

## My Approach to Imaging in Sickle Cell Anemia

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### Abstract

Sickle cell disease (SCD) is recognized as a global problem in public health, characterized by the alteration in the red blood cells to the sickle form. Moreover, chronic anemia can also be observed through the change in the rheology of the red blood cells, leading to a scenario of inflammation and oxidative stress, making SCD a multisystem disease. Cardiac output (CO) proved to be high, leading to an overall increase in the heart chambers and an eccentric myocardial hypertrophy. These heart alterations were attributed only to adaptive reactions to chronic anemia. Recent studies have more clearly recognized an association with pulmonary hypertension (PH), left ventricular diastolic dysfunction, arrhythmias, and sudden death. Moreover, what has also arisen in this context is the hypothesis of the existence of a sickle-cell cardiomyopathy, characterized by diastolic dysfunction and restrictive physiology. The echocardiogram represents a key tool in determining cavitory volumes, diastolic dysfunction, and the estimation of pulmonary pressure, as well as constitutes a valuable resource in the diagnosis and therapeutic treatment of acute chest syndrome. The myocardial strain, rotational variables, myocardial work, and 3D echocardiography can be applied in an attempt to aid in the early detection of patients who are at a higher risk of developing complications and evolving to death related to SCD.

### Introduction

Sickle cell disease (SCD) is the most prevalent hereditary hematological condition in the world, affecting about 5 million people, and it is estimated that 300,000 babies are born with SCD per year, being recognized by the World Health Organization (WHO) and Organization of the United Nations (UN) as a global public health concern.<sup>1,2</sup> A typical

characteristic is the inheritance of mutant hemoglobin S, resulting from the replacement of a glutamic acid by a valine in position 6 of the beta chain, with consequent physical-chemistry modification in hemoglobin molecule.<sup>3</sup> SCD encompasses the homozygosity of hemoglobin S (SS), which constitutes sickle cell anemia (SCA), and associations with other hemoglobin variants, such as Hb C (SC), Hb D (SD), Hb E (SE), and interactions with thalassemias (S $\beta^0$ , S $\beta^+$  and S $\alpha$ ). Sickle cell trait, heterozygosity for HbS, is not considered a disease.<sup>4</sup>

SCD is characterized by the strong tendency of mutant hemoglobin to polymerize, causing the red blood cell to change into a sickle shape, altering the erythrocyte membrane and the rheology of red blood cells, causing a scenario of intense hemolysis, occlusion of microvasculature, endothelial dysfunction, nitric oxide (NO) deficiency, inflammation, oxidative stress, increased neutrophil adhesiveness, activation of coagulation, making SCD a multisystem disease with high mortality, with a current average survival close to 50 years, even in developed countries.<sup>5,6</sup> Mortality results mainly from target-organ lesion, with a high incidence of sudden death in young adults and, currently, cardiopulmonary complications are the most common cause of death in this population<sup>7</sup> (Figure 1).

### Cardiovascular manifestation of SCD

The regime of chronic anemia leads to adaptations that maintain adequate supply of oxygen to the tissues due to compensatory mechanisms. Non-hemodynamic mechanisms (stimulation of erythropoiesis) and hemodynamic mechanisms acting through afterload reduction (bradykinin, adenosine, NO) and preload increase (renin-angiotensin-aldosterone system) and even greater inotropic and chronotropic stimulation resulting from greater reflex sympathetic activity justify the increase in left ventricular function and the state of high cardiac output (CO).<sup>8</sup> These cardiac alterations classically found in SCD, such as enlargement of cardiac chambers, were only attributed to adaptive reactions to the chronic anemic state. Recent studies patently recognize the association with pulmonary hypertension (PH), left ventricular diastolic dysfunction, arrhythmia and sudden death and, in this context, the hypothesis of sickle cell cardiomyopathy characterized by diastolic dysfunction and restrictive physiology<sup>9</sup> (Figure 1). Coronary artery disease and cardiomyopathy secondary to iron overload are infrequent in these patients.<sup>7</sup> The most important aspects to be evaluated by echocardiography in SCD are presented below, as well as the indications for

### Keywords

Sickle Cell Anemia; Diastolic Dysfunction; Pulmonary Hypertension

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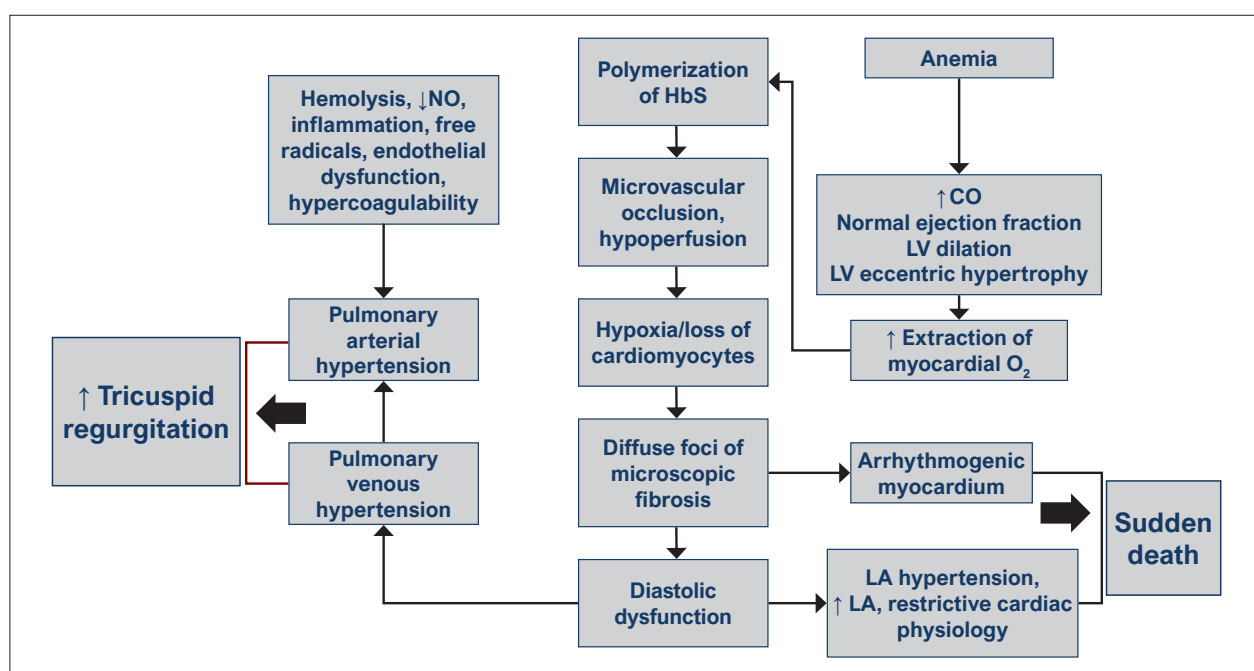
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**Figure 1** – Mechanism proposed for sickle cell cardiomyopathy. Source: modified Rai et al. 2017.<sup>7</sup> LV: left ventricle; LA: left atrial; HbS: hemoglobin; NO: nitric oxide; O<sub>2</sub>: oxygen; CO: cardiac output.

echocardiography in the cardiological evaluation in this population (Table 1).

### Quantification of the heart chambers

In SCD, CO is high due to increased systolic volume, with increased blood volume resulting from increased plasma volume and decreased peripheral resistance. Increased CO leads to enlargement of cardiac chambers globally, and eccentric-type myocardial hypertrophy. Abnormalities are of a progressive nature, and are more exuberant in the more advanced age groups. It is believed that right ventricle (RV) dilation occurs later and is less intense than that of the left cavities.

In order to properly quantify the cardiac chambers in this population, the internal linear measurement of the cardiac cavities and their walls should be carried out routinely and, ideally, cavity volumes must be measured by indexing the patient's body surface on two-dimensional echocardiography (Figure 2). Three-dimensional echocardiography, if available, can more accurately and reproducibly assess not only cavity volumes, but also left ventricle (LV) mass and function.

It is also relevant to highlight some difficulties related to the echocardiographic evaluation of this particular population, since most patients have body mass index significantly reduced, chronic pain with relative limitation of mobility and, often, tachycardia during the test.

### Systolic function and myocardial strain

Left ventricular systolic function seems to be preserved in most patients with SCD, despite significant LV dilation,

**Table 1** – Echocardiogram indications in the cardiac assessment of patients with SCD

Assessment of signs suggestive of PH and estimation of pulmonary pressure through maximum TRV.

Assessment of cavity diameters and volumes.

Assessment of ventricular hypertrophy.

Analysis of systolic function and diastolic function.

Assessment of heart murmur evaluation and associated valvopathy.

Analysis of cardiac impairment due to associated comorbidities.

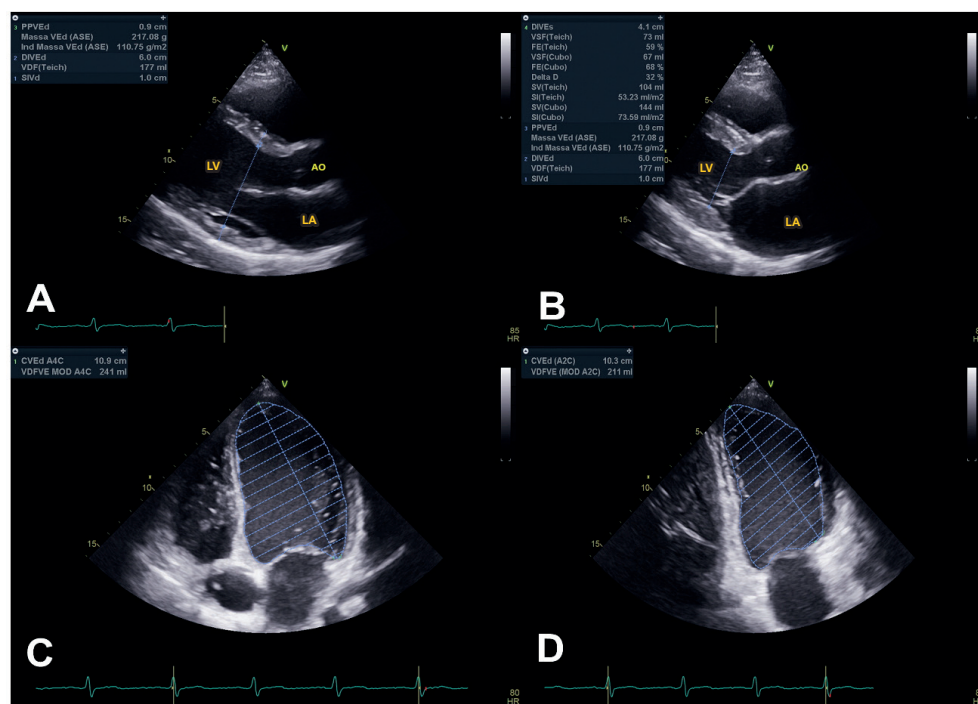
Cardiological assessment in ACS helps detect transient elevations in pulmonary pressure and right ventricular dysfunction in the acute period.

Assessment of patients with clinical and laboratory criteria of disease severity.

PH: pulmonary hypertension; TRV: tricuspid regurgitation velocity; ACS: acute chest syndrome.

which is the rule in this population (Figure 2). Segmental abnormalities and coronary artery disease are rare.<sup>9</sup> When systolic dysfunction is present, it is mainly identified in older patients with associated diseases, such as systemic arterial hypertension and kidney disease.<sup>10</sup>

For many years, it has been considered that conventional parameters for measuring ejection fraction, due to their



**Figure 2** – (A) Two-dimensional echocardiography (parasternal long-axis view) in a 20-year-old patient with SCA, showing left ventricular diastolic diameter of 60 mm. (B) Same patient, showing LA volume of 46 ml/m<sup>2</sup> (reference: <34 ml/m<sup>2</sup>). (C)/(D) Same patient, showing left ventricular volume of 118 ml/m<sup>2</sup> (reference: <74 ml/m<sup>2</sup>). LV: left ventricle; LA: left atrium; AO: aorta.

great influence from pre- and after-load abnormalities, would not serve to assess systolic function in patients with SCD, hiding the intrinsic function of the cardiac muscle. Therefore, preference should be given to the assessment of biventricular systolic function using two-dimensional and three-dimensional strain, if available, rotational variables (twist and torsion) and myocardial work (Figure 3).<sup>11-13</sup>

Several factors can influence the analysis by myocardial strain in the context of SCD: ethnicity, race, sex, age and hemodynamic factors (hyperdynamic state and hypervolemia).<sup>14</sup> And there may be technical limitations for three-dimensional echocardiography: mobility difficulty and respiratory apnea in image acquisition, difficulty in image acquisition with high heart rate, and difficulty acquiring the full image in the large ventricles.

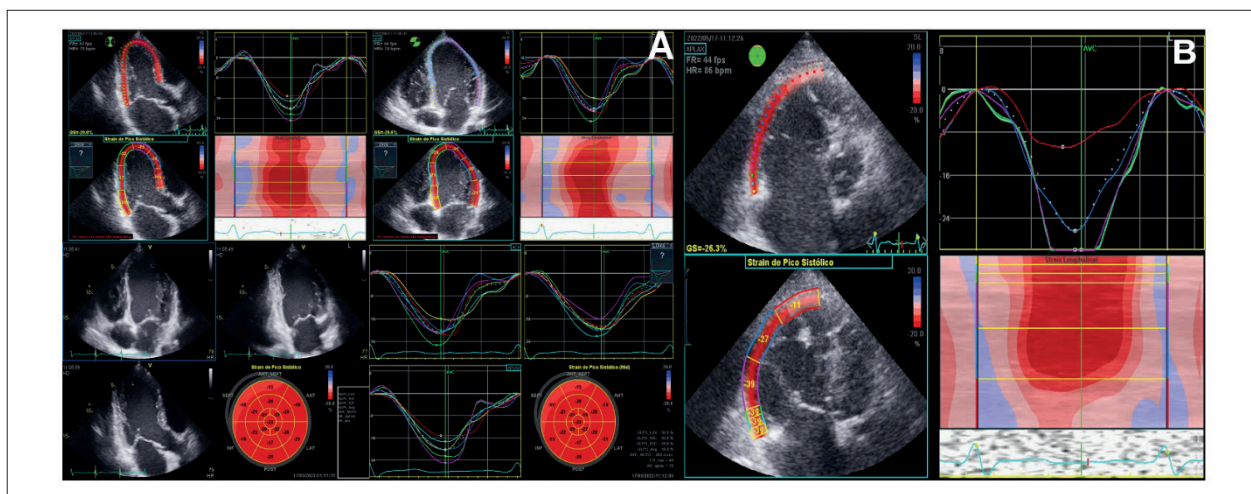
### Diastolic dysfunction

LV diastolic dysfunction is common in patients with SCD, classically related to ventricular dilation and eccentric myocardial hypertrophy in response to chronic anemia, being an independent predictor of reduced exercise tolerance and mortality in these patients.<sup>15</sup> Recently, some experimental studies with anatomopathological analysis and cardiac resonance analysis have considered the possibility of myocardial fibrotic involvement due to the sequelae of microscopic ischemic events, resulting in restrictive ventricular filling and left atrial (LA) enlargement<sup>9</sup> (Figures 1 and 4).

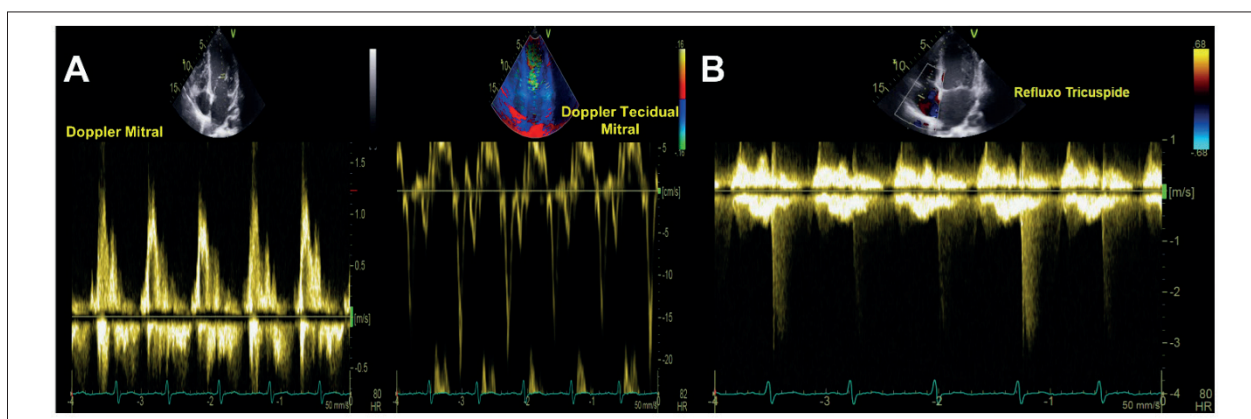
Echocardiographic analysis of LV diastolic function is an integral part of the routine evaluation of patients with symptoms of dyspnea or heart failure. Diagnosis of diastolic dysfunction in this population is highly challenging, as patients usually have dilated LV and preserved ejection fraction, in addition to obvious signs of volume overload. To start the evaluation, it must be determined whether there is myocardial disease (evidence of relevant structural or functional heart disease, such as left ventricular hypertrophy — LVH — and/or systolic dysfunction) and, considering this determination, we suggest the evaluation of LV with routine two-dimensional strain for all patients. In addition, objective measures should be taken to assess filling pressures and diastolic function, which should be determined by analyzing echocardiographic variables, including mitral flow velocities, mitral annulus velocities, E/e' ratio, maximum tricuspid regurgitation velocity (TRV) and indexed LA volume. The four currently recommended variables and abnormal cutoff values are: 1) Mean E/e' ratio >14; 2) Abnormal velocity of septal e' <7 cm/sec or lateral e' <10 cm/sec; 3) Indexed LA volume >34 ml/m<sup>2</sup>; 4) Maximum tricuspid regurgitation (TR) speed >2.8 m/sec.<sup>16</sup>

### PH

PH is a common serious complication in patients with SCD, being an important marker of mortality in these patients.<sup>17</sup> PH in SCD is mixed, having a pre-capillary



**Figure 3 –** (A) Transthoracic echocardiogram (apical view) for analysis of the longitudinal strain in 20-year-old patient with SCA, showing preserved contractile function in each of the segments with LV global longitudinal Strain : -19.9 (Reference: <-16.9). (B) Same patient, showing preserved contractile function in each of the RV free wall segments, analysis of right ventricular longitudinal strain with RV free wall strain result: -26.3 (Reference: <-20).



**Figure 4 –** (A) Diastolic flow in 20-year-old patient with SCA. Note the septal  $E/e'$  ratio of 21, resulting in a worse prognosis. (B) Same patient, showing TRV of 3.0 m/s, resulting in a worse prognosis.

arterial component (pulmonary arterial hypertension — PAH) due to progressive increase in pulmonary vascular resistance (hemolysis,  $\downarrow$ NO, inflammation, free radicals, endothelial dysfunction, hypercoagulability, chronic thromboembolism) and a post-capillary venous component (venous pulmonary hypertension — VPH) (LV diastolic dysfunction). It is currently classified in PH group 5 due to multifactorial mechanisms (Figure 4). Estimation of pulmonary pressure by echocardiography is carried out mainly by measuring the TRV by which the pulmonary artery systolic pressure — PASP — is estimated (derived from the Bernoulli equation;  $PASP = 4 \text{ times the determination of TRV squared, then adding an estimated right atrial pressure}$ ). TRV greater than 2.9 m/s defines a subgroup of risk, occurring in approximately 10% of adults with SCD, and is associated with a relative risk of death of approximately 10, according to previous studies.<sup>18</sup> Intermediate TRV values between 2, 5 and 2.9 m/s remain a source of controversy. However, these patients also seem

to have decreased exercise capacity and increased mortality with 4 risk ratio of death.<sup>17</sup> Although the vast majority of epidemiological studies conducted to date have shown that a mild to moderate elevation of RV systolic pressure (TRV  $\geq 2.5$  m/s) is common in adults with SCD, it is associated with a higher rate of risk of early death. The 2.5 m/s cutoff leads to hyperdiagnosis of PH, and higher TRV thresholds ( $>2.9$  m/s) improves specificity.<sup>18</sup> Due to the high risk of developing PH, patients with SCD should undergo regular echocardiography scans at least every two or three years to identify the presence of increased pulmonary pressures.<sup>19</sup>

#### Acute chest syndrome

Acute chest syndrome (ACS) consists of a combination of signs and symptoms including dyspnea, chest pain, fever, cough and hypoxemia, associated with the emergence of a new pulmonary infiltrate. The etiology is complex and multifactorial, involving infectious and non-infectious causes



and in a high number of cases it is not possible to define the etiology. Diagnosis of ACS is extremely important due to significant morbidity and mortality and high recurrence. Echocardiography in this scenario is usually performed at the bedside and often shows a transient increase in pulmonary pressure and right ventricular dysfunction in the acute condition, having a fundamental diagnostic and prognostic application in this context. Patients with TRV  $\geq 3$  m/s on echocardiography during the acute event are at particularly higher risk of multiorgan failure and sudden death. Point-of-care lung ultrasound has also proven to be an important tool in ACS, reducing diagnostic radiation in the sickle cell population.<sup>20</sup>

## Conclusions

SCD evolves with cardiovascular manifestations characteristically with restrictive cardiomyopathy (diastolic dysfunction, LA enlargement and preserved ejection fraction) and PH (pulmonary arterial hypertension and pulmonary venous hypertension). The echocardiogram is a fundamental instrument for determining cavity volumes, diastolic function, and estimating pulmonary pressure, and constitutes a valuable resource in the diagnosis and therapeutic management of ACS. Myocardial strain, rotational variables, myocardial work and 3D echocardiography can be used in an attempt to support the

early identification of patients at greater risk of developing complications and death related to SCD.

## Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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## Study Association

This study is not associated with any thesis or dissertation work.

## Author Contributions

Writing of the manuscript: Braga JCMS; critical revision of the manuscript for intellectual content: Guimarães Filho FV, Rodrigues A, Silva RAB.

## Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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