haematologica
Journal of the Ferrata Storti Foundation

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Received: January 19, 2026.
Accepted: January 28, 2026.

Citation: Thomas d'Humières and Mariane de Montalembert. Heart starts suffering early in sickle cell disease. Haematologica. 2026 Feb 12. doi: 10.3324/haematol.2025.300395 [Epub ahead of print]

Heart starts suffering early in sickle cell disease

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Authors' contributions

Both authors contributed equally to the writing of this article.

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Disclosures

Thomas d'Humières: none

Mariane de Montalembert: Boards of Vertex and Theravia. Speakers' bureau of Novonordisk.

In this Issue, Bulbul and Abboud present original data on cardiac findings in a cohort of 118 children with sickle cell disease (SCD) (mean age 11.8 years, 66% with HbSS phenotype) compared with 67 age- and sex-matched controls (1). They evaluate left ventricular (LV) global longitudinal strain (GLS) using speckle-tracking echocardiography which enables early detection of myocardial dysfunction before abnormalities appear in conventional echocardiographic parameters (2). Compared to controls, SCD patients had significantly lower, but still normal, GLS (–21.5% vs. –22.3%; $p < 0.001$), together with chamber dilation and higher transmitral and tricuspid velocities. Although systolic function was preserved, prior stroke and avascular necrosis predicted lower strain, while markers of hemolysis, hemoglobin levels, and hydroxyurea use did not. They conclude that SCD patients exhibit significant cardiac remodeling and worse diastolic function parameters, with preserved, yet lower, LV GLS.

This article is particularly important as it sheds light on the heart in children with SCD, an organ that has rarely been studied in children to date (3,4) This is particularly surprising given that cardiovascular abnormalities are the leading contributors to SCD-related mortality in adults, accounting for more than 30% of all deaths in SCD patients in the United States (5).
In fact, what we call “cardiac complications” in adulthood are the visible endpoint of a process that starts in childhood, silent and cumulative. The study by Abboud and colleagues in this issue of *Haematologica* offers a rare window onto that continuum.

Children with SCD live in a state of chronic anemia and expanded plasma volume. Their hearts are large because they experience a chronic state of renin-angiotensin-aldosterone activation due to poor kidney perfusion, ultimately increasing cardiac preload. The enlarged left ventricle, higher E/A ratio, and increased left-atrial volume initially reflect volume adaptation, not necessarily diastolic impairment. That single fact should reshape how we look at the heart in these patients—not as an organ that fails late, but as one that begins adapting too early (6,7).

The absence of correlation between strain and hemolysis, coupled with its association with stroke and avascular necrosis, is particularly insightful. It mirrors what we recently reported: SCD adults with ventricular arrhythmias displayed lower LV strain despite identical anemia, hemolysis markers, and chamber dimensions (8). In both settings, the problem may not lie in red cell breakdown but in oxygen delivery—in how well oxygen reaches its targets. Several publications have reported impaired myocardial perfusion in children with SCD (3, 9).The

same inefficiency that compromises cerebral and bone perfusion during vaso-occlusive episodes likely affects the myocardium, producing subtle mechanical fatigue long before fibrosis. In this light, LV strain may act as a biological seismograph of oxygen debt—an integrative marker of perfusion adequacy rather than a reflection of hemolysis. This interpretation calls for further mechanistic evaluation but links the cardiac, neurologic, and skeletal manifestations of SCD as different expressions of a single mechanism: chronic, spatially heterogeneous hypoxia–reoxygenation injury.

GLS has become the emblem of "subclinical LV dysfunction" across cardiovascular medicine, yet its meaning in SCD remains elusive. In ischemic, hypertensive, or hypertrophic disease, reduced strain mirrors fibrosis and is associated with sudden death from rhythmic causes (10). In SCD, where preload is persistently elevated and myocardial fibers are chronically stretched, a modest reduction may instead signal altered energetics— being the mechanical trace of metabolic exhaustion rather than structural damage. The difference reported by Abboud's group (< 1 %) may appear negligible, but its reproducibility across cohorts argues that it is significant: perhaps the first measurable tremor of a long process.

The cardiovascular narrative of SCD must be written from childhood onward. This study pulmonary hypertension or arrhythmias—could shift our approach from repair to prevention. Even in "steady state," the heart changes as the disease progresses. The longitudinal decline in GLS over 3.7 years observed here reminds us that normality in SCD is a moving target. The integration of such monitoring into pediatric care could redefine what "stable condition" really means: not rest, but slow wear.

Current guidelines, such as the 2019 ASH recommendations, still discourage routine echocardiography in asymptomatic children (11). Yet the convergence of evidence—from cerebral imaging, bone necrosis, arrhythmia cohorts, and now myocardial strain—suggests that cardiac follow-up might one day become as essential as transcranial Doppler was twenty years ago.

The coherence between strain, stroke, and bone necrosis calls for further studies that might lead to a unifying model of SCD cardiomyopathy. The paradigm is no longer limited to hemolytic endothelial injury, but also includes multi-organ perfusion insufficiency. The myocardium is both victim and mirror: its strain reflects the cumulative failure of oxygen-delivery systems—mechanical, rheological, endothelial, and metabolic. The challenge now is

not merely to describe altered strain but to situate it within this broader “oxygen economy” that defines the systemic phenotype of SCD.

Abboud and colleagues remind us that the sickle heart does not wait for adulthood to suffer; it begins adapting in childhood. The small reduction in strain they report is not trivial—but clinically meaningful. It may be the cardiac echo of the same imbalance that drives stroke and osteonecrosis: an organism fighting to deliver enough oxygen to itself. Following that signal across the lifespan may do more than detect disease—it may chart the natural history of adaptation. The heart, like the brain and the bone, tells the story of oxygen supply—and sometimes it whispers the warning long before it breaks.

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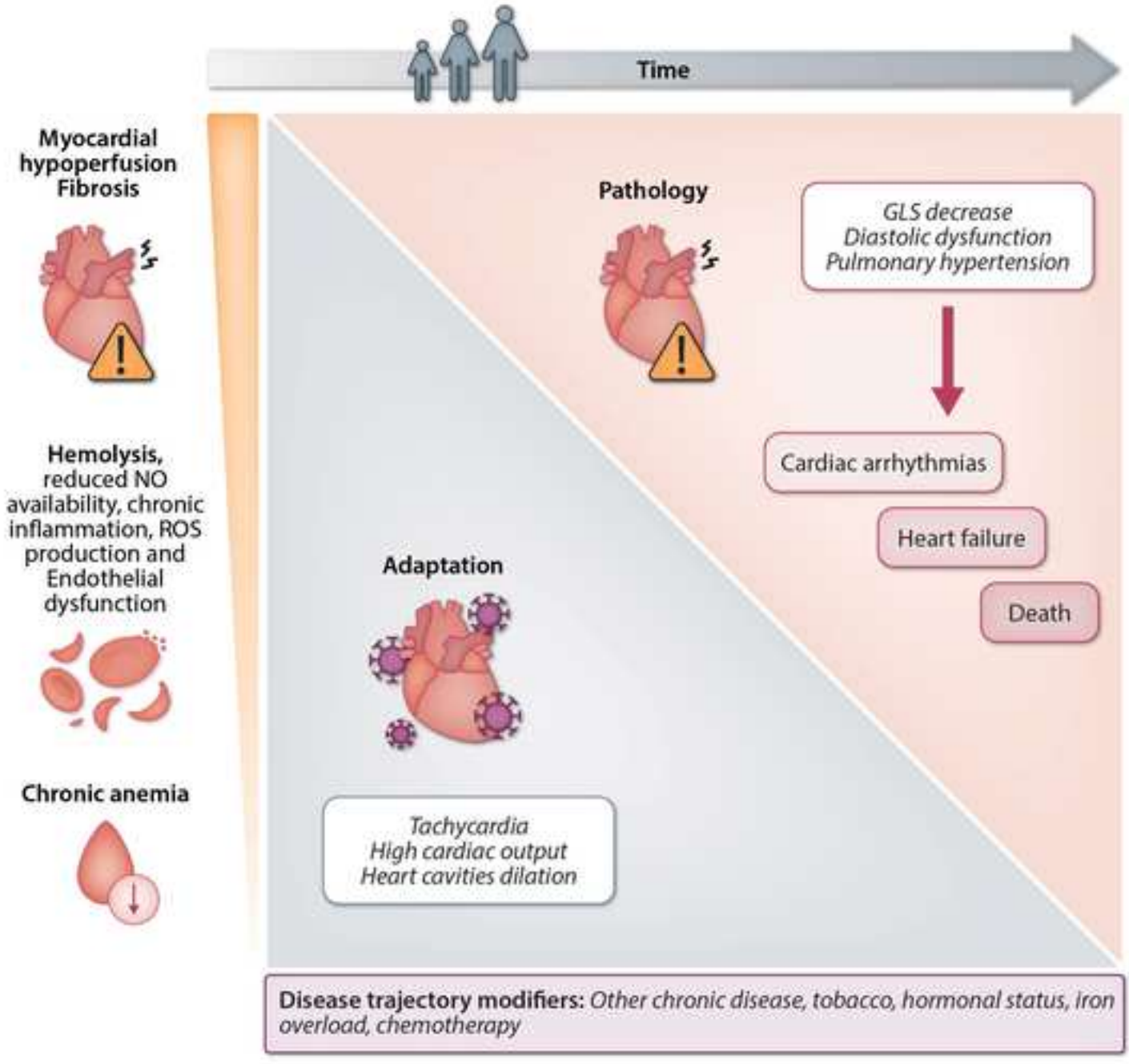
Figure 1: Age-related cardiac changes in sickle cell disease


Time
Myocardial hypoperfusion Fibrosis
Hemolysis, reduced NO availability, chronic inflammation, ROS production and Endothelial dysfunction
Chronic anemia
Pathology
GLS decrease
Diastolic dysfunction
Pulmonary hypertension
Cardiac arrhythmias
Heart failure
Death
Adaptation
Tachycardia
High cardiac output
Heart cavities dilation
Disease trajectory modifiers: Other chronic disease, tobacco, hormonal status, iron overload, chemotherapy