HHS Public Access

Author manuscript

Trends Cardiovasc Med. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

Trends Cardiovasc Med. 2021 April ; 31(3): 187–193. doi:10.1016/j.tcm.2020.02.002.

Cardiovascular Complications of Sickle Cell Disease

Vandana Sachdev[#], **Douglas R. Rosing**, **Swee Lay Thein**

National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD

Abstract

Sickle cell disease (SCD) is the most common inherited blood disorder in the United States, and a global health problem. Pathological features of the abnormal hemoglobin (HbS) result in 2 hallmarks of the disease - recurrent episodes of acute microvascular occlusion and chronic hemolytic anemia - that inflict continuous and insidious damage to multiple organs. With improved childhood survival, SCD in adults has evolved into a chronic degenerative disease with underlying damage to multiple organs including the heart and lungs. Cardiopulmonary complications, including cardiomyopathy, diastolic dysfunction, pulmonary hypertension (PH), and sudden cardiac death are the most common causes of morbidity and mortality. Awareness of the sickle-related cardiovascular phenotypes is important for screening, early diagnosis, and intervention of cardiac complications in this disorder.

Keywords

sickle cell; cardiac; diastolic dysfunction; pulmonary hypertension

1. Introduction to Hemoglobinopathies

The inherited disorders of hemoglobin (Hb) production are the most common human monogenic disorders. The most clinically significant among these are the ones affecting the adult β globin gene – β thalassemia and sickle cell disease (SCD)(1). β-thalassemia is caused by a quantitative deficiency of β-globin chains that are structurally normal, in contrast to SCD which is caused by a single base mutation in the β-globin gene, resulting in an abnormal Hb variant (Hb S, βGlu6Val) in which glutamic acid is substituted by valine in the sixth amino acid position. Deoxygenated HbS polymerizes within the red blood cells (RBCs) altering their structure and function. These damaged (typically sickle-shaped) RBCs are highly adhesive with a very shortened life span ($1/6^{th}$ that of normal RBCs) leading to the chronic hemolysis and recurrent acute painful vaso-occlusive crises (VOC) that are signature hallmarks of SCD. Vaso-occlusion in the microvasculature, with repeated episodes

[#]Address for correspondence: Vandana Sachdev, MD, Cardiology Branch, Division of Intramural Research, National Heart, Lung, and Blood Institute, National Institutes of Health, 10 Center Drive, CRC, 5-1436, Bethesda, MD 20892-1650, Phone: 301-496-3015, Fax: 301-435-8886, sachdevv@nhlbi.nih.gov.

Disclosures: none

of ischemia and reperfusion, causes widespread vasculopathy resulting in multi-system organ damage, including effects on the cardiovascular system. Although there are distinct differences in the clinical consequences of the molecular defects in these hemoglobinopathies, they may have similar etiologies for heart failure and other complications(2); therefore the term rheologic cardiomyopathy has been used (3). This review will focus specifically on cardiovascular manifestations in sickle cell disease and describe their pathophysiology, clinical phenotypes, and management.

2. Epidemiology and Causes of Death in SCD

In the United States, SCD affects approximately 100,000 Americans, the majority of whom are of African descent(4). It affects 1 in 365 African-American births and in 1 in 16,300 Hispanic-American births. Heterozygotes (carriers) for Hb S (Hb AS) have a substantial survival advantage in malaria-endemic regions, hence SCD is more prevalent in parts of the world where malaria is endemic including sub-Saharan Africa, the Mediterranean, and central India. Widespread immigration of affected populations has increased the global distribution of this problem.

The predominant clinical manifestations of SCD are acute clinical events due to tissue ischemia and infarction, of which pain is the most common. Over time, repeated episodes of ischemia-reperfusion injury and the effects of hemolysis result in a chronic inflammatory state and vasculopathy that underlies the chronic end-organ damage. The severity of clinical complications is related to a number of factors including the SCD genotype. Patients with homozygous HbS (HbSS) and HbS/severe β thalassemia have a more severe anemia and clinical course compared to those with Hb SC or HbS/mild β thalassemia (5,6). Clinical severity can also vary markedly in the same genotype and is affected not only by the genetic background (i.e. other co-inherited genetic variants), but even more so by lifestyle, environmental factors, access to healthcare, and social determinants of health.

With improvements in screening and management of acute complications, over 95% of newborns with SCD in medium- to high-resource countries survive to adulthood. As a consequence, in the better-resourced countries, the burden of SCD has shifted to adults, where it has evolved into a chronic disorder with substantial morbidity from the ongoing inflammation and vasculopathy leading to end-organ impairment. Conditions related to physiological aging add to the sickle-related complications, posing multiple challenges in management of this older population of SCD patients. Overall, life expectancy of patients with SCD is still reduced by more than 2 decades compared to the general population(5, 6), and cardiovascular complications are a notable feature in the premature deaths (7).

A report on over 5000 deaths in SCD patients between 1999–2009 found that most died in their mid-thirties to mid-fifties(8). The five main causes of death according to death certificates were cardiovascular in 32% of patients, respiratory in 28%, renal in 16%, infectious in 14% and neurologic in 12%. Approximately 70% of deaths occurred in inpatients and the main cardiac causes included pulseless electrical alternans, myocardial infarction, and arrhythmias.

In an autopsy study of 306 SCD patients, cardiac involvement was common with cardiomegaly seen in 58%, myocardial micro-infarcts in 20%, and heart failure in 10%. Clinical manifestations of chronic organ injury were reported in 25% of patients although autopsy reported evidence of chronic organ injury in 75% of cases suggesting that the clinical manifestations of the disease may significantly underestimate the degree of underlying chronic organ injury(9). Determining causes of death in SCD patients is problematic, due not only to a paucity of autopsy data, but often the final causes of death do not accurately portray the contribution of underlying chronic organ damage. Nonetheless, emerging evidence suggests that end-organ damage in the lung, heart, kidneys and liver is common and is the major contributor to premature mortality(10). These findings highlight the need to improve early detection and understanding of cardiac complications.

3. Cardiovascular Pathophysiology

Cardiac involvement in SCD is due to the anemia itself as well as the effects of HbS polymerization. Chronic anemia decreases the oxygen carrying capacity of the blood and results in a compensatory increase in cardiac output predominantly through a larger stroke volume. Peripheral vascular dilation to improve peripheral blood flow is another compensatory mechanism. High cardiac output and low systemic vascular resistance contribute to activation of the renin-angiotensin-aldosterone system, salt and water retention by the kidney, and a volume overload state(11). Chronic volume overload leads to dilation of all cardiac chambers and eccentric hypertrophy develops in response to increased wall stress. A volume overload state can be well-tolerated for many years as seen in valvular heart disease, but in the case of SCD, it can lead to increased venous return, increased filling pressures, and the syndrome of high-output heart failure(12).

Repeated vaso-occlusion and the continual release of cell-free hemoglobin from the ongoing hemolysis depletes the bioavailability of nitric oxide (NO), triggers a cascade of pro-inflammatory activity setting off multiple pathophysiological factors that also involve neutrophils, platelets and vascular endothelium, ultimately contributing to vascular endothelial dysfunction that underlies the chronic organ damage in SCD(5,13). Repeated acute occlusions of the microvasculature eventually become chronic due to the vasculopathy itself and the ischemia causing micro-infarcts in multiple organs. In a mouse model of SCD, features suggestive of chronic ischemia and diffuse myocardial fibrosis have been seen in the myocardium(13). Similar findings of diffuse fibrosis have also been seen in humans and may partially explain some of the diastolic abnormalities(14).

Treatments may exacerbate the disease process itself; SCD patients receiving chronic transfusion therapy can develop iron overload in the liver; however, a small fraction of patients also develop iron deposition in the myocardium(15). Myocardial iron overload is detected with T2* magnetic resonance imaging (MRI) and is directly related to systolic and diastolic dysfunction, arrhythmias, and other cardiac complications.

Increased pulmonary pressures develop in SCD patients due to a combination of etiologies. High cardiac output, volume overload and relatively increased systemic pressures may increase pulmonary pressures in the absence of increased pulmonary vascular resistance.

Intravascular hemolysis contributes to vasculopathy throughout the pulmonary vascular tree(16) and intimal thickening in the pulmonary arteries and veins, thrombosis, and plexiform lesions have all been noted. Other pathologies such as chronic hypoxia, pulmonary thromboembolism, and SCD-related lung injury (e.g. acute chest crises) are also likely contributors.

4. Cardiac Phenotype

Heart failure (HF) has been an infrequent complication of the rheologic cardiomyopathy seen in SCD patients; however, incidence rates may be on the rise due to increased survival. A study using the National Inpatient Database from 2005–2014 found close to 8000 HF admissions in SCD patients(17) and concomitant PH, renal failure, and chronic liver disease were significant predictors of mortality.

a. Clinical Manifestations

In the majority of patients, left and right ventricular systolic function remains preserved(18). In approximately 9% of patients, the LV ejection fraction (EF) falls below the normal threshold of 55%, and, consistent with other cardiovascular conditions, this is associated with higher mortality(19, 20). Speckle-tracking echocardiography has been used to detect subclinical LV dysfunction through measurements of myocardial strain, or deformation, and most studies in SCD patients have shown normal myocardial contractility(21). Right ventricular (RV) dysfunction is also uncommon, although cardiac MRI studies have shown that RVEF is lower than controls(22).

In contrast to LV systolic function, LV diastolic function is often abnormal in SCD, and approximately one-quarter of patients have been found to have diastolic dysfunction although there is significant variation based on age of participants and criteria used. An early study of 235 subjects(19) showed that a low E/A ratio was associated with mortality with a risk ratio of 3.5 (95% confidence interval 1.5 to 8.4, $p < 0.001$), even after adjustment for tricuspid regurgitation (TR) velocity. Other markers of diastolic function, including peak E velocity, deceleration time, and septal e'/a' ratio were also predictive of increased mortality. Diastolic dysfunction was associated with older age, increased blood pressure and creatinine, and lower hemoglobin level. In a larger study of 483 subjects with SCD(23), echo measures of tissue Doppler E/e' ratios were used to estimate LV filling pressure and diastolic function. A higher lateral E/e' ratio was associated with anemia, increasing age, blood pressure and creatinine level as seen in prior studies, as well as a higher body-mass index.

Diastolic dysfunction has also been associated with poor exercise capacity in SCD patients(23). While 6-minute walk distance correlated with younger age, male sex, lower body mass index, and a higher hemoglobin level, both the lateral E/e' ratio ($p=0.014$) and the TR velocity ($p=0.019$) were independent predictors of a lower 6-minute walk distance.

Left atrial size is recognized as a good marker of the severity and duration of diastolic dysfunction(24) and a predictor of cardiac events in the general population. In SCD, however, results are mixed and left atrial size remains tightly linked to anemia and volume

overload. In a cohort of 127 adult patients with HbSS-SCD, left atrial enlargement was common and linked with age, hemoglobin, and LV size, but was not associated with the E/e' ratio or diastolic dysfunction(25) while another study of children and young adults found some correlation between left atrial size and the E/e' ratio(26).

Obstructive atherosclerotic coronary artery disease is uncommon in SCD patients, but they may present with chest pain in the setting of an acute sickling episode. Younger age and low cholesterol levels due to high metabolic demand are thought to account for lack of atherosclerotic disease. Troponin(27) and galectin-3(28) elevations have been seen during vaso-occlusive crises and are indicative of myocardial injury. Microvascular disease is the likely mechanism for these events which are typically Type II non-ST elevation infarcts in the setting of chronic anemia.

There is growing evidence of autonomic nervous system (ANS) abnormalities in SCD. Heart rate variability (HRV) is one measure of cardiac ANS activity and reflects the activities of the sympathetic and parasympathetic components. Normal beat-to-beat variation in heart rate reflects a balanced sympathetic and parasympathetic response whereas low HRV reflects impaired ANS activity. Several studies have shown low HRV in SCD patients during vaso-occlusive crises(29, 30) although prognostic implications of this finding are still unknown.

Electrocardiographic assessment of the QTc interval is a known risk factor for ventricular arrhythmias and sudden death in the general population. In a cohort of 224 SCD patients, QTc using the Bazett formula (QTcB) was related to mortality with a hazard ratio (HR) of 1.22 per 10 ms, ($P = 0.015$), and a HR = 3.19 ($P = 0.045$) for a QTcB >480 ms(31). Other studies have shown a similar link to mortality as well as associations with TR velocity, hemolysis and acute chest syndrome(32, 33). Although a number of issues, including antibiotics, pain medications, and electrolyte abnormalities confound the interpretation of long QTc intervals in SCD patients, ECGs remain a simple, inexpensive screening tool for patients hospitalized with acute illness as well as symptomatic or higher risk outpatients.

Autopsy studies have shown that death in SCD patients is sudden and unexpected in at least 40% of cases(9). Although pulseless electrical alternans and tachyarrhythmias have been described, reports of arrhythmias in sickle cell patients have been mainly anecdotal. One study in which 24-hour electrocardiographic monitoring was performed during episodes of acute crisis found arrhythmias in 80% of patients with an even split between atrial and ventricular events(34). Arrhythmias were more likely to occur in patients with abnormal myocardial function. Further work in this area is urgently needed to better understand arrhythmias and sudden death in this population.

b. Diagnosis of Cardiac Complications

The current American Society of Echocardiography guidelines for diastolic function assessment(24) in patients with preserved LV function include four key parameters (e' velocity, E/e' ratio, TR velocity, and LA volume). Although the E/e' ratio is commonly used to assess LV filling pressure non-invasively, it has not been validated in an SCD population with high cardiac output and a volume overload state. As discussed below, left atrial size is

not a reliable measure of diastolic function in SCD since all cardiac chambers are dilated due to anemia and there may be several etiologies for an increased TR velocity. Thus, assessment of diastolic function in SCD patients is complicated by numerous confounders, and, as a result, invasive measurement by right heart catheterization remains the best approach if high LV filling pressures are suspected.

Late gadolinium enhancement (LGE) imaging by CMR has been used for detection of myocardial injury, edema, or fibrosis, and most studies have detected focal areas of LGE in only a small number of SCD patients(22, 35). Since LGE is dependent on signal intensity differences between abnormal areas of myocardium and surrounding normal tissue, it may not detect areas of diffuse myocardial fibrosis. T1 mapping by CMR is a method of quantitating the extracellular volume (ECV) fraction of the interstitium and elevated levels have been validated with histologic measures of increased tissue collagen fraction in the absence of edema or tissue infiltration. Niss and colleagues studied 25 SCD patients with CMR and found increased ECV levels indicating diffuse fibrosis in all patients(14). ECV levels were associated with diastolic dysfunction and were elevated in both children and adults suggesting that chronic effects of anemia, ischemia-reperfusion and micro-infarcts may lead to diffuse myocardial fibrosis(26).

Although microvascular occlusion is responsible for the tissue damage and clinical manifestations of SCD, measurement of microvascular blood flow in humans remains challenging. Most clinical trials of new therapies use frequency of pain crises or other surrogate measures due to this limitation. Contrast-enhanced ultrasound (CEUS) of forearm skeletal muscle in SCD patients is a research technique that can detect changes in microvascular flow. A 30% reduction in flow during episodes of crisis has been noted compared to steady-state levels of flow(36). This method has also demonstrated an increase in myocardial and skeletal muscle microvascular flow in patients treated with hydroxycarbamide (hydroxyurea) compared with untreated patients(37). Further work is needed to evaluate the prognostic value of these measures.

Nuclear imaging has demonstrated both fixed and reversible defects consistent with ischemia(38). CMR imaging is well suited to evaluate myocardial flow reserve and microvascular dysfunction and recent studies have shown decreased myocardial perfusion reserve in SCD patients(35, 39).

Numerous studies using CMR have confirmed the lack of significant myocardial iron deposition, as measured by T2* values, in the majority of patients(35). Cardiac iron loading developed only when prolonged elevated liver iron concentration was present with increased non-transferrin bound iron species. Ferritin, which is an acute phase marker, is not a good marker of iron loading in SCD, but in view of accessibility, serum ferritin and transferrin saturation are still valuable for screening in heavily transfused patients, and CMR remains the gold standard for diagnosis of myocardial iron overload.

c. Management of Cardiac Complications

Acute heart failure treatment generally involves relieving congestion with loop diuretics along with supportive care. Chronic heart failure therapies, including beta blockers,

angiotensin converting enzyme inhibitors, and mineralocorticoid receptor antagonists, are generally recommended even though evidence levels are low.

SCD patients hospitalized for HF manifest both systolic and diastolic HF(17). Although clinical similarities between diastolic HF in SCD and the syndrome of heart failure with preserved ejection fraction (HFpEF) in the general population exist (40), successful treatments for both are lacking. Current management includes intensification of SCD-tailored therapies including optimization of hydroxycarbamide therapy, careful attention to fluid status to avoid dehydration and fluid overload, and consideration of regular or exchange blood transfusion. If eligible, patients should also be considered for newer treatments such as Voxelotor (41) (FDA approved in November 2019) and pharmacy grade L-glutamine (42), (FDA approved in July 2017). Stem cell transplant(3) and gene therapy hold significant promise, but patients need to be able to undergo pre-procedure myeloablative conditioning, hence the importance of early detection of cardiac damage before the patient becomes ineligible.

Management of acute coronary syndromes and ischemic events requires a collaborative approach between hematologists and cardiologists for a case-by-case approach. Established therapies such as aspirin, nitroglycerin, beta-blockers and angiotensin converting enzyme inhibitors are often used. A report from the National Inpatient Sample database showed that SCD patients hospitalized with acute myocardial infarction had an odds ratio of 3.5 for higher mortality compared to non-SCD patients matched for age, gender, race, and year of admission(43). Since this was an administrative database, criteria for an acute myocardial infarction were not well-defined, and it is possible that in addition to type II infarctions secondary to microvascular disease, other confounding diagnoses such as acute chest syndrome, pulmonary emboli, and others may have been included.

For treatment of myocardial iron overload, iron chelation therapy is generally initiated at T2* levels <20 milliseconds on MRI. Treatment at higher T2* levels has recently been proposed to prevent permanent myocardial damage (44).

5. Pulmonary Vascular Phenotype

Pulmonary complications of SCD include acute chest syndrome, lower airways disease, sleep-disordered breathing, and pulmonary vascular complications. As these have been recently reviewed by a multidisciplinary group(45), the current discussion addresses only the pulmonary vascular complications and their relationship with cardiac manifestations.

a. Clinical Manifestations

Studies using echocardiography assessment of TR velocity have shown that approximately one-third of patients have a peak velocity of ≥2.5 m/s, and this is strongly associated with an increased risk of death (46, 47). A meta-analysis of studies confirmed this association, and found that patients with an increased TR velocity had a shorter exercise time and an approximately 5-fold higher hazard ratio for mortality (48).

SCD patients with increased pulmonary pressures on echocardiography (Figure 1) can have pulmonary arterial hypertension, pulmonary venous hypertension, or a combination of both according to right heart catheterization. Due to the multifactorial mechanisms of increased pulmonary pressures, the World Health Organization classification for PH due to SCD now considers this in the Group 5 category with other hematologic disorders(49). Importantly, it is now recognized that approximately half of patients with elevated pulmonary pressures have pulmonary venous hypertension caused by left heart disease and elevated LV filling pressure and half have pulmonary arterial hypertension(50). An elevated TR velocity ≥ 2.5 m/s should therefore be considered a marker of poor outcome since it is reflective of both cardiac and pulmonary end-organ involvement in SCD patients.

SCD patients are at high risk for venous thromboembolism (VTE) due to their hypercoagulable state. Deep vein thrombosis (DVT) and pulmonary emboli (PE) are increasingly being recognized as serious complications. Two large studies (51, 52) have shown that the incidence of VTE is 11–13%, with half presenting as PE and/or DVT, one-quarter as isolated lower-extremity DVT and one quarter as isolated upper-extremity DVT. VTE was associated with greater than a two-fold risk of mortality in these patients and recurrence rates were high, affecting one-third of patients within 5 years.

b. Diagnosis of Pulmonary Vascular Complications

Although non-invasive assessment of pulmonary pressures can identify SCD patients at higher mortality risk, right heart catheterization is necessary to diagnose pulmonary hypertension. Right heart catheterization studies found that approximately 10% of patients met the original definition of PH with a mean pulmonary artery pressure (MPAP) ≥25 mm Hg(53). Recently, the 6th World Symposia on Pulmonary Hypertension (WSPH) reconsidered the hemodynamic criteria for PH and determined that the threshold should be a MPAP ≥ 20 mm Hg with a pulmonary vascular resistance (PVR) ≥ 3 Woods Units(49). Prevalence of PH in SCD patients will likely be higher with this new definition. Determination of pre-capillary PH, post-capillary PH, or both has been discussed in detail elsewhere(54).

Despite high mortality rates in SCD patients, only mild-moderate elevations in pulmonary pressures have been seen in the resting state. Cardiopulmonary stressors such as exercise are known to increase pulmonary pressures; therefore, the effect of other stressors that may acutely increase pulmonary pressures and impair right heart function are important. In patients studied during vaso-occlusive crises(55), TR velocities are increased and correlate with elevations in cardiac biomarkers(56). These acute elevations in pulmonary pressures may contribute to morbidity and mortality in SCD patients through acute and chronic right heart failure, and cor pulmonale is often seen(56).

A validated blood biomarker can also provide important diagnostic and prognostic information about pulmonary vascular disease. N-terminal (NT) pro-brain natriuretic peptide (proBNP) is released by cardiomyocytes in response to stretch from chamber dilation. A NT-proBNP level ≥ 160 pg/ml identifies patients with a higher risk of PH, worse exercise capacity, and it is an independent predictor of mortality(57). An elevation of NT-proBNP combined with increased TR velocity ≥ 3m/s identified patients with the highest risk of

mortality (hazard ratio 14.9)(47). Although elevations in NT-proBNP levels were initially studied in the context of PH and were presumed to be due to right heart dilation, it is well known in heart failure patients that elevations in NT-proBNP can be due to left heart and/or right heart dilation. As discussed above for TR velocity, the NT-proBNP level is a valuable biomarker since it is reflective of left-sided and/or right-sided cardiac chamber involvement. As NT-proBNP is primarily cleared by the kidney, it could be falsely elevated in renal insufficiency that is commonly seen in SCD patients.

For clinical suspicion of VTE in SCD patients, ventilation/perfusion scanning is superior to computed tomographic angiography (CTA) and should be considered(58). In these patients, diagnosis is limited by the inability to use D-dimer levels due to chronic baseline elevations and the high prevalence of in situ pulmonary thrombosis seen on CTA(59) in one in six patients.

c. Management of Pulmonary Vascular Complications

Guidelines developed by the American Thoracic Society for management of PH in SCD patients recommend a baseline screening echo in all adult patients to evaluate TR velocity(54). If the TR velocity is ≥ 2.5m/s, further risk stratification with NT-proBNP and a 6-minute walk test is recommended. A right heart catheterization is suggested for patients with a TR velocity ≥ 3m/s and symptoms, evidence of right heart abnormalities, or other high-risk features. Patients may also require evaluation with pulmonary function tests, ventilation/perfusion scans or sleep studies to rule out other etiologies of PH. SCD patients with high TRV or PH are often treated with aggressive hydroxyurea therapy to reduce incidence of vaso-occlusive events and acute chest syndrome, and a small cohort study (60) suggested that chronic transfusion therapy increases oxygen-carrying capacity, minimizes the hemolytic anemia, and provides similar benefits. On a recent survey of transfusion practices, SCD patients are receiving chronic exchange transfusions for a variety of indications including PH, heart failure and high TR velocity(61). The effectiveness of exchange transfusions in this setting is unclear and likely related to an increase in hemoglobin and replacement of the sickle Hb with normal Hb, thus reducing the frequency of acute sickle-related events.

For patients with catheterization-defined pulmonary arterial hypertension (PAH), endothelin-receptor blockers, prostanoids and other group 1 PAH drugs may be considered after maximizing SCD-related care. Phoshodiesterase-5 inhibition is the only drug class studied in a randomized control trial in SCD patients. The Walk-PHaSST clinical trial (62) evaluated sildenafil use for PH in SCD, but was stopped early due to an increase in hospitalizations for pain in the sildenafil arm.

For VTE in SCD, management has been well summarized (59) and follows clinical guidelines for the general population, although more careful assessment of renal function is required to correctly dose direct oral anticoagulants. Patients with chronic thromboembolic PH could also be considered for riociguat therapy and percutaneous or surgical endarterectomy.

6. Peripheral Vascular Phenotype

a. Clinical Manifestations

Sickle cerebral vasculopathy may be due to a number of factors, including loss of endothelial elasticity, inflammation, hypoxia, anemia, and volume overload. Central nervous system complications are a major source of morbidity and mortality in adults with SCD and they may develop either thrombotic or hemorrhagic strokes. In a cohort of over 500 SCD patients, a history of stroke, seizure and transient ischemic attack was seen in over 30% of patients and this doubled the risk of mortality(6). Cerebral aneurysms are common findings on MRI and may explain the high rate of hemorrhagic strokes (63, 64). In addition, silent cerebral infarcts are seen in over half of SCD patients undergoing MRI scans and may explain the neurocognitive decline seen in these patients(64). Non-sickle cell related co-morbidities (hypertension, atrial fibrillation, smoking, obesity, obstructive sleep apnea) may also contribute to neurologic events and cognitive decline, especially as these individuals live longer through improved medical care and access.

SCD patients have lower mean blood pressure (BP) than the general population, including age-, sex-, and race-matched controls(65). They develop vasculopathy-associated organ dysfunction at “normal” blood pressure and relatively higher levels are associated with higher rates of stroke(66) and mortality. In a group of 163 SCD patients, 47% had a normal BP<120/70, 43% had pre-hypertension or relative systemic hypertension with a systolic BP120–139, diastolic BP 70–89, and 10% had a diagnosis of hypertension(67). Patients with relative systemic hypertension had a higher prevalence of elevated pulmonary pressures and renal dysfunction, and over 2 years, developed more complications than those with normal BP. A smaller study of 45 patients found that 38% were hypertensive and 20% were obese(68). With the increasing longevity of SCD patients, hypertension, relative systemic hypertension and other co-morbidities related to physiological aging add to the complexity of managing the older adult. These co-morbidities should be diagnosed early and effectively managed.

b. Diagnosis of Peripheral Vascular Abnormalities

Endothelial dysfunction, as measured by flow mediated dilation of the brachial artery, and arterial stiffness, has been described as abnormal in SCD patients(69), although results are mixed and testing remains challenging for clinical use. Abnormal carotid arterial stiffness and elevated transcranial Doppler velocities may be associated with risk of stroke in adult SCD patients(70, 71). Although transcranial Doppler screening and regular transfusions in children have led to improvements in the incidence of SCD-related stroke, this has not been determined in adults. For assessment of blood pressure, guidelines from the United Kingdom (UK) recommend blood pressure monitoring at every clinical encounter and careful treatment by primary care providers (72).

c. Management of Peripheral Vascular Abnormalities

UK Guidelines suggest that in the absence of albuminuria (albumin/creatinine ratio of <3.5mg/mmol), the target blood pressure should be <140/90 mm Hg. Above this level, treatment with a calcium channel blocker is recommended if patients are of African or

Caribbean origin. For patients with albuminuria, target blood pressure is <130/80 mm Hg and treatment recommendations include an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, or a calcium channel blocker (72).7.

Conclusions

Microvascular injury and vasculopathy emanating from the primary event of HbS polymerization and sickling manifests in numerous organ systems, and involvement of the heart, lungs, and vasculature significantly impacts the morbidity and mortality of this condition. Currently, established treatment options are hydroxyurea and blood transfusion for this condition. Hydroxyurea reduces frequency of the vaso-occlusive episodes decreasing hospitalizations and enhancing survival in HbSS patients. It is unclear, however, whether hydroxyurea can reverse end-organ damage. Long term hydroxyurea starting in very early childhood may produce a generation of adults with fewer acute complications, fewer hospital admissions, decreased organ damage and improved survival. Red blood cell exchange transfusion is also being increasingly utilized for acute and chronic complications of SCD; however, the cardiovascular effects of this therapy are largely unknown. Newer therapies, including hematopoietic stem cell transplant (HSCT) and gene therapy hold promise for correcting the underlying defect in SCD. In a recent report of patients undergoing HSCT(3), significant cardiac improvements were seen over the first year following successful transplants. Although most patients improved from baseline levels in terms of atrial and ventricular dilation, almost one-third of them continued to have a dilated LV suggesting that some element of end-organ damage is irreversible. Thus, early detection and treatment remains critical.

Collaboration between primary care providers, hematologists, and cardiologists is required to improve the clinical care and address research gaps in this condition. While there are no pathognomonic features of cardiac pathology in SCD, the conglomeration of cardio-pulmonary and vascular complications on a background of SCD defines the cardiac phenotype in a patient with SCD. Given the importance of cardiovascular involvement in risk stratification, acute decompensation, and chronic management, providers and cardiologists should have a low threshold to screen and evaluate patients with ECG, Holter or event monitors, echocardiogram, and cardiac MRI.

Sources of Funding

This research was supported by the Intramural Research Program of the National Heart Lung and Blood Institute, NIH, DHHS.

References

1. Williams TN, Weatherall DJ. World distribution, population genetics, and health burden of the hemoglobinopathies. Cold Spring Harb Perspect Med. 2012;2(9):a011692. [PubMed: 22951448]
2. Farmakis D, Triposkiadis F, Lekakis J, Parissis J. Heart failure in haemoglobinopathies: pathophysiology, clinical phenotypes, and management. Eur J Heart Fail. 2017;19(4):479–89. [PubMed: 28000341]
3. Sachdev V, Hsieh M, Jeffries N, Noreuil A, Li W, Sidenko S, et al. Reversal of a rheologic cardiomyopathy following hematopoietic stem cell transplantation for sickle cell disease. Blood Adv. 2019;3(19):2816–24. [PubMed: 31578191]

4. Centers for Disease Control and Prevention. Data & Statistics on Sickle Cell Disease [updated 10/8/2019. Available from: https://www.cdc.gov/ncbddd/sicklecell/data.html.
5. Gardner K, Douiri A, Drasar E, Allman M, Mwirigi A, Awogbade M, et al. Survival in adults with sickle cell disease in a high-income setting. Blood. 2016;128(10):1436–8. [PubMed: 27439910]
6. Elmariah H, Garrett ME, De Castro LM, Jonassaint JC, Ataga KI, Eckman JR, et al. Factors associated with survival in a contemporary adult sickle cell disease cohort. Am J Hematol. 2014;89(5):530–5. [PubMed: 24478166]
7. Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. J Am Coll Cardiol. 2012;59(13):1123–33. [PubMed: 22440212]
8. Hamideh D, Alvarez O. Sickle cell disease related mortality in the United States (1999–2009). Pediatr Blood Cancer. 2013;60(9):1482–6. [PubMed: 23637037]
9. Manci EA, Culberson DE, Yang YM, Gardner TM, Powell R, Haynes J Jr., et al. Causes of death in sickle cell disease: an autopsy study. Br J Haematol. 2003;123(2):359–65. [PubMed: 14531921]
10. Chaturvedi S, Ghafuri DL, Jordan N, Kassim A, Rodeghier M, DeBaun MR. Clustering of end-organ disease and earlier mortality in adults with sickle cell disease: A retrospective-prospective cohort study. Am J Hematol. 2018;93(9):1153–60. [PubMed: 29981283]
11. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson PA, Harris PC. Pathogenesis of oedema in chronic severe anaemia: studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. Br Heart J. 1993;70(4):357–62. [PubMed: 8217445]
12. Reddy YNV, Borlaug BA. High-Output Heart Failure in Sickle Cell Anemia. JACC Cardiovasc Imaging. 2016;9(9):1122–3. [PubMed: 27609152]
13. Bakeer N, James J, Roy S, Wansapura J, Shanmukhappa SK, Lorenz JN, et al. Sickle cell anemia mice develop a unique cardiomyopathy with restrictive physiology. Proc Natl Acad Sci U S A. 2016;113(35):E5182–91. [PubMed: 27503873]
14. Niss O, Fleck R, Makue F, Alsaied T, Desai P, Towbin JA, et al. Association between diffuse myocardial fibrosis and diastolic dysfunction in sickle cell anemia. Blood. 2017;130(2):205–13. [PubMed: 28507082]
15. Meloni A, Puliyel M, Pepe A, Berdoukas V, Coates TD, Wood JC. Cardiac iron overload in sickle-cell disease. Am J Hematol. 2014;89(7):678–83. [PubMed: 24664847]
16. Carstens GR, Paulino BBA, Katayama EH, Amato-Lourenco LF, Fonseca GH, Souza R, et al. Clinical relevance of pulmonary vasculature involvement in sickle cell disease. Br J Haematol. 2019;185(2):317–26. [PubMed: 30739309]
17. Fadiran O, Balogun AF, Ogunti R, Buhari O, Lanka C, Atanda A, et al. In-hospital Outcomes and Characteristics of Heart Failure in Sickle Cell Disease. Cureus. 2019;11(9):e5660. [PubMed: 31720136]
18. Poludasu S, Ramkissoon K, Salciccioli L, Kamran H, Lazar JM. Left ventricular systolic function in sickle cell anemia: a meta-analysis. J Card Fail. 2013;19(5):333–41. [PubMed: 23663816]
19. 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(4):472–9. [PubMed: 17258093]
20. 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. 2016;37(14):1158–67. [PubMed: 26516176]
21. Barbosa MM, Vasconcelos MC, Ferrari TC, Fernandes BM, Passaglia LG, Silva CM, et al. Assessment of ventricular function in adults with sickle cell disease: role of two-dimensional speckle-tracking strain. J Am Soc Echocardiogr. 2014;27(11):1216–22. [PubMed: 25193638]
22. Junqueira FP, Fernandes JL, Cunha GM, TAK T, MAOL C, BPL 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. [PubMed: 24050721]
23. Sachdev V, Kato GJ, Gibbs JS, 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(13):1452–60. [PubMed: 21900080]

24. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277–314. [PubMed: 27037982]
25. Hammoudi N, Charbonnier M, Levy P, Djebbar M, Stankovic Stojanovic K, Ederhy S, et al. Left atrial volume is not an index of left ventricular diastolic dysfunction in patients with sickle cell anaemia. Arch Cardiovasc Dis. 2015;108(3):156–62. [PubMed: 25662698]
26. 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(3):243–52. [PubMed: 26897687]
27. Dang NC, Johnson C, Eslami-Farsani M, Haywood LJ. Myocardial injury or infarction associated with fat embolism in sickle cell disease: a report of three cases with survival. Am J Hematol. 2005;80(2):133–6. [PubMed: 16184576]
28. Wagdy R, Suliman H, Bamashmose B, Aidaroos A, Haneef Z, Samonti A, et al. Subclinical myocardial injury during vaso-occlusive crisis in pediatric sickle cell disease. Eur J Pediatr. 2018;177(12):1745–52. [PubMed: 30194527]
29. Charlot K, Hierso R, Lemonne N, Romana M, Tressieres B, Lalanne-Mistrih ML, et al. Changes in autonomic nervous activity during vaso-occlusive crisis in patients with sickle cell anaemia. Br J Haematol. 2017;177(3):484–6. [PubMed: 27009926]
30. Adebiyi AA, Oyebowale OM, Olaniyi AJ, Falase AO. Heart rate variability study in adult Nigerian subjects with sickle cell disease during vaso-occlusive crisis. Niger Postgrad Med J. 2019;26(1):8–12. [PubMed: 30860193]
31. Indik JH, Nair V, Rafikov R, Nyotowidjojo IS, Bisla J, Kansal M, et al. Associations of Prolonged QTc in Sickle Cell Disease. PLoS One. 2016;11(10):e0164526. [PubMed: 27736922]
32. Upadhya B, Ntim W, Brandon Stacey R, Henderson R, Leedy D, O'Brien FX, et al. Prolongation of QTc intervals and risk of death among patients with sickle cell disease. Eur J Haematol. 2013;91(2):170–8. [PubMed: 23621844]
33. Liem RI, Young LT, Thompson AA. Prolonged QTc interval in children and young adults with sickle cell disease at steady state. Pediatr Blood Cancer. 2009;52(7):842–6. [PubMed: 19229972]
34. Maisel A, Friedman H, Flint L, Koshy M, Prabhu R. Continuous electrocardiographic monitoring in patients with sickle-cell anemia during pain crisis. Clin Cardiol. 1983;6(7):339–44. [PubMed: 6883828]
35. Desai AA, Patel AR, Ahmad H, Groth JV, Thiruvoipati T, Turner K, et al. Mechanistic insights and characterization of sickle cell disease-associated cardiomyopathy. Circ Cardiovasc Imaging. 2014;7(3):430–7. [PubMed: 24676783]
36. Lindner JR, Belcik T, Widlansky M, Harmann LM, Karafin MS, Wandersee NJ, et al. Contrast-enhanced ultrasound detects changes in microvascular blood flow in adults with sickle cell disease. PLoS One. 2019;14(7):e0218783. [PubMed: 31276520]
37. Sachdev V, Sidenko S, Wu MD, Minniti CP, Hannoush H, Brenneman CL, et al. Skeletal and myocardial microvascular blood flow in hydroxycarbamide-treated patients with sickle cell disease. Br J Haematol. 2017;179(4):648–56. [PubMed: 28880374]
38. de Montalembert M, Maunoury C, Acar P, Brousse V, Sidi D, Lenoir G. Myocardial ischaemia in children with sickle cell disease. Arch Dis Child. 2004;89(4):359–62. [PubMed: 15033848]
39. Raman SV, Simonetti OP, Cataland SR, Kraut EH. Myocardial ischemia and right ventricular dysfunction in adult patients with sickle cell disease. Haematologica. 2006;91(10):1329–35. [PubMed: 17018381]
40. Wood JC. The heart in sickle cell disease, a model for heart failure with preserved ejection fraction. Proc Natl Acad Sci U S A. 2016;113(35):9670–2. [PubMed: 27512036]
41. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. N Engl J Med. 2019;381(6):509–19. [PubMed: 31199090]
42. Niihara Y, Miller ST, Kanter J, Lanzkron S, Smith WR, Hsu LL, et al. A Phase 3 Trial of l-Glutamine in Sickle Cell Disease. N Engl J Med. 2018;379(3):226–35. [PubMed: 30021096]

43. Ogunbayo GO, Misumida N, Olorunfemi O, Elbadawi A, Saheed D, Messerli A, et al. Comparison of Outcomes in Patients Having Acute Myocardial Infarction With Versus Without Sickle-Cell Anemia. Am J Cardiol. 2017;120(10):1768–71. [PubMed: 28867123]
44. Ginwalla M, AlMasoud A, Tofovic D, Alin T, Al-Kindi S, Oliveira G, et al. Cardiovascular evaluation and management of iron overload cardiomyopathy in sickle cell disease. Am J Hematol. 2018;93(1):E7–E9. [PubMed: 28971490]
45. Ruhl AP, Sadreameli SC, Allen JL, Bennett DP, Campbell AD, Coates TD, et al. Identifying Clinical and Research Priorities in Sickle Cell Lung Disease. An Official American Thoracic Society Workshop Report. Ann Am Thorac Soc. 2019;16(9):e17–e32. [PubMed: 31469310]
46. 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(9):886–95. [PubMed: 14985486]
47. Gladwin MT, Barst RJ, Gibbs JS, 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. PLoS One. 2014;9(7):e99489. [PubMed: 24988120]
48. 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(3):416–24. [PubMed: 25854714]
49. 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. 2019;53(1).
50. Anthi A, Machado RF, Jison ML, Taveira-Dasilva AM, Rubin LJ, Hunter L, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. Am J Respir Crit Care Med. 2007;175(12):1272–9. [PubMed: 17379852]
51. Naik RP, Streiff MB, Haywood C, Jr., Segal JB, Lanzkron S. Venous thromboembolism incidence in the Cooperative Study of Sickle Cell Disease. J Thromb Haemost. 2014;12(12):2010–6. [PubMed: 25280124]
52. Brunson A, Lei A, Rosenberg AS, White RH, Keegan T, Wun T. Increased incidence of VTE in sickle cell disease patients: risk factors, recurrence and impact on mortality. Br J Haematol. 2017;178(2):319–26. [PubMed: 28369826]
53. Mehari A, Gladwin MT, Tian X, Machado RF, Kato GJ. Mortality in adults with sickle cell disease and pulmonary hypertension. JAMA. 2012;307(12):1254–6.
54. 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(6):727–40. [PubMed: 24628312]
55. Machado RF, Mack AK, Martyr S, Barnett C, Macarthur P, Sachdev V, et al. Severity of pulmonary hypertension during vaso-occlusive pain crisis and exercise in patients with sickle cell disease. Br J Haematol. 2007;136(2):319–25. [PubMed: 17156401]
56. Mekontso Dessap A, Leon R, Habibi A, Nzouakou R, Roudot-Thoraval F, Adnot S, et al. Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease. Am J Respir Crit Care Med. 2008;177(6):646–53. [PubMed: 18174543]
57. 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(3):310–8. [PubMed: 16849664]
58. Mehari A, Igbineweka N, Allen D, Nichols J, Thein SL, Weir NA. Abnormal Ventilation-Perfusion Scan Is Associated with Pulmonary Hypertension in Sickle Cell Adults. J Nucl Med. 2019;60(1):86–92. [PubMed: 29880507]
59. Shet AS, Wun T. How I diagnose and treat venous thromboembolism in sickle cell disease. Blood. 2018;132(17):1761–9. [PubMed: 29764840]
60. 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(6):703–10. [PubMed: 26036801]

61. Kelly S, Quirolo K, Marsh A, Neumayr L, Garcia A, Custer B. Erythrocytapheresis for chronic transfusion therapy in sickle cell disease: survey of current practices and review of the literature. Transfusion. 2016;56(11):2877–88. [PubMed: 27759170]
62. 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(4):855–64. [PubMed: 21527519]
63. Birkeland P, Gardner K, Kesse-Adu R, Davies J, Lauritsen J, Rom Poulsen F, et al. Intracranial Aneurysms in Sickle-Cell Disease Are Associated With the Hemoglobin SS Genotype But Not With Moyamoya Syndrome. Stroke. 2016;47(7):1710–3. [PubMed: 27301940]
64. Kassim AA, Pruthi S, Day M, Rodeghier M, Gindville MC, Brodsky MA, et al. Silent cerebral infarcts and cerebral aneurysms are prevalent in adults with sickle cell anemia. Blood. 2016;127(16):2038–40. [PubMed: 26941400]
65. Pegelow CH, Colangelo L, Steinberg M, Wright EC, Smith J, Phillips G, et al. Natural history of blood pressure in sickle cell disease: risks for stroke and death associated with relative hypertension in sickle cell anemia. Am J Med. 1997;102(2):171–7. [PubMed: 9217567]
66. Rodgers GP, Walker EC, Podgor MJ. Is “relative” hypertension a risk factor for vaso-occlusive complications in sickle cell disease? Am J Med Sci. 1993;305(3):150–6. [PubMed: 8447334]
67. Gordeuk VR, Sachdev V, Taylor JG, Gladwin MT, Kato G, Castro OL. Relative systemic hypertension in patients with sickle cell disease is associated with risk of pulmonary hypertension and renal insufficiency. Am J Hematol. 2008;83(1):15–8. [PubMed: 17696198]
68. Sandhu MK, Cohen A. Aging in Sickle Cell Disease: Co-morbidities and New Issues in Management. Hemoglobin. 2015;39(4):221–4. [PubMed: 26182337]
69. Aessopos A, Farmakis D, Tsironi M, Diamanti-Kandarakis E, Matzourani M, Fragodimiri C, et al. Endothelial function and arterial stiffness in sickle-thalassemia patients. Atherosclerosis. 2007;191(2):427–32. [PubMed: 16712855]
70. Belizna C, Loufrani L, Ghali A, Lahary A, Primard E, Louvel JP, et al. Arterial stiffness and stroke in sickle cell disease. Stroke. 2012;43(4):1129–30. [PubMed: 22198986]
71. Graziadei G, Casoni FM, Annoni F, Cortinovis I, Ridolfi P, Gandolfi I, et al. Transcranial color Doppler in stroke-free adult patients with sickle cell disease. Ann Hematol. 2017;96(9):1547–55. [PubMed: 28730452]
72. Standards for Clinical Care of Adults with Sickle Cell Disease in the UK, 2nd Edition 2108 [Available from: https://www.sicklecellsociety.org/wp-content/uploads/2018/05/Standards-for-the-Clinical-Care-of-Adults-with-Sickle-Cell-in-the-UK-2018.pdf.

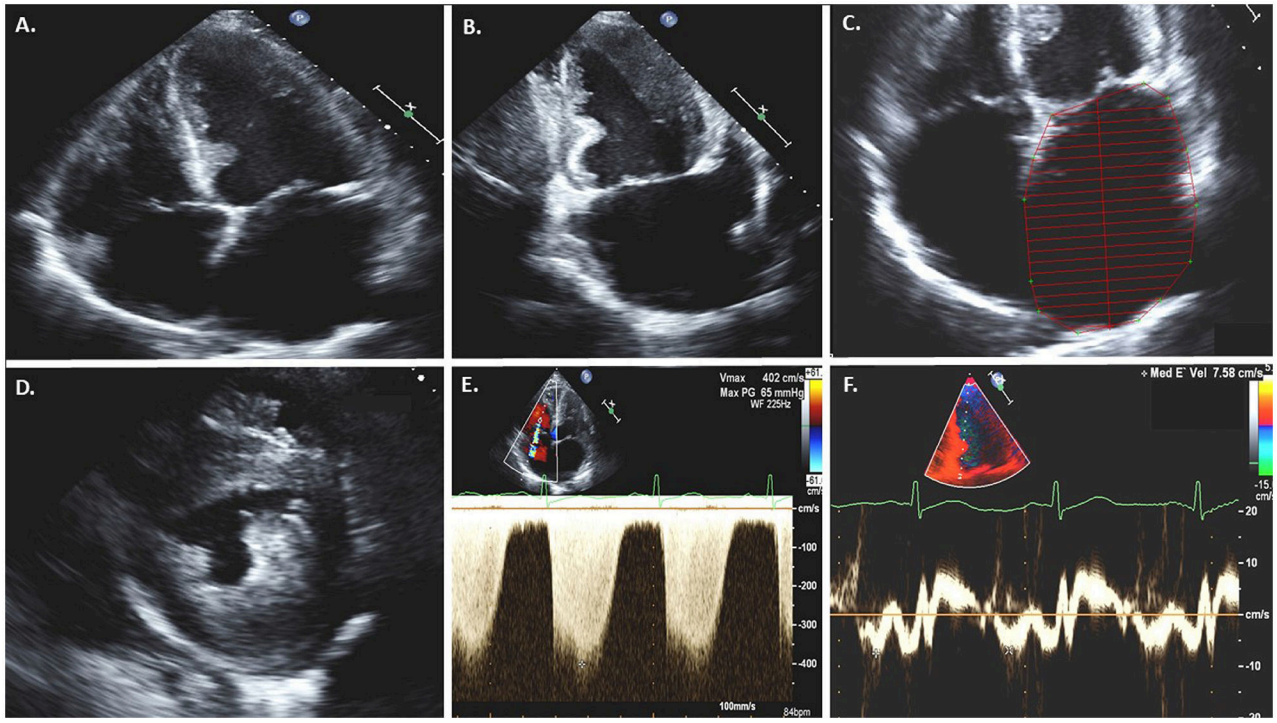

Figure 1.

60 year old man with sickle cell disease (HbSS), HTN, paroxysmal atrial fibrillation, and pulmonary hypertension. A. There is right heart dilation. B. The left atrium is severely dilated. C. Left atrial volume index is 105 ml/m^2 (normal ≤ 34 ml/m^2). D. Septal flattening is suggestive of RV pressure overload. E. Peak TR velocity is 4 m/s, gradient of 65 mmHg, estimated RVSP 75mmHg. F. Mitral annulus tissue Doppler peak septal e' velocity is 7.6 cm/s with E/e' ratio of 14 suggesting elevated LV filling pressure.