

# Cardiac Complications of Sickle Cell Disease



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## Mona's Case

A 33-year-old, African-American female presents with nonproductive cough and progressive dyspnea on exertion over the past two months. On examination, she has a hyperdynamic precordium, a displaced apex, and a regurgitant systolic murmur. She desaturates upon walking. Her past medical history is significant for sickle cell disease with previous hospital admissions for acute chest syndrome.

## Sickle Cell Disease

Sickle cell disease is the most common structural hemoglobinopathy in the world, affecting 30 million individuals worldwide.<sup>1</sup> It affects 8% of the African American population in its heterozygous form, and 0.15% of African Americans are homozygous for the single nucleotide substitution in the B-globin gene that forms the mutated Hemoglobin S molecule.<sup>1</sup> When deoxygenated, Hemoglobin S is much less soluble than Hemoglobin A. Subsequent polymerization and aggregation within the microcirculation can lead to acute sickle crisis and acute chest syndrome (vaso-occlusion and ischemia within the pulmonary vasculature characterized by chest pain, fever, tachypnea, wheeze, cough, and new radiographic infiltrate). With improved treatment,

many individuals are now surviving well into adulthood, where they now face a different set of challenges.

## Cardiac Complications

Cardiac complications (generally attributed to chronic hemolysis) include cardiac enlargement, biventricular dysfunction, myocardial ischemia, and pulmonary hypertension. Iron overload from chronic transfusions can also result in cardiac hemosiderosis.

### Heart Failure

Chronic anemia can lead to a chronic high-cardiac output state. By the fourth or fifth decade of life, this chronic volume overload leads to cardiomegaly, ventricular dilatation, and diastolic dysfunction, often with preserved ejection fraction.

### Myocardial Infarction (MI)

Acute myocardial infarction is an often unsuspected complication that can lead to premature death. Clumping within the coronary arteries leads to acute reduction in flow, even in the absence of atherosclerosis. Chest pain may mimic the more commonly seen acute chest syndrome. The diagnosis is further complicated by the fact that ECG changes are often

nonspecific, and bloodwork is often negative. In a recent systematic review, just over half of sickle cell patients with MI had initial elevation in cardiac enzymes.<sup>2</sup> Management includes hydration, transfusion as needed, oxygen, and pain management to help prevent sympathetic overstimulation. There is no good evidence regarding typical management strategies, such as ASA, heparin, or thrombolytics.

### *Pulmonary Hypertension*

One of the most life-altering complications with sickle cell disease is pulmonary hypertension, which is associated with an impaired exercise tolerance, progressive heart failure, and a high mortality rate (as high as 50% 2-year mortality rate in confirmed cases).<sup>1</sup> The prevalence of pulmonary hypertension in this population based on echocardiographic criteria ranges from 30 to 63% in various studies and is more common in those who are older and those with multiple prior acute chest syndrome events.<sup>3</sup> Pulmonary arterial pressures were also significantly higher in those who were more severely anemic.<sup>3</sup>

The pathogenesis of pulmonary hypertension in this population is multifactorial. Potential theories contend that the free hemoglobin that arises from hemolysis both inactivates and impairs nitric oxide synthesis, resulting in inhibition of vasodilation. Chronic hypoxemia, recurrent thromboembolism,

parenchymal and vascular injury due to sequestration of sickle red blood cells, chronic liver disease, and asplenia also contribute. Half of the patients with pulmonary hypertension have elevated left-sided pressures as a contributing factor.<sup>4</sup>

Routine annual screening with echocardiography has been suggested. However, a recent study suggests poor correlation between echocardiographic and invasively determined pulmonary pressures in this population. The positive predictive value of echo for pulmonary hypertension was found to be only 25%, suggesting a lower true prevalence of pulmonary hypertension in the sickle cell disease population (< 10%) than originally thought.<sup>4</sup> The inclusion of additional criteria, such as elevated NT-proBNP levels and reduced six minute walking distance, still did not provide an adequate tool for screening for pulmonary hypertension. The optimal approach for screening remains uncertain. A high degree of suspicion is needed in higher risk individuals, including older patients and those with exertional dyspnea, iron overload, chronic liver disease, nocturnal hypoxia, or HIV. A multi-investigational algorithm that includes right-heart catheterization has also been proposed.

Prostacyclin analogs, phosphodiesterase-5 inhibitors, and endothelin receptor antagonists are agents currently employed in the treatment of pulmonary hypertension, but there is no

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current long-term data on the safety and efficacy of these medications within the sickle cell disease population. A recent clinical trial evaluating the role of sildenafil in this population was halted early due to a significant increase in adverse events (mainly acute pain crises) in the treatment arm.<sup>5</sup> As such, the focus currently remains on maximizing sickle cell disease-specific therapy and treating identified associated conditions, with consideration for employing targeted therapy with pulmonary vasodilator and anti-remodeling agents after weighing the risks and benefits. **Dx**

#### References

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3. Ahmed S, Siddiqui AK, Sadiq A, *et al*: Echocardiographic Abnormalities in Sickle Cell Disease. *Am J Hematol* 2004; 76(3): 195–198.

## Take-home Messages

Cardiac dysfunction and pulmonary hypertension are becoming more common as survival with sickle cell disease improves. A good understanding of the basic pathophysiology and a high degree of suspicion may help identify those patients who could benefit from further testing.

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