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Pulmonary complications of sickle cell disease: a narrative clinical review

Abstract

Sickle cell disease (SCD) is associated with vaso-occlusive episodes that affect different organs. Pulmonary involvement is a major cause of morbidity and mortality in this patient population.

We performed a literature search in the PubMed database for articles addressing SCD and pulmonary diseases. Acute chest syndrome is defined as a new radiodensity on chest radiograph imaging with a history consistent of the disease. Management includes broad spectrum antibiotics, pain control, and blood transfusions. Microvasculature infarcts lead to functional asplenia, which in turn increases the risk of being infected with encapsulated organisms. Universal vaccinations and antibiotic prophylaxis play a significant role in decreasing mortality from pulmonary infections. Venous thromboembolism in patients with SCD should be treated in the same manner as in the general population. Pulmonary hypertension in patients with SCD also increases mortality. The American Thoracic Society treatment modalities are based on the underlying etiology which is either directed at treating SCD itself, using vasodilator medications if the patient is in group 1, or using long-term anticoagulation if the patient is group 4 (in terms of etiology). Patients with SCD are more likely to suffer from asthma in comparison to controls. Sleep disorders of breathing should be considered in patients with unexplained nocturnal and daytime hypoxemia, or recurrent vaso-occlusive events. Lastly, the utility of pulmonary function tests still needs to be established.

Key words: sickle cell disease, acute chest syndrome, pneumonia, venous thromboembolic disease, pulmonary hypertension

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Introduction

Sickle cell disease (SCD) is one of the most common monogenetic disorders in the world affecting nearly 300 million people worldwide. It is estimated that approximately 100,000 people in the United States have the disease, with a higher prevalence amongst African Americans [1, 2]. The sickle point mutation is a substitution of valine for glutamic acid at the sixth position of the β-hemoglobin gene resulting in sickled hemoglobin (HbS) that is less soluble than normal adult and fetal hemoglobin. Upon deoxygenation, HbS undergoes polymerization resulting in a decreased flexibility of the erythrocyte forming the infamous "sickled" shaped. These changes alter cellular rheological properties, enhance adhesion molecule expression, impair microvasculature blood flow, and promote hemolysis and vaso-occlusive episodes [3].

When the sickle mutation is co-inherited with a mutation at the other β-globin allele, then the production of normal beta-globin becomes obsolete or, at the very least, reduced. The majority of infants with sickle cell disease (60–65%) are diagnosed as having homozygous sickle mutations (HbSS). The second most common affliction is when a patient inherits hemoglobin S and hemoglobin C (HbSC disease), and this is seen in 25–30% of patients. Lastly, there is sickle beta thalassemia with a sickle mutation and a β thalassemia mutation (HbSβ0/+) affecting 9% of patients. People with HbSS and HbSβ0 thalassemia have a more severe disease course in contrast to those with HbSC and HbSβ+ thalassemia [3].

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Sickle cell chronic lung disease was the term used to describe pulmonary complications of SCD; however, advances in this field demonstrate that there are different entities of pulmonary conditions with characteristic pathophysiological changes, clinical manifestations, and outcomes. It is discouraged to use the term 'sickle cell chronic lung disease' and efforts should be made to identify the specific phenotype of pulmonary disease in this patient population. This article will describe these conditions which include acute chest syndrome (ACS), pulmonary infections, venous thromboembolism (VTE), and pulmonary hypertension. This article will also review asthma and sleep disorders of breathing in patients with SCD. Lastly, this article will review the abnormal pulmonary function tests seen in SCD. The Pubmed database was used to obtain the relevant references. The database was searched using the keywords 'SCD' and 'pulmonary disease'. English language articles that were deemed relevant by the consensus of authors were reviewed. These articles included original observations, review articles, meta-analyses, and guidelines. When appropriate, references in the bibliography of these articles were also reviewed.

Acute chest syndrome

Acute chest syndrome (ACS) is a severe complication of SCD defined most simply as a new radiodensity on chest radiograph imaging coupled with respiratory symptoms. In fact, in a Jamaican study by Thomas *et al*. [4], they cited ACS as the principal cause of death after 10 years of age in patients with SCD. According to the Cooperative Study of Sickle Cell Disease by Castro *et al*. [5], of the 3751 patients they followed over a decade, approximately 29% (1085 patients) were prospectively witnessed to suffer at least a single episode of ACS [5]. They also found that patients with severe genotypes of the disease (HbSS disease and HbSβ0) were at greater risk of developing ACS when compared to those with milder genotypes (HbSC disease and HbSβ+ thalassemia). Other risk factors include older age, increased white blood cell count, higher hemoglobin levels, lower fetal hemoglobin, and smoking prior to vaso-occlusive pain events.

Pathogenesis

The exact cause of ACS remains unclear in most cases. Vichinsky *et al*. [6] initiated a prospective, multicenter study to explore the causes of ACS. A specific initiating agent was identified in 38% of episodes studied. The etiologies were fat embolism, infection (ranked from most to least common: chlamydia, mycoplasma, viral, bacterial, mixed infection, and legionella), and pulmonary infarct (Figure 1). However, approximately 46% of the cases were found to have no known etiology. Specifically, regarding the pathogenesis of fat emboli, it is believed that bone marrow infarcts, which have been noted in patients with SCD post-mortem secondary to veno-occlusion, lead to bone marrow necrosis and the release of bone marrow fat into the venous circula-

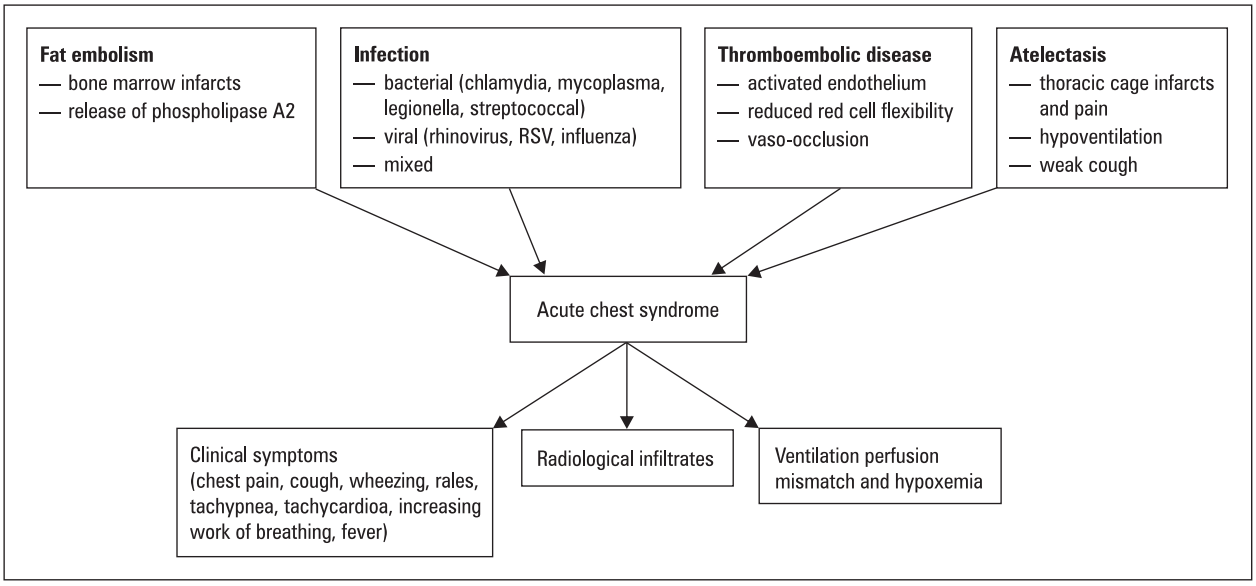

Figure 1. Pathogenesis of acute chest syndrome. PH — pulmonary hypertension; mPAP — mean pulmonary arterial pressure; PAWP — pulmonary artery wedge pressure; PVR — pulmonary vascular resistance; WU — woods unit

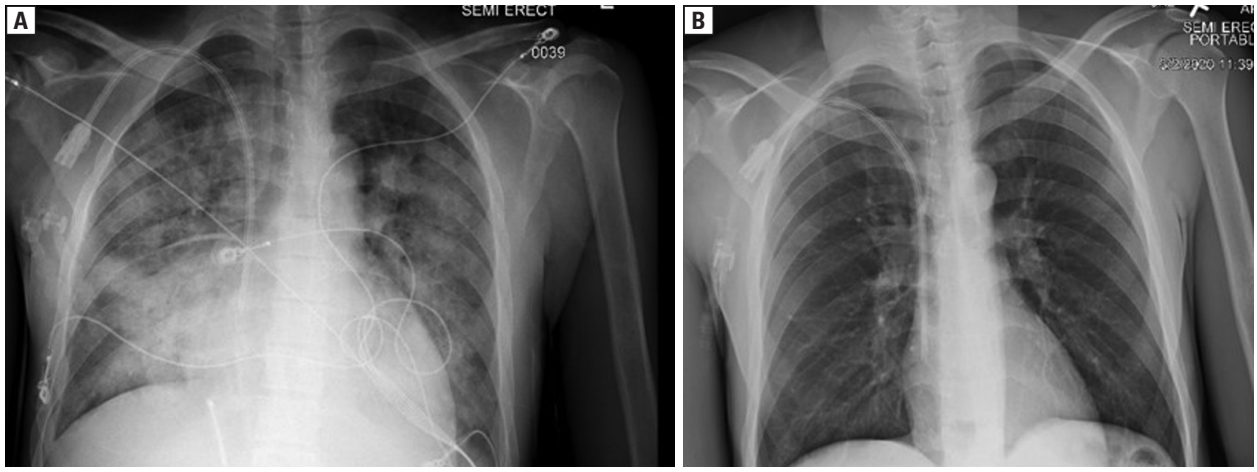

Figure 2. Chest radiograph of a patient during a severe attack of acute chest syndrome (**A**) and after resolution of the episode (**B**)

tion. Secretory phospholipase A2 then converts the neutral fat into free fatty acids, which are highly pro-inflammatory and further propagate tissue injury [7]. This lung injury then precipitates a vicious cycle which results in worsening ventilation-perfusion mismatch and worsening hypoxemia. This hypoxemia then causes HbS deoxygenation, which causes HbS polymerization resulting in decreased erythrocyte flexibility and, in turn, increased vaso-occlusive events. This, again, precipitates more bone marrow infarctions and restarts the vicious cycle.

Clinical presentation

ACS is defined as a new radiodensity on chest radiograph imaging (Figure 2) with at least one of the following clinical findings: fever (≥ 38.5ºC), hypoxia [≥ 3% decrease in oxygen saturation from baseline or oxygen saturation (SpO_2) < 94%], chest pain/discomfort, cough, wheezing, rales, tachypnea, tachycardia, or an increased work of breathing [8]. The severity of ACS has been categorized as: mild, moderate, severe, and very severe (Table 1) [9].

Interestingly, ACS was found to have significant differences in presentation, etiology, and clinical course when comparing adults (≥ 20 years old) to children (< 20 years old). In Vichinsky *et al*.'s study of the National Acute Chest Syndrome Study Group, it was noted that adults were more likely to present with chest pain (55% *vs* 41%), rib/sternal pain (30% *vs* 18%), and shortness of breath (58% *vs* 36%) than children [6]. Multiple other studies found that bone marrow and fat emboli were more common in adults than in children [5, 7], and this is believed to be the reason why adults have worse disease severity (i.e. adults required higher rates of mechanical ventilation (22% *vs* 10%) and higher mortality rates (9% *vs* 1%) when compared to children [6].

Differential diagnosis

ACS can be clinically difficult, if not impossible, to differentiate from an acute pulmonary infection as they both have similar clinical and radiological presentations and may in fact occur simultaneously. Treating all ACS cases as purely infective episodes may lead to progression of the disease and rapid clinical deterioration of the patient as other etiologies such as pulmonary embolism, iatrogenic fluid overload, transfusion related lung injury, opiate narcosis, alveolar hypoventilation, and acute coronary syndrome are overlooked [8].

Diagnostic tests

The diagnosis of ACS can be straightforward when a high level of clinical suspicion is combined with the aforementioned clinical features. The following investigations are essential for all patients presenting with a suspicion of ACS: chest radiograph (most pertinent) (Fig. 2), complete blood count with differential, basic metabolic panel, liver function tests, blood group and screen/crossmatch, blood cultures, arterial blood gas (preferably on room air), respiratory cultures/serology (including atypical respiratory organisms), urine pneumococcal and legionella antigen, and nasopharyngeal aspirate for immunofluorescence or polymerase chain reaction for viruses in patients with coryzal symptoms. It is important to note that computed tomography is not routinely recommended due to high radiation exposure and the tendency of ACS to recur. In addition, there is limited added benefit over chest

Table 1. Severity index of ACS9

Mild*	$tcpO_2$ > 90% on room air CXR showing segmental or lobar infiltrates involving no more than 1 lobe Response to simple transfusion ≤ 2 units of RBC (or 15 cc/kg)
Moderate*	$tcpO_2$ > 85% on room air CXR showing segmental or lobar infiltrates involving no more than 2 lobes Response to simple transfusion ≥ 3 units of RBC (or more than 20 cc/kg)
Severe‡	Respiratory failure (PaO_2 < 60 mm Hg or PCO_2 > 50 mm Hg) Requiring mechanical ventilation $tcpO_2$ < 85% on room air or ≤ 90% despite FiO_2 of 100% CXR showing segmental or lobar infiltrates involving 3 or more lobes Requiring transfusion or exchange transfusion of RBCs to a goal hemoglobin A ≥ 70%
Very severe	Once ARDS is diagnosed. ARDS is defined as: — Acute onset of bilateral infiltrates on CXR — PAWP < 19 mm Hg or lack of clinical evidence of left atrial hypertension — PaO_2/FiO_2 ≤ 200 regardless of PEEP level

*Categories must meet the previously discussed diagnostic criteria above AND all of the following; ‡Must meet the previously discussed diagnostic criteria above AND 1 or more of the following; $tcpO_2$: transcutaneous oxygen saturation. CXR — chest radiograph; RBC — red blood cells; PaO_2 — partial pressure of oxygen; PCO_2 — partial pressure of carbon dioxide; FiO_2 — fraction of inspired oxygen; ARDS — acute respiratory distress syndrome; PAWP — pulmonary artery wedge pressure; PEEP — positive end expiratory pressure

radiography. The only indication for computed tomography is with the addition of pulmonary angiography if there is a high clinical suspicion of pulmonary embolism. Ventilation perfusion (V/Q) scans are also not recommended as they usually reveal diffuse perfusion defects with normal ventilation and can be easily confused with other pulmonary pathologies [8].

Other tests that have been considered include measuring plasma secretory phospholipase A2 (sPLA2) levels and administering bronchoalveolar lavage for lipid laden macrophages via oil red O staining. The enzyme sPLA2 is found in the plasma and it releases inflammatory free fatty acids from bone marrow lipids. Since fat emboli have been noted as a common etiology of ACS, it was previously suggested that measurement of its levels might be useful in the diagnosis of ACS. However, despite its high sensitivity of 100%, its low specificity of 67% and even lower positive predictive value of only 24% makes the test rather weak [10]. Also, bronchoalveolar lavage used to evaluate for lipid laden macrophages via oil red O staining has been proposed for similar reasons as mentioned above [11]; however, the complications of bronchoscopy, including hypoxia and need for mechanical ventilation, outweigh the added benefit. Neither of these tests have sufficient evidence at this point for them to be recommended for routine testing.

Management

The cornerstones for management of ACS include broad-spectrum antibiotics, pain control, and blood transfusion(s) (simple and/or exchange). Firstly, all patients with a diagnosis of ACS should be started on empiric antibiotic therapy with coverage for atypical bacterial organisms as infection is one of the major inciting causes. The antibiotic regimen should then be de-escalated based on culture results. Adequate pain control is pivotal. Usually parenteral opioids are given in the form of patient-controlled analgesia (preferred administration method), which usually avoids over-sedation and minimizes opioid-induced hypoventilation. The mainstay of acute treatment is transfusion therapy. The decision between simple or exchange transfusion is usually dependent on the severity of the episode. The process of exchange transfusion involves phlebotomy to slowly remove the patient's blood followed by replacing it with allogeneic blood, therefore diluting the amount of HbS. It is the preferred modality over simple transfusions. The ability to rapidly give large amounts of blood in order to reduce HbS percentage without increasing the blood viscosity (usually seen at Hb > 11 g/dL) is significantly advantageous; however, it does require trained personnel and equipment which is not readily available at all centers. The general practice is to intervene in cases of mild or developing ACS with a simple transfusion to raise hemoglobin up to 10 g/dL. It has been noted that with early therapy, many episodes of moderate to severe ACS can be avoided. Exchange transfusions are typically reserved for those who show features of severe disease with recurrent vaso-occlusive crises, for those who do not respond

to simple transfusions, or for those with a higher baseline total hemoglobin S concentration [9, 12–14].

In addition to the above therapies, use of supplemental oxygen, incentive spirometry, and intravenous hydration are also pertinent. Patients suffering from ACS can have a low oxygen saturation or a low partial pressure of oxygen and should therefore be provided with supplemental oxygen to avoid hypoxemia, which could propagate ACS. Incentive spirometry decreases the risk of ACS by reducing hypoventilation and atelectasis in patients with bone pain [15]. Incentive spirometry should be encouraged with 10 maximal breaths every two hours while awake to prevent ACS during vaso-occlusive pain episodes. Intravenous hydration is also paramount as individuals with SCD frequently are hypovolemic during pain episodes secondary to poor oral intake and ongoing insensible losses; however, it is prudent to balance volume status to avoid fluid overload and pulmonary edema, which would worsen ACS.

Clinicians should also consider using bronchodilators and venous thromboembolic (VTE) prophylaxis. Bronchodilators are recommended due to the prevalence of wheezing and airway hyperresponsiveness in patients with SCD, but their efficacy has not been appropriately tested in any randomized controlled trials [6]. Patients with ACS are predisposed to VTE events and must receive adequate prophylaxis with unfractionated heparin, low-molecular-weight heparin, or fondaparinux. Systemic steroids have been used previously; however, they are no longer part of standard practice. Previous studies have shown an emergence of rebound vaso-occlusive phenomena after the discontinuation of steroids in children [16].

Prevention

Hydroxyurea has been shown to decrease the incidence of ACS. All patients with a history of ACS with absent absolute contraindications should be started on hydroxyurea [17]. Current practice is to titrate up to a dose of 30 mg/kg or an absolute neutrophil count of 2000/uL. Chronic transfusion therapy is another option. Current practice is to initiate chronic transfusion therapy in patients who have experienced 2 or more moderate to severe episodes of ACS. These transfusions are usually performed every 4–6 weeks with the goal being to maintain a HbS percentage < 50%. Lastly, hematopoietic stem cell transplantation has been proposed as it is a curative option; however, it is not a standard of practice in adults due to the toxicity associated with the myeloablative regimen. Nonetheless, it can be considered in select patients with severe disease who may benefit from the therapy [18].

Pulmonary infections in sickle cell disease

Patients with SCD are at increased risk of infections due to abnormalities in host defenses secondary to functional asplenia. Specifically, they are at increased risk of infection by encapsulated organisms. Pulmonary infections have also been cited as a major etiology of ACS. Despite increased availability of pneumococcal and H influenza vaccines, and the general use of penicillin prophylaxis in children and older adults, patients with SCD are still at risk for invasive infections secondary to pneumococcus and other organisms.

Pathophysiology

SCD patients are prone to infections for a wide variety of reasons. These include splenic dysfunction, defective opsonization, impairment of adaptive immunity, and immunodeficiency. Together, these are likely play a strong role in the higher incidence of pulmonary infections in this patient population [19].

The spleen is a multifunctional organ which plays an important role in the filtration of pathogens and damaged cells, and also aids in the production of antibodies required for adaptive immunity [20]. The spleen plays an important role in the synthesis of tuftsin and properdin that participate in complement activation. Blood flows through the splenic artery and traverses the white pulp (which is composed of lymphocytes) before entering the splenic cords of red pulp to ultimately reach the venous sinuses for removal of defective red blood cells (RBCs), bacteria, and splenic macrophages.

Patients with SCD are functionally asplenic by the age of 3–5 years secondary to ischemia from chronic vascular occlusion and increased blood viscosity from sickling of red blood cells. This results in auto-infarction of the spleen thus increasing the risk of infection by encapsulated organisms such as Streptococcus pneumoniae and *H. influenzae* via the pathophysiology described above [20, 21].

Opsonization refers to the process involving binding of specific antimicrobial proteins called opsonins to the pathogens to enhance the efficiency of phagocytosis. Opsonized bacteria are filtered by both the spleen and the liver; however, poorly opsonized bacteria are only filtered by the

spleen [19]. Splenic opsonization is impaired due to an insufficient availability of splenic immunoglobulins and impaired production of opsonins.

Impairment of B- and T-lymphocyte function results in inadequate memory B-cell function and anti-polysaccharide antibody production [19, 22–24]. There is a diminished humoral response and cell-mediated response in patients with SCD attributed to reduced circulating CD4+ and CD8+ T-lymphocytes. The IgM response after administration of the influenza vaccine is also suboptimal in SCD patients [24].

Infection and acute chest syndrome

One of the major etiologies of the development of ACS is from an acute pulmonary infection. In fact, in Vinchinsky's national acute chest syndrome study group, they identified that 38% of patients with ACS who underwent infectious work-up were found to have a specific infectious organism [6]. In children under the age of 10 years, viral infections were the most common identifiable etiology. In adults, however, atypical bacterial organisms were more commonly identified. *Chlamydia pneumoniae* was the most common, followed by *Mycoplasma pneumoniae*, and then Respiratory Syncytial Virus. It was also reported that these organisms were more commonly linked with ACS than encapsulated organisms such as *Streptococcus pneumoniae* and *H. Influenzae* [6, 8, 25].

Antimicrobials

Due to functional asplenia, patients with SCD are more susceptible to infection with encapsulated organisms than the general population. In addition, if associated with ACS, they are at a higher likelihood of being infected by multiple atypical organisms. Therefore, it is prudent for antibiotic combinations to cover for typical and atypical causes of pneumonia [26]. Clinicians should consider their local biogram and local antibiotic resistance profiles when considering empiric antibiotic therapy. Antibiotics should also be tailored once an appropriate culture and/or sensitivity has been attained.

Prevention

As with all individuals, patients with SCD should be emphasized to practice meticulous hand-washing techniques to protect from typical spread of infections. Also, patients should seek medical attention early if they develop a fever or respiratory symptoms, especially if accompanied by chest pain [21]. However, the two major changes that decreased mortality in patients with SCD were: 1) initiation of antibiotic prophylaxis, and 2) vaccinations [27].

In 1986 and 1995, two groundbreaking studies called the PROPS (Penicillin Prophylaxis in Sickle Cell Disease) and the PROPS-II trial, respectively, showed that prophylactic oral penicillin significantly reduced the risk of invasive pneumococcal infections in children [28, 29] and that penicillin prophylaxis could be safely discontinued at 5 years of age [30]. Also, adherence to lifelong prophylaxis has been called into question further supporting discontinuation of prophylaxis at the age of 5 [31]. In patients with a confirmed penicillin allergy, a macrolide may be used instead [32]. The initiation of a vaccination schedule has also been paramount in decreasing the rate of preventable infections in patients both with and without SCD. The following vaccine series are crucial in preventing pulmonary infections in patients with SCD: pneumococcal conjugate vaccine (PCV13), pneumococcal polysaccharide vaccine (PPSV23), Haemophilus influenza type b (Hib) vaccine, and the seasonal influenza vaccine.

Venous thromboembolism

Venous thromboembolism (VTE) is a significant cause of morbidity and mortality in patients with SCD. Patients with SCD are also at an increased risk to suffer from VTE than the general population. The etiology is multifactorial and relates to both increased traditional risk factors and SCD-specific risk factors. Traditional risk factors that increase the risk of VTE are seen in the general population but are more frequent in patients with SCD due to disease complications such as frequent hospitalizations (some requiring central venous catheter placement), and orthopedic surgeries for avascular necrosis. SCD also has disease specific risk factors such as thrombophilic defects and splenectomy which may modify the risk of VTE. VTE may also increase SCD complications such as acute chest syndrome and pulmonary hypertension [33].

Pathophysiology

All three aspects of Virchow's triad (hypercoagulability, endothelial dysfunction, and hemostasis) have been associated with SCD and result in a highly thrombogenic environment leading to VTE.

The alterations in sickled RBC structure lead to intravascular hemolysis and externalization of

highly procoagulant phosphatidylserines on the RBC membrane. These sickled RBC's become more adhesive to the endothelium. The capture of adhesive red cells, leukocytes, and platelets to the endothelium of the blood vessel wall triggers the vaso-occlusion [34–36]. The endothelial cells and leukocytes also activate proinflammatory molecules such as tumor necrosis factor and interleukin-1b, chemokines, growth factors, eicosanoids, and peptides, all of which can further stimulate cells and induce expression of surface adhesion molecules leading to the continuation of the vicious cycle.

There is extensive laboratory and clinical evidence in literature to safely say that SCD is a condition in which the hemostatic balance is tipped to the prothrombotic state. There are studies showing dysregulation of factors causing the initiation and perpetuation of hemostasis activation. These include studies showing decreased levels of natural anticoagulants such as protein C and protein S [37, 38]. increased expression and/or activity of tissue factor (TF) in whole blood, increased monocytes and circulating endothelial cells, increased levels of von Willebrand factor (vWF) coupled with decreased levels of ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), increased numbers of TF- and phosphatidylserine-bearing microparticles [39, 40] decreased levels of contact pathway factors (factor XII, prekallikrein, and high molecular weight kininogen), and increased markers of neutrophil extracellular trap (NET) formation.

Platelet activation plays a major role in vascular inflammation and thrombosis. A large body of literature suggests that circulating platelets are activated in SCD patients in a steady state as well as in acute painful crises. The following mechanisms are involved in the platelet activation:

The ruptured RBCs release the cell free hemoglobin which reacts with the vascular nitric oxide (NO) leading to vasoconstriction and platelet activation. In addition to the platelet activation by NO depletion, there is ongoing platelet activation in SCD patients evidenced by the increased expression of P-selectin on circulating platelets, plasma soluble factors 3 and 4, β-thromboglobulin, and platelet-derived soluble CD40 ligand [41].

Literature shows that platelets express the pattern recognition receptor nucleotide-binding domain leucine-rich repeat containing protein 3 (NLRP3), apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (CARD), and Bruton tyrosine kinase (BTK), which together control activation of caspase-1 and cleavage of interleukin-1b (IL-1b) within inflammasome complexes. The activation of the NLRP3 inflammasome in platelets promotes platelet aggregation, thrombus formation, and vascular leakage, and can be targeted by BTK inhibitors. The damage-associated molecular pattern molecule high-mobility group box 1 (HMGB1) is a regulatory trigger of the NLRP3 inflammasome16; it stimulates thrombosis and inflammation when released by the activated platelets. The NLRP3 inflammasome in platelets is upregulated in SCD via high-mobility group box protein and toll-like receptor 4 (HMGB1/TLR4) [42].

There is evidence in the literature that bioenergetic dysfunction mechanically contributes to SCD-induced platelet activation. This evidence was found by directly examining mitochondrial function in SCD patients. The bioenergetic alteration is induced by free hemoglobin and is characterized by inhibited complex V activity which leads to augmented oxidant generation. This bioenergetic dysfunction is associated with enhanced platelet activation in vivo. Further, partial inhibition of complex V in healthy platelets in vitro recapitulates the bioenergetic dysfunction observed in SCD patients and results in platelet activation. This proves that a causal relationship is established between this bioenergetic alteration and platelet activation [43].

Diagnosis

In the general population, a D-dimer test is very useful in guiding the diagnosis of VTE due to its high negative predictive value when adjusted for age. Unfortunately, due to the pathophysiology of SCD and the chronic activation of the coagulation cascade, the D-dimer test is unreliable. In addition, some may track the D-dimer to decide whether anticoagulation should be extended; however, due to vasocclusive episodes in SCD, tracking the D-dimer can be deceptive and difficult [44]. Current guidelines recommend starting with a compression ultrasound Doppler for patients with SCD who are suspected of having either upper or lower-extremity DVTs. At this time, there are no studies showing any differences between ultrasound interpretation in patients with SCD from the general population.

If pulmonary embolism is suspected, computerized tomographic pulmonary angiography (CTPA) is currently the test of choice. However, there are current debates whether radionuclide scans (i.e. ventilation-perfusion [V/Q] studies) can be practically advantageous over CTPAs. Specifi-

cally, they minimize radiational exposure and they have no risk of contrast-induced kidney injury. This is particularly important for patients who undergo frequent testing. However, there have been no head-to-head studies comparing CTPA to V/Q studies in patients with SCD at this time [44].

Treatment

There are no current studies or recommendations stating that VTE in patients with SCD should be treated differently from the general population. Antithrombotic therapy guidelines, as per the most recent CHEST guidelines of 2016, state that patients with a proximal DVT or pulmonary embolism should receive a minimum of 3 months of anticoagulation. They also recommend that, in patients with DVT of the leg or pulmonary embolism who do not have cancer, dabigatran, rivaroxaban, apixaban, and edoxaban are preferred over vitamin K antagonist therapy. The duration of therapy can be altered for several reasons including: resolution of the VTE on imaging, bleeding risk, provoked or unprovoked etiology, or if the VTE is recurrent [45]. However, due to the paucity of data, further studies are needed to establish a formalized approach to anticoagulation therapy for first-time VTE in patients with SCD [46].

Pulmonary hypertension

Pulmonary hypertension (PH) is quite prevalent in patients with SCD afflicting approximately 6% to 10.5% of patients based on right heart catheterization [47–49]. There are five different groups of PH: 1) pulmonary arterial hypertension, 2) PH due to left heart disease, 3) PH due to chronic lung disease/hypoxia, 4) PH due to chronic pulmonary thromboembolisms, and 5) PH due to unclear multifactorial mechanisms. PH related to SCD is currently in group 5 as some patients show hemodynamic changes consistent with group 1, while others have features of group 2 or group 4 PH [50, 51].

Pathophysiology

Half of the reported cases of pulmonary hypertension in SCD have precapillary pulmonary hypertension on right heart catheterization, and the other half have postcapillary pulmonary hypertension.

The pathogenesis of precapillary pulmonary hypertension in SCD is well documented in literature and involves the activation of inflammatory and cytokine pathways. A number of factors are involved in the activation of these pathways with abnormal nitric oxide (NO) signaling being the major contributor [52, 53].

Chronic intravascular hemolysis plays a key role in inhibiting NO signaling and impairing vascular endothelial function. Intravascular hemolysis causes the release of cell free hemoglobin, red blood cell microparticles containing hemoglobin, and heme and arginase-1 in the plasma, which in turn inhibit NO signaling. Cell free hemoglobin reacts with NO to form nitrate, and arginase-1 inhibits arginine by breaking it down to ornithine, which is the substrate for NO synthases and further inhibits NO signaling.

Elevated plasma levels of asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, are an independent risk factor for endothelial dysfunction. Furthermore, heme from the hemoglobin molecule in the plasma causes activation of LTR4 and NALP inflammasome pathways and stimulates the systemic and vascular inflammatory response.

Chronic hemolysis also causes platelet and hemostatic activation, generates reactive oxygen species, and activates vascular oxidases which causes an increased oxidant-derived metabolism of NO. As a result, its decreased bioavailability causes it to act as a vasodilator. There is evidence in the literature to support the association of increased levels of markers of hemolysis, including cell free hemoglobin and red blood cell microparticles, with elevated systolic pulmonary artery pressure and precapillary pulmonary hypertension on right heart catheterization [48, 54, 55].

Although hemolysis is thought to play a main role in the pathogenesis of precapillary pulmonary HTN in SCD, it is likely that other factors such as the impact of local hypoxia on vascular remodeling, genetic variability, and thrombosis contribute to this pathogenesis as well.

Chronic hypoxia is a well-recognized cause of pulmonary hypertension because it stimulates various cellular and metabolic processes. There is upregulation of hypoxic responses in SCD via elevated erythropoietin levels. Tissue hypoxia in SCD causes increased expression of the erythropoietin gene resulting in high concentrations of circulating erythropoietin and hypoxia inducible factor (HIF)-α, the major regulator of the body's response to hypoxia [56]. The activation of HIF-1α contributes to the etiology of various forms of pulmonary hypertension through changes in mitochondrial redox signaling, fission, and numbers, and leads to the development of a proliferative, apoptosis-resistant phenotype in pulmonary vascular cells [34,

35]. Furthermore, the elevated levels of placental growth factor in SCD activates HIF-1α in normoxia and has been associated with elevated systolic pulmonary artery pressures in SCD.

Chronic thromboembolic pulmonary hypertension (CTEPH) is a major category of pulmonary hypertension in SCD secondary to the increased predilection for chronic VTE in patients with SCD. Establishing the diagnosis of CTEPH as an etiology of pulmonary hypertension in SCD is imperative in order to offer curative treatment (i.e pulmonary endarterectomy for proximal lesions versus medical therapy for distal lesions).

The pathophysiology of CTEPH is the same as discussed under the VTE section and includes platelet and hemostatic activation pathways via hemolysis and chronic inflammation contributing to the hypercoagulable state. Auto-splenectomy is a well-known risk factor for thrombosis and CTEPH and is commonly seen in patients with hemoglobin SS disease [36]. In one case series which studied 11 SCD patients, acute or organizing thrombi in the distal pulmonary arteries were a common finding [37].

As mentioned earlier, postcapillary pulmonary hypertension comprises almost half of the cases of pulmonary HTN in SCD patients. Chronic anemia and systemic hypertension are common in patients with SCD. This leads to left ventricular diastolic dysfunction from left ventricular dilatation and concentric hypertrophy of the myocardium eventually leading to postcapillary pulmonary hypertension [38, 39].

Clinical presentation

Common symptoms of PH include exertional dyspnea, fatigue, chest pain, lower extremity edema, near syncope, syncope, and palpitations. This makes it challenging to diagnose clinically as there is significant overlap with other complications of SCD. For example, exertional dyspnea could be due to PH or could be due to acute worsening of the patient's chronic anemia. Physical examination findings consistent with PH are a loud P2 heart sound, jugular venous distension, and bilateral lower extremity swelling.

Diagnostic tests

The American Thoracic Society (ATS) has put forth PH screening guidelines for patients with SCD with the rationale that a link exists between elevated tricuspid regurgitant jet velocity (TRV) and mortality [57]. At this time, the ATS recommends a one-time transthoracic Doppler echocardiograph (TTE) for asymptomatic pediatric patients (age 8–18) and follow-up evaluation based on the results. Once an individual reaches the age of 18, they recommend a TTE once every three years or at a shorter interval depending on the results.

The preferred initial test in the diagnosis of PH is TTE (Figure 3). An elevated TRV can be used to estimate right ventricular systolic pressure or pulmonary artery systolic pressure. In adults, a TRV between 2.5–2.9 m/s can identify 25–44% of patients with a mean pulmonary artery pressure ≥ 25 mm Hg. However, values > 3.0 m/s identify about 75% of patients with PH. In adults, even borderline values (> 2.5 m/s) are associated with early mortality [58]. N-terminal-pro-brain natriuretic peptide (NT-pro-BNP) can be used as a screening test for PH when TTE is unavailable or if sonographers are incapable of obtaining adequate images [59]. A serum NT-pro-BNP level ≥ 160 pg/mL detects PH with a sensitivity and specificity of 57 and 91 percent, respectively [42]. However, it is important to note that NT-pro-BNP may be falsely elevated in patients with renal insufficiency or if the patient has pre-existing left heart failure. Obesity may also cause false negatives. Nonetheless, the gold standard for diagnosis of PH is right heart catheterization. The hemodynamic definitions of pre- and postcapillary PH can be seen in Table 3 [60].

Another test used in the evaluation of PH is the six-minute walk test (6MWT). It is intended to evaluate the distance a patient can walk and examines oxygen desaturation with exertion. A study compared the distance walked by 17 patients with SCD alone in comparison to 26 patients with SCD plus PH; they found that the group with SCD plus PH walked a shorter distance during the 6MWT (320 versus 435 meters). They also noted that the distance walked in the 6MWT was inversely correlated to the mean pulmonary arterial pressure (mPAP) measured by right heart catheterization [61].

Management

Patients with SCD have an increased risk of mortality if they develop PH. Risk factors associated with increased mortality are: TRV ≥ 2.5 m/s, NT-pro-BNP ≥ 160 pg/ml, or RHC-confirmed PH. Therefore, the American Thoracic Society has published an evidence-based consensus on guidelines for the management of PH in patients with SCD [57]. These treatment modalities can be divided into three categories: 1) SCD-specific therapies; 2) PH directed therapy; 3) long-term anticoagulation.

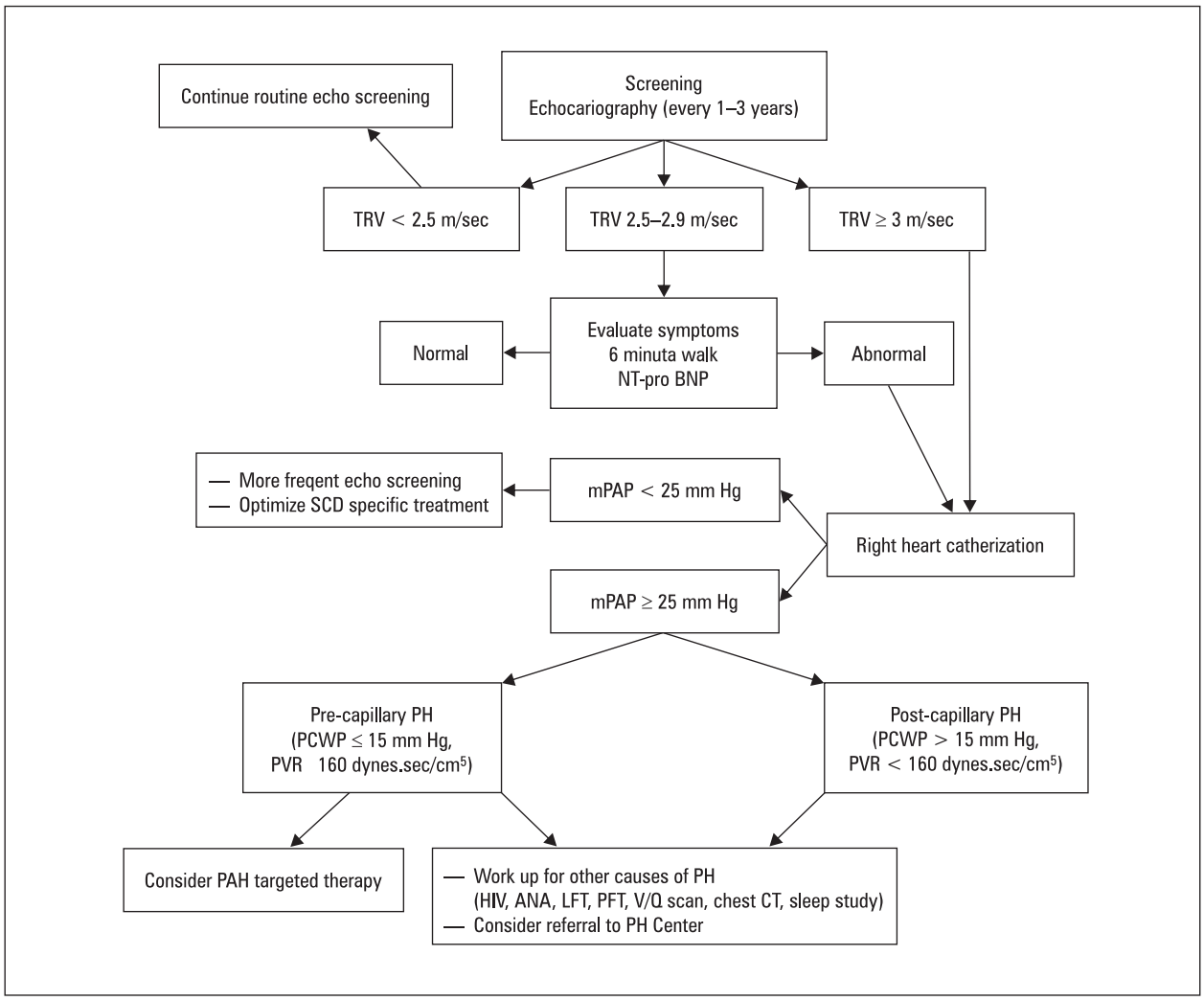

Figure 3. Diagnostic work up for pulmonary hypertension in SCD based on The American Thoracic Society guidelines [36]. TRV — tricuspid regurgitant jet velocity; SCD — sickle cell disease; PH — pulmonary hypertension; PAH — pulmonary arterial hypertension; NT-pro-BNP — N-terminal-pro-brain natriuretic peptide; mPAP — mean pulmonary artery pressure; PAWP — pulmonary artery wedge pressure; PVR — pulmonary vascular resistance; ANA — anti-nuclear antibody; HIV — human immunodeficiency virus; LFTs — liver function tests; V/Q scan — ventilation/perfusion scan

Patients with the aforementioned risk factors should undergo intensive SCD-specific therapies to reduce the severity of their hemolytic anemia via the use of hydroxyurea (HU) or chronic red blood cell transfusion regimens if they cannot tolerate HU. HU increases the concentration of fetal hemoglobin and thus, decreases the frequency of vaso-occlusive crises and acute chest syndrome occurrence thereby improving mortality in HbSS patients. The ATS practice guidelines have a strong recommendation for the use of HU in patients with an increased risk of mortality; therefore, this includes patients with PH. Per the largest trial to date, after 17.5 years of follow-up, it was reported that HU improved patient survival without accompanying serious adverse events [62]. Unfortunately, there are no clinical trials to assess the mortality benefit of chronic transfusions in the management of PH in SCD. However, a recent retrospective study of 13 HbSS patients with precapillary PH reported that chronic transfusion therapy improved their New York Heart Association functional class and hemodynamics, particularly pulmonary vascular resistance ($p = 0.01$) [63].

Pulmonary arterial hypertension (PAH) directed therapies are complicated and unfortunately, there is a paucity of data evaluating their efficacy in patients with SCD. Typical PAH treatment options include endothelin receptor antagonists (bosentan, macitentan, ambrisentan), prostacyclin agonists (epoprostenol, treprostinil, iloprost), soluble guanylate cyclase stimulators (riociguat), phosphodiesterase-5 inhibitors (sildenafil, tadalafil), and calcium channel blockers (nifedipine, diltiazem). However, in PAH patients

with SCD, it is recommended against using phosphodiesterase-5 inhibitors and calcium channel blockers. There is a study titled the Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy (Walk-PHaSST) trial which compared sildenafil to placebo (n = 74). The study was terminated due to increased hospitalizations for pain crises in the sildenafil group [64, 65]. Endothelin receptor antagonists like bosentan are typically used. There were also two randomized control trials comparing treatment with an endothelin receptor antagonist (bosentan) against placebo in patients with SCD with RHC with precapillary PH (the ASSET-1 trial) or postcapillary PH with a PVR of at least 100 dyn seconds cm − 5 (the ASSET-2 trial). Regrettably, the trials were prematurely terminated due to a withdrawal of support from their sponsors because of slow patient enrollment (n = 14) [66]. Therefore, due to the inherent complexity of PH management, it is recommended that these patients be referred to institutions who specialize in PAH therapy.

The American Thoracic Society currently recommends that a patient with SCD who has right heart catheter confirmed PH and venous thromboembolism (VTE), but without additional risk factors for bleeding, be placed on indefinite anticoagulant therapy rather than on therapy over a limited duration of time. This recommendation is regarded as weak with low quality evidence. They came to this conclusion after performing a meta-analysis of four randomized trials that compared long-term anticoagulation therapy to therapy over a limited duration of time. Their analysis showed that indefinite anticoagulation had less recurrent VTEs by 13.8% and, possibly, lower mortality. They believed this outweighed the 2.4% increase in bleeding risk, cost, and burden of monitoring [57].

Asthma in SCD

The diagnosis of asthma in a patient with SCD has been associated with increased rates of pain, acute chest syndrome episodes, and premature death [67]. The etiology is not quite clear; however, it has been demonstrated that patients with SCD were more likely to suffer from asthma and bronchial hyperreactivity in comparison to their ethnic matched and similar aged counterparts. Bronchial hyperreactivity is the measurement of forced expiratory volume in 1 second before and after bronchodilator use (albuterol 200 μg) and it is important to assess seeing as patients with asthma may be asymptomatic [68].

Pathophysiology

The pathophysiology of asthma in SCD is not clear. It is unknown whether its pathogenesis is secondary to the pathophysiology of SCD itself or caused by similar genetic and environmental factors that are found in standard asthma. However, the fact that asthma is more prevalent in patients with SCD patients than in their counterparts lends to the theory that the asthma is a manifestation of SCD. One theory is that the inflammatory pathway implicated in the pathogenesis of asthma is similar to that of pain. Ultimately, it is postulated that leukotrienes (cysteinyl leukotrienes and leukotriene B4), which are lipid mediators of inflammation, are elevated in both asthma and SCD pain crises and are implicated in bronchoconstriction, smooth muscle proliferation, mucous production, and vasoconstriction [68]. There is also the potential role of nitric oxide as exhaled NO has been noted to be a marker for asthma severity; however, no direct study has implicated the NO pathway in the process of asthma in patients with SCD [67].

Treatment

According to the National Institute of Health guidelines, asthma in patients with SCD should be treated similarly to how it is treated in patients without SCD. Acute exacerbations are treated with oxygen therapy, short acting beta-agonists, and systemic steroids. Magnesium sulfate may also be considered in severe refractory cases. However, it is important to note that patients with asthma who are treated with short-term corticosteroids may be at increased risk of suffering a rebound vaso-occlusive crisis within two weeks. Nonetheless, the risk of asthma itself outweighs those of corticosteroid use; therefore, they should not be withheld for these concerns [69].

Sleep-disordered breathing

Sleep-disordered breathing refers to a group of conditions characterized by complete or partial cessation of breathing while sleeping. An evaluation for sleep-disordered breathing should be considered in patients with SCD who have unexplained nocturnal and daytime hypoxemia, recurrent vaso-occlusive events, or enuresis (mainly in pediatrics). Obstructive sleep apnea (OSA) is the most common etiology of sleep-disordered breathing affecting approximately 2–4% of the adult population. Men tend to be most commonly affected; however, women and children are not impervious to this disorder [70]. OSA should be suspected in patients who snore, have witnessed

apneic, gasping, or choking episodes during sleep, or have excessive daytime sleepiness. A common screening tool used by primary care providers for OSA is the STOP-BANG questionnaire.

Sleep-disordered breathing appears to be more prevalent in patients with SCD than in the general population. One prospective study of 32 adult patients with SCD found sleep-disordered breathing in 44 percent with a mean apnea-hypopnea index (AHI) of 17/hour (95% CI 10–24/hour) [71]. Another small prospective study of 20 young adults found that 10 had an AHI > 5 consistent with OSA. This finding did not correlate with symptoms or obesity; however it was associated with reduced health-related quality of life and increased systolic blood pressure [72].

However, it remains uncertain whether the risk factors for OSA in the general population are the same as in patients with SCD. Many studies have reported that increased neck size and a higher body mass index are significant risk factors for sleep disordered breathing in adults with SCD, as in the general population [73]. Something that is more unique to SCD patients is the chronic use of opioids secondary to sickle cell pain, and it has been found that chronic use of opioids is an independent risk factor for sleep apnea [74]. Sleep-disordered breathing in patients with SCD is important to watch out for because intermittent oxyhemoglobin desaturation could result in increased vaso-occlusive episodes. There is evidence of increased rates of both vaso-occlusive episodes and cerebrovascular events linked to nocturnal hypoxemia [75]. Furthermore, sleep-disordered breathing should be evaluated by a formal sleep study in SCD patients with pulmonary hypertension.

The treatment of sleep-disordered breathing complicating SCD is essentially the same as that in patients without SCD. The use of oxygen supplementation and/or bilevel (BPAP) or continuous non-invasive positive airway pressure (CPAP) with sleep is recommended [70].

Pulmonary function tests in sickle cell disease

Screening pulmonary function tests (PFTs) are not recommended in the management of SCD by the National Heart, Lung, and Blood Institute (NHLBI) guidelines [76]. However, PFTs are routinely obtained as part of the evaluation of dyspnea in patients with SCD or for monitoring of a known diagnosis of asthma.

In children with SCD, PFTs tend to show an obstructive pattern which could be confounded by the increased incidence of asthma in children with SCD [77]. In comparison, many adults have restrictive pathophysiological findings [78]. In a multicenter study, PFTs were performed on 310 adult African-Americans with SCD irrespective of symptoms [21]. Only 10 percent of these patients had normal PFTs. The most common finding was a restrictive defect (74%). An isolated reduction in diffusing capacity for carbon monoxide (DLCO) was seen in 13%, while an obstructive pattern was seen in around 1% [79]. It is unclear though if the obstructive defects in childhood transition to restrictive defects in adulthood.

Longitudinal studies of pulmonary function in adults with SCD demonstrate an average annual decline in FEV_1 double that of the general population [78]. Furthermore, there is evidence that reduced FEV_1 in patients with SCD is associated with an increased mortality risk [80, 81].

Recurrent episodes of ACS with pulmonary infarctions may lead to chronic scarring and pulmonary fibrosis. These may result in a restrictive pattern with reduced diffusion capacity for carbon monoxide on PFT, and scattered areas of honeycombing on high-resolution computed tomography (HRCT) of the chest.

Despite these observations, the importance of abnormal PFTs in SCD remains unknown. This could be because of inconsistent study designs and classification strategies when comparing results across studies, and a lack of longitudinal data. Further research is required to find associations between abnormal lung function, respiratory symptoms, and SCD outcomes.

Conclusion

SCD, as demonstrated in this review, results in a spectrum of pulmonary diseases that include acute chest syndrome, respiratory infections, and pulmonary vascular diseases that can worsen other respiratory conditions such as asthma, lung function, and sleep-disordered breathing. There have been advances in the understanding and management of these diseases; however, more transitional research and clinical trials are needed to prevent and find more effective and better tolerated therapies. Knowledge of these pulmonary complications and maintaining a high clinical suspicion are important in preventing long-term complications and improving patient quality of life.

Conflict of interest

None declared.

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