolysis and the pathophysiology of sickle cell disease. J Clin Invest [Internet]. American Society for Clinical Investigation. 2017;127:750–60.
27. Gordeuk VR, Castro OL, Machado RF. Pathophysiology and treatment of pulmonary hypertension in sickle cell disease. Blood. 2016;127:820–8.
28. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, et al. Updated Clinical Classification of Pulmonary Hypertension. J Am Coll Cardiol. 2009;54:S43–54.
29. Hatano S, Strasser T. Primary Pulmonary Hypertension: report on a WHO meeting. Geneva: World Heal Organ.
30. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated Clinical Classification of Pulmonary Hypertension. J Am Coll Cardiol [Internet]. Journal of the American College of Cardiology. 2013;62:D34–41.
31. Rosenzweig EB, Abman SH, Adatia I, Beghetti M, Bonnet D, Haworth S, Ivy DD, Berger RMF Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management. Eur Respir J. 2019;53.
32. Graham JK, Mosunjac M, Hanzlick RL, Mosunjac M. Sickle Cell Lung Disease and Sudden Death. Am J Forensic Med Pathol. 2007;28:168–72.
33. Manci EA, Culberson DE, Yang Y-M, Gardner TM, Powell R, Haynes J, et al. Causes of death in sickle cell disease: an autopsy study. Br J Haematol. 2003;123:359–65.
34. Haque AK, Gokhale S, Rampy BA, Adegboyega P, Duarte A, Saldana MJ. Pulmonary hypertension in sickle cell hemoglobinopathy: a clinicopathologic study of 20 cases. Hum Pathol. 2002;33:1037–43.
35. Parent F, Bachir D, Inamo J, Lionnet F, Driss F, Loko G, et al. A Hemodynamic Study of Pulmonary Hypertension in Sickle Cell Disease. N Engl J Med. 2011;365:44–53.
36. Fonseca GHH, Souza R, Salemi VMC, Jardim CVP, Gualandro SFM. Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. Eur Respir J. 2012;39:112–8.
37. Gladwin MT, Machado RF. Pulmonary Hypertension in Sickle Cell Disease. N Engl J Med. 2011;365:1645–9.
38. Machado RF, Barst RJ, Yovetich NA, Hassell KL, Kato GJ, Gordeuk VR, et al. Hospitalization for pain in patients with sickle cell disease treated with sildenafil for elevated TRV and low exercise capacity. Blood. 2011;118:855–64.
39. Barst RJ, Mubarak KK, Machado RF, Ataga KI, Benza RL, Castro O, et al. Exercise capacity and haemodynamics in patients with sickle cell disease with pulmonary hypertension treated with

bosentan: results of the ASSET studies. Br J Haematol. 2010;149: 426–35.
40. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2018;53:1801913.
41. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, et al. Definitions and Diagnosis of Pulmonary Hypertension. J Am Coll Cardiol. 2013;62:D42–50.
42. Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery J-L, Barbera JA, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J Off J Eur Soc Clin Respir Physiol. 2009;34:1219–63.
43. Skinner GJ. Echocardiographic Assessment of Pulmonary Arterial Hypertension for Pediatricians and Neonatologists. Front Pediatr [Internet]. Frontiers Media SA. 2017;5:168.
44. Jone P-N, Ivy DD. Echocardiography in pediatric pulmonary hypertension. Front Pediatr [Internet]. Frontiers Media SA. 2014;2: 124.
45. Gladwin MT. Revisiting the hyperhemolysis paradigm. Blood. American Society of Hematology. 2015;126:695–6.
46. Gladwin MT, Barst RJ, Castro OL, Gordeuk VR, Hillery CA, Kato GJ, et al. Pulmonary hypertension and NO in sickle cell. Blood [Internet]. American Society of Hematology. 2010;116: 852–4.
47. Reiter CD, Wang X, Tanus-Santos JE, Hogg N, Cannon RO, Schechter AN, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. Nat Med. 2002;8:1383–9.
48. Hsu LL, Champion HC, Campbell-Lee SA, Bivalacqua TJ, Manci EA, Diwan BA, et al. Hemolysis in sickle cell mice causes pulmonary hypertension due to global impairment in nitric oxide bioavailability. Blood [Internet]. American Society of Hematology. 2007;109:3088–98.
49. Rother RP, Bell L, Hillmen P, Gladwin MT. The Clinical Sequelae of Intravascular Hemolysis and Extracellular Plasma Hemoglobin. JAMA. 2005;293:1653.
50. Ballas SK, Kesen MR, Goldberg MF, Lutty GA, Dampier C, Osunkwo I, et al. Beyond the definitions of the phenotypic complications of sickle cell disease: an update on management. ScientificWorldJournal. Hindawi Limited. 2012;2012:949535.
51. Zuckerman WA, Rosenzweig EB. Pulmonary hypertension in children with sickle cell disease. Expert Rev Respir Med. 2011;5:233–43.
52. DeMartino AW, Kim-Shapiro D, Patel RP, Gladwin MT. Nitrite and nitrate chemical biology and signaling. Br J Pharmacol. 2018.
53. Walford G, Loscalzo J. Nitric oxide in vascular biology. J Thromb Haemost. 2003;1:2112–8.
54. Morris CR, Kato GJ, Poljakovic M, Wang X, Blackwelder WC, Sachdev V, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. JAMA. 2005;294:81–90.
55. Landburg PP, Teerlink T, Biemond BJ, Brandjes DPM, Muskiet FAJ, Duits AJ, et al. Plasma asymmetric dimethylarginine concentrations in sickle cell disease are related to the hemolytic phenotype. Blood Cells, Mol Dis. 2010;44:229–32.
56. Kalra VK, Zhang S, Malik P, Tahara SM. Placenta growth factor mediated gene regulation in sickle cell disease. Blood Rev. 2018;32:61–70.
57. Bilan VP, Schneider F, Novelli EM, Kelley EE, Shiva S, Gladwin MT, et al. Experimental intravascular hemolysis induces hemodynamic and pathological pulmonary hypertension: association with accelerated purine metabolism. Pulm Circ. 2018;8: 204589401879155.
58. Conran N, Belcher JD. Inflammation in sickle cell disease. Connes P, ed. Clin Hemorheol Microcirc. 2018;68:263–99.
59. Figueiredo RT, Fernandez PL, Mourao-Sa DS, Porto BN, Dutra FF, Alves LS, et al. Characterization of heme as activator of Toll-like receptor 4. J Biol Chem [Internet]. American Society for Biochemistry and Molecular Biology. 2007;282:20221–9.
60. Dutra FF, Alves LS, Rodrigues D, Fernandez PL, de Oliveira RB, Golenbock DT, et al. Hemolysis-induced lethality involves inflammasome activation by heme. Proc Natl Acad Sci. 2014;111:E4110–8.
61. Hebbel RP, Key NS. Microparticles in sickle cell anaemia: promise and pitfalls. Br J Haematol. 2016;174:16–29.
62. Camus SM, De Moraes JA, Bonnin P, Abbyad P, Le Jeune S, Lionnet F, et al. Circulating cell membrane microparticles transfer heme to endothelial cells and trigger vasoocclusions in sickle cell disease. Blood. 2015;125:3805–14.
63. Gladwin MT, Ofori-Acquah SF. Erythroid DAMPs drive inflammation in SCD. Blood. 2014;123:3689–90.
64. Mendonça R, Silveira AAA, Conran N. Red cell DAMPs and inflammation. Inflamm Res. 2016;65:665–78.
65. Tantawy AAG, Adly AAM, Ismail EAR, Habeeb NM, Farouk A. Circulating platelet and erythrocyte microparticles in young children and adolescents with sickle cell disease: Relation to cardiovascular complications. Platelets. 2013;24:605–14.
66. Niss O, Quinn CT, Lane A, Daily J, Khoury PR, Bakeer N, et al. Cardiomyopathy With Restrictive Physiology in Sickle Cell Disease. JACC Cardiovasc Imaging. 2016;9:243–52.
67. Desai AA, Patel AR, Ahmad H, Groth J V., Thiruvoipati T, Turner K, et al. Mechanistic Insights and Characterization of Sickle Cell Disease–Associated Cardiomyopathy. Circ Cardiovasc Imaging. 2014;7:430–7.
68. Junqueira FP, Fernandes JL, Cunha GM, TA Kubo T, MAO Lima C, BP Lima D, et al. Right and left ventricular function and myocardial scarring in adult patients with sickle cell disease: a comprehensive magnetic resonance assessment of hepatic and myocardial iron overload. J Cardiovasc Magn Reson. 2013;15:83.
69. Bratis K, Kattamis A, Athanasiou K, Hautemann D, van Wijk K, Reiber H, et al. Abnormal myocardial perfusion–fibrosis pattern in sickle cell disease assessed by cardiac magnetic resonance imaging. Int J Cardiol. 2013;166:e75–6.
70. Milton JN, Rooks H, Drasar E, McCabe EL, Baldwin CT, Melista E, et al. Genetic determinants of haemolysis in sickle cell anaemia. Br J Haematol. 2013;161:270–8.
71. Steinberg MH, Sebastiani P. Genetic modifiers of sickle cell disease. Am J Hematol. 2012;87:795–803.
72. Chang AK, Ginter Summarell CC, Birdie PT, Sheehan VA. Genetic modifiers of severity in sickle cell disease. Connes P, editor. Clin Hemorheol Microcirc. 2018;68:147–64.
73. Renoux C, Joly P, Faes C, Mury P, Eglenen B, Turkay M, et al. Association between Oxidative Stress, Genetic Factors, and Clinical Severity in Children with Sickle Cell Anemia. J Pediatr. 2018;195:228–35.
74. Habara A, Steinberg MH. Minireview: Genetic basis of heterogeneity and severity in sickle cell disease. Exp Biol Med. 2016;241: 689–96.
75. Khorshied MM, Mohamed NS, Hamza RS, Ali RM, El-Ghamrawy MK. Protein Z and Endothelin-1 genetic polymorphisms in pediatric Egyptian sickle cell disease patients. J Clin Lab Anal. 2018;32:e22264.
76. Dahoui HA, Hayek MN, Nietert PJ, Arabi MT, Muwakkit SA, Saab RH, et al. Pulmonary hypertension in children and young adults with sickle cell disease: Evidence for familial clustering. Pediatr Blood Cancer. 2010;54:398–402.
77. Sokunbi OJ, Ekure EN, Temiye EO, Anyanwu R, Okoromah CAN. Pulmonary hypertension among 5 to 18 year old children with sickle cell anaemia in Nigeria. Tayo BO, editor. PLoS One. 2017;12:e0184287.

78. Al-Allawi N, Mohammad AM, Jamal S. Doppler-Defined Pulmonary Hypertension in Sickle Cell Anemia in Kurdistan, Iraq. West J, editor. PLoS One. 2016;11:e0162036.
79. Harrington JK, Krishnan U, Jin Z, Mardy C, Kobsa S, Lee MT. Longitudinal Analysis of Echocardiographic Abnormalities in Children With Sickle Cell Disease. J Pediatr Hematol Oncol. 2017;39:500–5.
80. Nelson SC, Adade BB, McDonough EA, Moquist KL, Hennessy JM. High Prevalence of Pulmonary Hypertension in Children With Sickle Cell Disease. J Pediatr Hematol Oncol. 2007;29: 334–7.
81. Sedrak A, Rao SP, Miller ST, Hekmat V, Rao M. A Prospective Appraisal of Pulmonary Hypertension in Children With Sickle Cell Disease. J Pediatr Hematol Oncol. 2009;31:97–100.
82. Onyekwere OC, Campbell A, Teshome M, Onyeagoro S, Sylvan C, Akintilo A, et al. Pulmonary Hypertension in Children and Adolescents with Sickle Cell Disease. Pediatr Cardiol. 2008;29: 309–12.
83. Minniti CP, Sable C, Campbell A, Rana S, Ensing G, Dham N, et al. Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: association with hemolysis and hemoglobin oxygen desaturation. Haematologica. 2009;94: 340–7.
84. Agha H, El Tagui M, El Ghamrawy M, Hady MA. The 6-min walk test: an independent correlate of elevated tricuspid regurgitant jet velocity in children and young adult sickle cell patients. Ann Hematol. 2014;93:1131–8.
85. Hebson C, New T, Record E, Oster M, Ehrlich A, Border W, et al. Elevated tricuspid regurgitant velocity as a marker for pulmonary hypertension in children with sickle cell disease: less prevalent and predictive than previously thought? J Pediatr Hematol Oncol. 2015;37:134–9.
86. Lee MT, Small T, Khan MA, Rosenzweig EB, Barst RJ, Brittenham GM. Doppler-defined pulmonary hypertension and the risk of death in children with sickle cell disease followed for a mean of three years. Br J Haematol. 2009;146:437–41.
87. Kato GJ, Onyekwere OC, Gladwin MT. Pulmonary hypertension in sickle cell disease: relevance to Children. Pediatr Hematol Oncol. 2007;24:159–70.
88. Nouraie M, Lee JS, Zhang Y, Kanias T, Zhao X, Xiong Z, et al. The relationship between the severity of hemolysis, clinical manifestations and risk of death in 415 patients with sickle cell anemia in the US and Europe. Haematologica. 2013;98:464–72.
89. Elalfy MS, Youssef OI, Deghedy MMR, Abdel Naby MM. Left Ventricular Structural and Functional Changes in Children With β-Thalassemia and Sickle Cell Disease. J Pediatr Hematol Oncol. 2018;40:171–7.
90. Liem RI, Nevin MA, Prestridge A, Young LT, Thompson AA. Tricuspid regurgitant jet velocity elevation and its relationship to lung function in pediatric sickle cell disease. Pediatr Pulmonol. 2009;44:281–9.
91. Mondal P, Stefek B, Sinharoy A, Sankoorikal B-J, Abu-Hasan M, Aluquin V. The association of nocturnal hypoxia and an echocardiographic measure of pulmonary hypertension in children with sickle cell disease. Pediatr Res. 2018.
92. Newaskar M, Hardy KA, Morris CR. Asthma in Sickle Cell Disease. Sci World J. 2011;11:1138–52.
93. Morris CR. Asthma management: Reinventing the wheel in sickle cell disease. Am J Hematol. 2009;84:234–41.
94. Minniti CP, Taylor JG, Hildesheim M, O'Neal P, Wilson J, Castro O, et al. Laboratory and echocardiography markers in sickle cell patients with leg ulcers. Am J Hematol. 2011;86:705–8.
95. De Castro LM, Jonassaint JC, Graham FL, Ashley-Koch A, Telen MJ. Pulmonary hypertension associated with sickle cell disease: Clinical and laboratory endpoints and disease outcomes. Am J Hematol. 2008;83:19–25.
96. Naik RP, Streiff MB, Haywood C, Nelson JA, Lanzkron S. Venous Thromboembolism in Adults with Sickle Cell Disease: A Serious and Under-recognized Complication. Am J Med. 2013;126:443–9.
97. Leveziel N, Bastuji-Garin S, Lalloum F, Querques G, Benlian P, Binaghi M, et al. Clinical and Laboratory Factors Associated With the Severity of Proliferative Sickle Cell Retinopathy in Patients With Sickle Cell Hemoglobin C (SC) and Homozygous Sickle Cell (SS) Disease. Medicine (Baltimore). 2011;90:372–8.
98. Forrest S, Kim A, Carbonella J, Pashankar F. Proteinuria is associated with elevated tricuspid regurgitant jet velocity in children with sickle cell disease. Pediatr Blood Cancer. 2012;58:937–40.
99. Lorch D, Spevack D, Little J. An Elevated Estimated Pulmonary Arterial Systolic Pressure, Whenever Measured, Is Associated with Excess Mortality in Adults with Sickle Cell Disease. Acta Haematol. 2011;125:225–9.
100. Sachdev V, Kato GJ, Gibbs JSR, Barst RJ, Machado RF, Nouraie M, et al. Echocardiographic markers of elevated pulmonary pressure and left ventricular diastolic dysfunction are associated with exercise intolerance in adults and adolescents with homozygous sickle cell anemia in the United States and United Kingdom. Circulation. 2011;124:1452–60.
101. Ataga KI, Moore CG, Jones S, Olajide O, Strayhorn D, Hinderliter A, et al. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. Br J Haematol. 2006;134:109–15.
102. Paul R, Minniti CP, Nouraie M, Luchtman-Jones L, Campbell A, Rana S, et al. Clinical correlates of acute pulmonary events in children and adolescents with sickle cell disease. Eur J Haematol. 2013;91:62–8.
103. Gordeuk VR, Minniti CP, Nouraie M, Campbell AD, Rana SR, Luchtman-Jones L, et al. Elevated tricuspid regurgitation velocity and decline in exercise capacity over 22 months of follow up in children and adolescents with sickle cell anemia. Haematologica. 2011;96:33–40.
104. Dham N, Ensing G, Minniti C, Campbell A, Arteta M, Rana S, et al. Prospective echocardiography assessment of pulmonary hypertension and its potential etiologies in children with sickle cell disease. Am J Cardiol. 2009;104:713–20.
105. Darbari DS, Onyekwere O, Nouraie M, Minniti CP, Luchtman-Jones L, Rana S, et al. Markers of Severe Vaso-Occlusive Painful Episode Frequency in Children and Adolescents with Sickle Cell Anemia. J Pediatr. 2012;160:286–90.
106. Liem RI, Young LT, Lay AS, Pelligra SA, Labotka RJ, Thompson AA. Reproducibility of tricuspid regurgitant jet velocity measurements in children and young adults with sickle cell disease undergoing screening for pulmonary hypertension. Am J Hematol. 2010;85:741–5.
107.• Kato GJ. TRV: a physiological biomarker in sickle cell disease. Pediatr Blood Cancer. 2012;58:831–2. **This is a recent article recommending a modified noninvasive echocardiogram screening protocol for children with sickle cell disease with suggested recommendations to consider invasive evaluation based on the tricuspid regurgitant jet velocity.**
108. Sachdev V, Machado RF, Shizukuda Y, Rao YN, Sidenko S, Ernst I, et al. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. J Am Coll Cardiol. 2007;49:472–9.
109. Lilje C, Harry J, Gajewski KK, Gardner R V. A modified noninvasive screening protocol for pulmonary hypertension in children with sickle cell disease-Who should be sent for invasive evaluation? Pediatr Blood Cancer. 2017;64:e26606.
110. van der Land V, Peters M, Biemond BJ, Heijboer H, Harteveld CL, Fijnvandraat K. Markers of endothelial dysfunction differ between subphenotypes in children with sickle cell disease. Thromb Res. 2013;132:712–7.

111. El-Shanshory M, Badraia I, Donia A, Abd El-hameed F, Mabrouk M. Asymmetric dimethylarginine levels in children with sickle cell disease and its correlation to tricuspid regurgitant jet velocity. Eur J Haematol. 2013;91:55–61.
112. Elbarbary NS, Ismail EAR, Roushdy A, Fahmy E. Serum apelin as a novel non-invasive marker for subclinical cardiopulmonary complications in children and adolescents with sickle cell disease. Blood Cells, Mol Dis. 2016;57:1–7.
113. Machado RF, Anthi A, Steinberg MH, Bonds D, Sachdev V, Kato GJ, et al. N-Terminal Pro-Brain Natriuretic Peptide Levels and Risk of Death in Sickle Cell Disease. JAMA. 2006;296:310.
114. Voskaridou E, Tsetsos G, Tsoutsias A, Spyropoulou E, Christoulas D, Terpos E. Pulmonary hypertension in patients with sickle cell/beta thalassemia: incidence and correlation with serum N-terminal pro-brain natriuretic peptide concentrations. Haematologica. 2007;92:738–43.
115. Mokhtar GM, Adly AAM, Alfy MS El, Tawfik LM, Khairy AT. N-Terminal Natriuretic Peptide and Ventilation-Perfusion Lung Scan in Sickle Cell Disease and Thalassemia Patients with Pulmonary Hypertension. Hemoglobin. 2010;34:78–94.
116. Tantawy AAG, Adly AAM, Ismail EAR. Soluble CD163 in young sickle cell disease patients and their trait siblings. Blood Coagul Fibrinolysis. 2012;23:640–8.
117. Adly AA, Ismail EA, Andrawes NG, Mahmoud MM, Eladawy R. Soluble Fas/FasL ratio as a marker of vasculopathy in children and adolescents with sickle cell disease. Cytokine. 2016;79:52–8.
118. Saleemi S. Saudi Guidelines on the Diagnosis and Treatment of Pulmonary Hypertension: Pulmonary hypertension associated with hemolytic anemia. Ann Thorac Med. 2014;9:67.
119. Almeida CB, Souza LEB, Leonardo FC, Costa FTM, Werneck CC, Covas DT, et al. Acute hemolytic vascular inflammatory processes are prevented by nitric oxide replacement or a single dose of hydroxyurea. Blood. 2015;126:711–20.
120. Olnes M, Chi A, Haney C, May R, Minniti C, Taylor J, et al. Improvement in hemolysis and pulmonary arterial systolic pressure in adult patients with sickle cell disease during treatment with hydroxyurea. Am J Hematol [Internet]. NIH Public Access. 2009;84:530–2.
121. Gordeuk VR, Campbell A, Rana S, Nouraie M, Niu X, Minniti CP, et al. Relationship of erythropoietin, fetal hemoglobin, and hydroxyurea treatment to tricuspid regurgitation velocity in children with sickle cell disease. Blood. 2009;114:4639–44.
122. Detterich JA, Kato RM, Rabai M, Meiselman HJ, Coates TD, Wood JC. Chronic transfusion therapy improves but does not normalize systemic and pulmonary vasculopathy in sickle cell disease. Blood. 2015;126:703–10.
123. Covi S, Ravindranath Y, Farooqi A, Savasan S, Chu R, Aggarwal S. Changes in Bi-ventricular Function After Hematopoietic Stem Cell Transplant as Assessed by Speckle Tracking Echocardiography. Pediatr Cardiol. 2018;39:365–74.
124. Dallas MH, Triplett B, Shook DR, Hartford C, Srinivasan A, Laver J, et al. Long-term outcome and evaluation of organ function in pediatric patients undergoing haploidentical and matched related hematopoietic cell transplantation for sickle cell disease. Biol Blood Marrow Transplant. 2013;19:820–30.
125. Quimby KR, Hambleton IR, Landis RC. Intravenous infusion of haptoglobin for the prevention of adverse clinical outcome in Sickle Cell Disease. Med Hypotheses. 2015;85:424–32.
126. Schaer CA, Deuel JW, Schildknecht D, Mahmoudi L, Garcia-Rubio I, Owczarek C, et al. Haptoglobin Preserves Vascular Nitric Oxide Signaling during Hemolysis. Am J Respir Crit Care Med. 2016;193:1111–22.
127. Baek JH, D'Agnillo F, Vallelian F, Pereira CP, Williams MC, Jia Y, et al. Hemoglobin-driven pathophysiology is an in vivo consequence of the red blood cell storage lesion that can be attenuated in guinea pigs by haptoglobin therapy. J Clin Invest. 2012;122:1444–58.
128. Haw A, Palevsky HI. Pulmonary hypertension in chronic hemolytic anemias: Pathophysiology and treatment. Respir Med. 2018;137:191–200.
129. Minniti CP, Machado RF, Coles WA, Sachdev V, Gladwin MT, Kato GJ. Endothelin receptor antagonists for pulmonary hypertension in adult patients with sickle cell disease. Br J Haematol. 2009;147:737–43.
130. Sabaa N, de Franceschi L, Bonnin P, Castier Y, Malpeli G, Debbabi H, et al. Endothelin receptor antagonism prevents hypoxia-induced mortality and morbidity in a mouse model of sickle-cell disease. J Clin Invest. 2008;118:1924–33.