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Left ventricular strain and chamber dimensions in pediatric sickle cell disease: age-related reduction in myocardial deformation independent of hemolysis and hydroxyurea therapy

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Abstract

Sickle cell disease (SCD) is associated with cardiovascular complications. Speckle-tracking echocardiography enables early detection of myocardial dysfunction before abnormalities appear in conventional echocardiographic parameters. This study evaluated left ventricular (LV) global longitudinal strain (GLS) in pediatric SCD patients, and its relationship with traditional LV function indices, disease complications, hemolysis markers, and disease-modifying therapy. We retrospectively analyzed 278 echocardiograms from 185 participants (118 SCD patients, mean age 12.2 years; 67 age- and sex-matched controls, mean age 11.8 years) obtained between 2015 and 2023. Among the SCD cohort, 66.1% had the HbSS genotype, 9.3% had HbSβ^0-thalassemia, and 17.8% had HbSβ^+-thalassemia; the majority (83.9%) were on hydroxyurea. Compared to controls, SCD patients had significantly lower, but still normal, GLS (–21.5% vs. –22.3%; $p < 0.001$), along with significantly larger chamber diameters, elevated mitral valve E velocity, E/A ratio, and tricuspid regurgitation maximal velocity. Prior stroke ($\beta = 0.9$) and avascular necrosis ($\beta = 1.51$) were independently associated with worse GLS. The different genotypes did not exhibit significant difference in GLS. The strain values did not correlate with hemolysis markers, suggesting that other mechanisms may underlie myocardial impairment. A significant age-related decline in GLS was detected, with an inflection point at approximately 9.9 years. Longitudinal analysis of LV strain in the SCD cohort demonstrated a small decline from –21.6% to –21.2% over a 3.7-year follow-up period. Finally, pediatric SCD patients exhibit significant cardiac remodeling and diastolic dysfunction with preserved, yet lower, LV GLS, underscoring the need for further research in this population.

Introduction

Sickle cell disease (SCD) is the most common monogenic disorder, with an estimated 300,000 live births affected annually worldwide [1]. It is particularly prevalent in sub-Saharan Africa and the Middle East, as well as in regions with a high proportion of individuals of African descent [2]. SCD is characterized by chronic hemolytic anemia, recurrent vaso-occlusive episodes, and multiorgan ischemia, often worsened by reperfusion injury [2, 3]. Cardiovascular complications represent a major source of morbidity and mortality in adult patients with SCD [4]. Notably, the prevalence of cardiovascular complications in this population appears to be increasing, primarily due to increased awareness and overall survival [5]. Myocardial injury in SCD patients begins early in life and often remains subclinical for years [6]. The underlying pathophysiology is multifactorial. Chronic anemia leads to increased cardiac output and chamber dilation as a compensatory response. In parallel, microvascular occlusion, vascular remodeling, hypoxia, and hemolytic endothelial injury promote progressive myocardial dysfunction and pulmonary hypertension. Hemolysis further exacerbates this process by scavenging nitric oxide, which causes endothelial dysfunction, vasoconstriction, and oxidative stress. In some cases, iron overload is suggested to exacerbate the process [5]. In addition to these mechanisms, both acute and chronic inflammation play a critical role in overall SCD complications including cardiovascular complications [7]. The acute inflammatory surges during vaso-occlusive crises and acute chest syndrome, and the chronic low-grade inflammation during steady state, promote endothelial activation, leukocyte recruitment, and vascular remodeling [8]. The most notable cardiac sequelae include pulmonary hypertension, as well as ventricular systolic and diastolic dysfunction [5, 9]. While such implications manifest in adulthood, regular cardiac surveillance during early childhood is essential to detect early myocardial changes. Formal guidelines currently do not endorse routine cardiac imaging in asymptomatic pediatric SCD. The

American Society of Hematology (ASH) 2019 Guidelines recommends against regular routine echocardiographic screening in asymptomatic children and emphasizes the importance of a targeted history and physical examination to idnetify those who warrant further cardiac evaluation [10].

Traditionally, left ventricular (LV) systolic function is assessed using two-dimensional transthoracic echocardiography (TTE). However, conventional parameters such as ejection fraction are dependent on loading conditions and heart rate and may lack sensitivity to early myocardial dysfunction [11]. In this context, myocardial strain analysis using speckle-tracking echocardiography (STE) has emerged as a promising technique to evaluate myocardial deformation in longitudinal, radial, and circumferential planes [12]. STE enables the detection of subclinical myocardial dysfunction at earlier stages than conventional echocardiographic parameters and has demonstrated utility across diverse cardiovascular diseases [13, 14].

STE is a post-processing software technique that identifies and tracks natural acoustic markers, or "speckles," created by the interaction of ultrasound waves with myocardial fibers. By tracking the motion of these speckles frame by frame throughout the cardiac cycle, STE quantifies myocardial deformation (strain) in different directions- longitudinal, circumferential, and radial- providing a detailed assessment of systolic and diastolic function. Unlike Doppler-based methods, STE is angle-independent and provides reproducible measurements of systolic and diastolic function. The technique does not require specialized hardware beyond conventional echocardiography equipment, but it relies on vendor-specific or independent software platforms and standardized acquisition protocols. Accurate image acquisition and interpretation require training and expertise, typically by cardiologists or experienced sonographers, and inter-vendor variability remains an important limitation despite ongoing international efforts toward standardization [12, 15]. In the pediatric population,

longitudinal strain is the most commonly used parameter due to easier acquisition of apical views and the relatively low incidence of regional wall motion abnormalities [16].

A growing body of research has explored the use of myocardial strain in patients with SCD as an early marker of cardiac involvement [17, 18], with some studies highlighting its potential role in patients with preserved ejection fraction [18]. However, the extent and clinical significance of ventricular strain abnormalities in this population remain insufficiently investigated, particularly in children. Although studies on myocardial strain in children with SCD are relatively limited, early work such as the 2012 report by Blanc et al. demonstrated altered right ventricular systolic strain, and more recent investigations have expanded this field by evaluating longitudinal strain in larger pediatric cohorts [19-21]. Nevertheless, the findings remain inconsistent and are highly limited by small sample sizes and potential confounding factors, including varying degrees of anemia and differences in the use of disease-modifying therapies and transfusion regimens.

Given these gaps in knowledge, there is a critical need for larger studies to better characterize myocardial strain in pediatric SCD patients and to identify its clinical implications. This study aims to evaluate LV function in children with SCD using longitudinal strain imaging and to explore its relationship with disease complications, hemolytic markers, and the use of disease-modifying therapies.

Methods:

Study design and population:

This was a retrospective, observational, single-center study conducted at the Children's Heart Center (CHC) of the American University of Beirut Medical Center between 2015 and 2023. The study was approved by the Institutional Review Board.

All genetically confirmed SCD patients who underwent TTE at the CHC were included. Age- and sex-matched healthy controls were selected from individuals with normal TTE and no family history of heart disease, evaluated during the same period for murmurs, chest pain, or routine screening.

Clinical data included demographics, vitals at TTE, SCD complications (e.g., vaso-occlusive crises), transfusion history, treatments (hydroxyurea, iron chelators, folic acid), and laboratory values (hemoglobin, reticulocytes, ferritin, bilirubin, LDH, liver enzymes, creatinine).

Echocardiographic Evaluation

Since 2015, TTE has been performed by three experienced pediatric cardiac sonographers, with standardized views for LV strain using STE incorporated into the protocol specifically designed for patients with SCD. All analyses were performed offline using TomTec® LV AutoStrain® software (TomTec Imaging Systems Munich Germany), by a pediatric cardiologist, blinded to conventional findings, with each study measured twice and averaged. The following parameters were obtained: End-diastolic, end-systolic dimensions, end-diastolic posterior wall thickness, interventricular septal thickness, indexed LV mass, LV ejection fraction and indexed left atrial volume, using Simpson's biplane method. Mitral inflow peak velocities: Early and late waves, deceleration time, isovolumic relaxation time, and maximal tricuspid regurgitation velocity were obtained by spectral doppler. Using Tissue Doppler Imaging, early diastolic (E′) and late diastolic (A′), E′/A′ and mitral E/E′ ratio were measured.

Echocardiographic parameters were selected to capture different aspects of cardiac function: LV GLS as an early marker of systolic dysfunction; chamber size, wall thickness, and mass to reflect remodeling; left atrial volume index as an indicator of chronic diastolic burden;

mitral inflow and tissue Doppler indices to assess relaxation and filling pressures; and tricuspid regurgitant velocity as an estimate of pulmonary artery systolic pressure. These parameters are detailed in Supplementary Table 1.

Statistical Analysis

Data cleaning and analysis were performed using the Statistical Package for the Social Sciences (SPSS), version 25.0. Continuous variables are reported as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. Associations between LV GLS and categorical variables were assessed with the Chi-square test, and with continuous variables using Student's t-test. ANOVA was used to compare echocardiographic parameters across genotypes. Correlations between LV GLS and other continuous variables were assessed by using Pearson correlation coefficient. Differences between first and last visit was carried out using paired t-test.

Variables significant in bivariate analyses or deemed clinically relevant were entered into a multivariate linear regression model to identify independent predictors of LV GLS. Results are presented as beta coefficient (β) and their corresponding 95% confidence intervals (CI). A p-value < 0.05 was considered statistically significant.

A decision-tree model using the Chi-squared Automatic Interaction Detection (CHAID) algorithm was performed to determine whether an optimal data-driven age threshold exists for differentiating LV GLS values.

Results:

Demographic and baseline charactersitics:

A total of 301 echocardiographic studies performed at the Children's Heart Center during the study period were reviewed. After chart review and selection of complete and relevant studies, 278 echocardiographic studies were analyzed, representing 185 participants: 118

children with SCD and 67 matched controls. Table 1 represents the demographic characteristics of the included participants. Males constituted 51.4% of the total cohort. The mean age at the time of the initial echocardiogram was 12.1 ± 5.3 years. For SCD patients, the average age was 12.2 years (range: 1–21 years) with 51.7% being male; for the control group, the average age was 11.8 years (range: 1–21 years). The SCD cohort had a significantly higher baseline heart rate (94.2 vs 83.0 bmp). Among the SCD group, 66.1% had the HbSS genotype, 9.3% had HbSβ^0-thalassemia, 17.8% had HbSβ$^+$-thalassemia, 5.9% had HbSC, and 0.8% had HbSD. A total of 50 patients had more than one echocardiogram: 22 patients had 2 studies, 14 had 3, 8 had 4, 1 had 5, 4 had 6, and 1 patient had 7 echocardiograms.

At the time of the study, the majority of SCD patients (83.9%, 99 children) were receiving hydroxyurea, with average dose of approximately 25 mg/kg/day. Treatment was typically initiated at 15–20 mg/kg/day, with gradual dose escalation to 25–30 mg/kg/day. Of the 19 children not receiving hydroxyurea, 12 (63.2%) had HbSS, 5 (26.3%) had HbSβ$^+$, and 2 (10.5%) had HbSβ^0 genotypes.

During the study period, there were 33 cases of acute chest syndrome, 9 cases of osteomyelitis, 38 patients with cholelithiasis or cholecystectomy, 21 cases of avascular necrosis, 59 splenectomies, 7 strokes, and 4 instances of pulmonary embolism. Among the seven patients with prior stroke, all events were ischemic; two were receiving regular transfusion therapy, while five were not.

Echocardiographic parameters:

Table 2 summarizes the echocardiographic parameters in both groups. Compared to healthy controls, patients with SCD demonstrated a small but significant reduction LV GLS (-21.5 vs. -22.3%; $p < 0.001$). They also exhibited significantly larger LV end-diastolic dimensions

index (LVEDdi: 40.0 vs. 35.4 mm/m²; $p < 0.001$), LV end-systolic diameter (LVESd: 30.6 vs. 27.1 mm; $p < 0.001$), left atrial volume index (LAVi: 28.5 vs. 16.4 ml/m²; $p < 0.001$), and LV mass index (73.9 vs. 51.8 g/m²; $p < 0.001$), with thinner left ventricular posterior wall (6.0 vs. 6.6 mm, p= 0.004). Additionally, they displayed thicker interventricular septae when compared to controls (6.9 vs 6.4 mm), although the difference didn't reach statistical significance. Using the Simpson's method to measure the LVEF, there was a small yet statistically significant difference between the two groups (62.2 vs. 63.5%, p= 0.01).

Transmitral Doppler analysis revealed significantly higher mitral E-wave velocity (105.8 vs. 89.9 cm/s; $p < 0.001$), an elevated E/A ratio (1.9 vs. 1.7; $p < 0.001$), and a prolonged isovolumic relaxation time (68.7 vs. 58.8 ms; $p < 0.001$) in SCD patients. Tissue Doppler imaging at the mitral annulus showed a higher E/Lat E′ ratio (6.3 vs. 5.5; $p = 0.003$), while early (E′) and late (A′) diastolic velocities and the E′/A′ ratio were higher but not statistically significant. Continuous-wave Doppler analysis revealed a significantly increased tricuspid regurgitation maximal velocity (2.2 vs. 2.0 m/s; $p < 0.001$) in the SCD cohort.

Echocardiographic Parameters by Genotype

Echocardiographic parameters were largely comparable across SCD genotypes ($HbS\beta^+$, $HbS\beta^0$, and HbSS) (Table 3). LV GLS remained within the normal range and showed no significant difference among groups ($p = 0.57$). LV dimensions, wall thickness, and ejection fraction were similarly preserved. Although the HbSS subgroup showed numerically larger LV end-diastolic (46.8 ± 7.8 mm) and end-systolic (30.9 ± 5.8 mm) diameters compared with $HbS\beta^+$ and $HbS\beta^0$, these differences did not reach statistical significance. The indexed LV mass was significantly higher in HbSS patients (78.7 ± 26.8 g/m²) compared with $HbS\beta^+$ and $HbS\beta^0$ ($p = 0.03$). Diastolic indices including transmitral flow velocities (E and A waves), E/A ratio, mitral deceleration time, isovolumic relaxation time, and tissue Doppler indices

(E′, A′, E′/A′, and E/E′ ratios), did not differ significantly among groups. Likewise, the maximal tricuspid regurgitation velocity was similar across genotypes ($p = 0.29$). Collectively, these findings suggest that while LV systolic function and strain remain preserved across all SCD genotypes, HbSS patients exhibit a trend toward increased LV mass and chamber dimensions, reflecting early structural remodeling.

Association Between LV GLS and Clinical Parameters

We investigated the association of LV GLS with echocardiographic parameters: indexed LVEDd, LVESd, LVEF, IVSd, LVPWd, LV mass index, LA volume index, MV E and MV A (Table 4). Higher GLS was associated with increased indexed LVEDdi ($r = -0.38$, $p < 0.001$) and LVEF ($r = -0.31$, $p < 0.001$). The association of LV strain with clinical parameters was also examined to assess relationships with disease-modifying therapy, iron chelation, hemolysis, anemia, and disease complications (Figure 1). GLS was found to worsen with increasing age. A history of stroke or avascular necrosis was significantly associated with lower strain, whereas splenectomized patients exhibited significantly higher LV strain values. No significant associations were found with the use of hydroxyurea, folic acid, or iron chelation therapy (Figure 1), nor with the degree of anemia, frequency of vaso-occlusive crises, or transfusions during the year preceding the echocardiographic study (Table 4). Interestingly, there were no significant associations between LV strain and markers of hemolysis (including lactate dehydrogenase, indirect bilirubin, and reticulocyte count).

Multivariate Analysis

In multivariate analysis (Figure 2), factors independently associated with worsening LV longitudinal strain included prior stroke ($\beta = 1.5$, $p = 0.02$) and avascular necrosis ($\beta = 0.9$, $p = 0.048$), which decreased the strain by an average of 1.5% and 0.9%, respectively. On the contrary, an increase in LVEDdi was independntly associated with better LV strain (β = -

0.05, $p < 0.001$). However, the degree of anemia, markers of hemolysis, and hydroxyurea use were not significantly associated with LV strain.

Longitudinal Changes in LV Strain

Table 5 reflects the change of LV longitudinal strain of children with SCD overtime. In patients with serial echocardiograms, longitudinal changes in LV strain were analyzed between baseline and final assessments, spanning a mean follow-up of 3.7 years. There was a small but statistically significant decrease in strain between the first and last echocardiograms, a finding that persisted after adjustment for sex.

Effect of age on LV global longitudinal strain:

The CHAID algorithm identified a statistically significant split in LV GLS at 9.9 years ($F = 18.1$, $p < 0.001$). Children with SCD ≤9.9 years demonstrated more negative strain (–22.25 ± 1.02) compared with those >9.9 years (–21.38 ± 1.40). Based on this data-derived threshold, participants were categorized into ≤9.9 years and >9.9 years for group comparisons. In SCD patients, younger children had significantly more negative LV GLS values ($p < 0.001$). No significant difference was observed in controls (≤9.9 years: –22.32 ± 1.15 vs. >9.9 years: –22.35 ± 0.97; $p = 0.93$).

Discussion:

Although patients with SCD experience significant cardiovascular morbidity and mortality, studies focusing on the early and subclinical cardiac dysfunction in children remain limited. In this study, we retrospectively analyzed 118 pediatric patients with SCD from a large tertiary care center in the Middle East. Echocardiographic parameters were compared with those of healthy, age- and sex-matched controls. To our knowledge, this is the first study to incorporate a substantial cohort of SCD patients and matched controls in comparative

analysis. Left ventricular strain, using STE, has emerged as a valuable method for identifying subtle abnormalities in ventricular motion. The version of the software used in this study (TomTec AutoStrain LVE) to measure strain is semiautomatic and requires minimal human interference. This and the fact that one single cardiologist measure strain in all the studies, improved the reproducibility and eliminated interobserver variability. The fact that a single cardiologist performed all strain measurements improved reproducibility and eliminated interobserver variability. This technique is also relatively less influenced by changes in preload and afterload [22].

While LV strain values were within normal range in our cohort, a statistically significant difference was observed when compared to healthy controls. Although myocardial injury in patients with SCD begins in childhood and progresses overtime [6], and although some studies have reported impaired myocardial deformation in this population [21, 23, 24], our findings did not reflect similar results. The mean GLS was slightly but significantly lower in SCD patients (–21.5%) compared with controls (–22.3%). Indeed, Whipple et al., didn't find a significant difference in LV strain measurements between SCD patients and controls (-22.04 vs -22.05, respectively) [21]. In our cohort, the absolute differences in GLS between groups were numerically small (e.g., –21.5% vs –22.3%); Nonetheless, GLS is a reproducible, validated marker of LV systolic function, and even subtle reductions within the normal range have been associated with adverse cardiovascular outcomes in the normal population and in patients with other conditions [25-27]. For instance, Aashish et al., demonstrated that in patients with heart failure, each 1% absolute increase in LV GLS was linked to ~5% lower risk of mortality, independent of LVEF [28]. Unlike transcranial Doppler (TCD), which directly informs clinical decisions for stroke prevention in SCD, GLS is not yet a screening tool for routine clinical practice. Rather, it provides insight into subclinical myocardial abnormalities

and may serve as a biomarker to identify patients at risk for progressive cardiac involvement, warranting longitudinal study.

Our study also demonstrated significant cardiac remodeling in children with SCD characterized by increasing chamber size and Doppler abnormalities. The SCD cohort exhibited significantly larger LVEDd index, LA volume index, and LV mass index with decreased LVPWd compared with controls. In response to chronic anemia, patients with SCD typically adapt by progressively increasing their cardiac output, primarily through elevating stroke volume rather than a rise in heart rate [29]. This adaptation initially manifests as LV dilation, followed by compensatory myocardial hypertrophy, ultimately leading to an increase in LV mass. Despite these structural changes, systolic and diastolic functions are often preserved in the early stages [29]. In fact, this is reflected at the clinical level by initial improvement in systolic function.

However, with recurrent microvascular occlusion, myocardial ischemia, reperfusion injury, oxidative stress and loss of cardiomyocytes, fibrosis is promoted and contributes to diastolic dysfunction [29, 30]. Myocardial fibrosis has been documented through cardiac MRI in previous studies [31]. This pathophysiology explains the LA dilation observed in patients with SCD, as seen in our cohort. It is also associated with mild increase in LA pressure and volume, and in pulmonary venous pressure which might explain in part the increase in maximal tricuspid regurgitation velocity. Additionally, a higher mitral E velocity and E/A ratio, suggestive of increased preload and filling pressure, were also observed in our cohort. Other studies have also reported LA dilation and diatsolic dysfunctin in SCD patients [30, 32].

Analysis by genotype showed that HbSS patients consistently demonstrated the most pronounced cardiac remodeling, including the highest LV mass, largest chamber dimensions, and most elevated LA volumes. On the other hand, HbSB^0 patients exhibited generally more

preserved systolic function, lower LV mass, and less dilation, suggesting a milder cardiac phenotype within the SCD spectrum.

The inclusion of age in our model revealed a clear threshold effect around 10 years. Younger children demonstrated better myocardial deformation. This aligns with the progressive nature of subclinical myocardial involvement in SCD. The absence of a similar trend in controls supports that the observed strain reduction reflects disease-related rather than physiologic maturation changes. These findings highlight a critical window for early detection of subclinical LV dysfunction and suggest that incorporating longitudinal strain assessment into routine echocardiographic screening, particularly before 10 years of age, could enable earlier identification of at-risk patients and potentially guide timing for closer surveillance or intervention.

Hydroxyurea remains a key disease-modifying therapy in SCD. It promotes fetal hemoglobin production, improves hemoglobin levels, and decreases erythrocytes sickling and its complications. Several studies have explored the potential role of hydroxyurea in improving cardiac manifestations of SCD, however the results have been inconsistent [21, 33]. In this study, the majority of patients (99 patients, 87%) were receiving hydroxyurea at the time of evaluation. Although hydroxyurea use was not associated with improved myocardial strain in our study, this finding may be influenced by the lack of a substantial untreated comparison group, and the fact that patients not on hydroxurea often have less severe disease. In fact, other researchers have reported that hydroxyurea is associated not only with a lower prevalence of LV dilation but also with improvement in the degree of LV dilation and hypertrophy with long-term treatment [34]. This was not the case in our cohort as LV dilation was apparent as compared to controls. This highlights the need for further prospective and large-scale studies to explore the effect of disease-modifying therapy in SCD patients.

Importantly, we also explored the relationship between LV strain and various clinical variables, including hemolytic markers, anemia severity, history of complications, and use of folic acid and iron-chelation therapy. Our results suggest that patients with a history of complications, particularly prior stroke or avascular necrosis, tended to have lower LV strain values. This may be attributed to recurrent sickling events, leading to ischemia, reperfusion injury, and oxidative stress, which are clinically pronounced as complications but remain subclinical when affecting the myocardium.

No significant correlation was found between LV strain and the degree of hemolysis, anemia severity, use of medications, or chronic transfusion therapy. Some investigators have reported significant associations. For instance, Wadgy et al. reported a significant correlation between inflammatory markers (TGF-β, IL-18), lactate dehydrogenase (LDH), and LV strain [35]. Similarly, Santi et al. found that worsening GLS to be associated with elevated ferritin levels and increased anemia severity in children with SCD [20]. Additionally, our study did not identify a significant relationship between LV strain and markers of hemolysis, including LDH, bilirubin level, reticulocyte count, SGOT, and SGPT. It is suggested that when hemolysis in SCD releases hemoglobin into the plasma, it scavenges nitric oxide and enhances oxidative stress, thereby disrupting vascular redox balance, impairing endothelial function, and promoting pulmonary and systemic vasculopathy [36]. While distinguishing the contributions of intravascular hemolysis from those of anemia is difficult, large cohort studies have demonstrated associations between hemolysis markers and pulmonary artery systolic pressure after adjusting for anemia. In a study of 415 sickle cell disease patients, a significant positive association was suggested between hemolysis makers and pulmonary artery systolic pressure, when adjusted for anemia [37]. At the same time other research groups didn't find significant correlation with hemolysis [29]. Thus, although prior studies have suggested hemolysis as a central driver of vasculopathy, we did not observe significant correlations

between markers of hemolysis and cardiac dysfunction. Our findings suggest that other mechanisms, including chronic anemia, high cardiac output, iron overload, or microvascular injury, may contribute more prominently to myocardial impairment in children with SCD.

Finally, our study evaluated the progression of LV GLS over time in children with SCD, revealing a small but significant decline in strain values over a 3.7-year follow-up period. We sought to compare these findings with normative values reported in healthy pediatric populations. The LV longitudinal strain in our SCD cohort (-21.2 ± 1.3) falls within the normal range for age- and sex-matched healthy children reported by other research groups using TomTec AutoSTRAIN [38, 39].

To our knowledge, this represents one of the largest single-center studies to comprehensively evaluate myocardial strain in pediatric SCD patients compared with matched controls and to assess its progression over time. However, several limitations must be acknowledged. First, the retrospective nature of the study introduces inherent biases, including selection bias and incomplete or inconsistent data collection, which may affect the validity of the findings. Second, the majority of patients in our cohort were receiving hydroxyurea, limiting our ability to evaluate its independent impact on myocardial function or to compare outcomes between treated and untreated groups. Additionally, true adherence to therapy was not consistently available for analysis. Third, a large proportion of our patients had echocardiographic evaluations performed at a single time. These limitations highlight the need for prospective, multicenter studies with standardized imaging protocols and long-term follow-up to better understand myocardial remodeling in children with SCD.

Our study highlights that children with SCD demonstrate significant cardiac remodeling manifested with increased chamber dimensions and abnormal diastolic parameters. Although LV strain remained within the normal range, it was significantly lower than that of healthy

controls. Therefore, it illustrates the role of STE as a valuable tool for early detection of cardiac involvement in SCD. Furthermore, the lack of association between hemoglobin levels and LV strain suggests that factors beyond anemia alone contribute to myocardial impairment. These findings underscore the need for further research to better understand and mitigate cardiovascular complications.

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Tables:

	All (N=185)	SCD (N=118)	Control (N=67)	p-value
Gender, N (%)				
Female	90 (48.6%)	57 (48.3%)	33 (49.3%)	0.90
Male	95 (51.4%)	61 (51.7%)	34 (50.7%)	
Age, months, mean ± SD	12.1± 5.3	12.2 ± 5.3	11.8 ± 5.2	0.08
BSA m^2, mean ± SD	1.2 ± 0.4	1.2 ± 0.4	1.3 ± 0.5	0.46
HR, mean ± SD	90 ± 15.3	94.2 ± 15.7	83 ± 11.7	<0.001

Table 1. Demographic characteristics of the included patients. (BSA, Body surface area; HR, Heart rate; SCD, sickle cell diseasse; SD, Standard deviation)

Echocardiographic Parameters	All	SCD	Control	p-value
LV Longitudinal strain, mean ± Standard deviation (SD)	-21.7 ± 1.3	-21.5 ± 1.3	-22.3 ± 1.1	<0.001*
LVEDd (mm), mean ± SD	44.4 ± 7.8	46.2 ± 7.2	41.3 ± 7.8	<0.001*
LVEDd/BSA (mm/m^2) , mean ± SD	38.4 ±9.5	40 ± 9.1	35.4 ± 9.6	0.001*
LVESd (mm), mean ± SD	29.3 ± 5.5	30.6 ± 5.3	27.1 ± 5.1	<0.001*
LVEF (%), mean ± SD	62.7 ± 3.3	62.19 ± 3.31	63.5 ± 3.1	0.01*
IVSd (mm), mean ± SD	6.7 ± 1.8	6.9 ± 2	6.4 ± 1.4	0.05
LVPWd (mm), mean ± SD	6.2 ± 1.6	6 ± 1.5	6.6 ± 1.7	0.004*
Indexes LV mass (g/m2), mean ± SD	65.7 ± 23.5	73.9 ± 24.5	51.8 ± 12.9	<0.001*
LA volume index (mL/m2), mean ± SD	24 ± 8.3	28.5 ± 6.7	16.4 ± 4.1	<0.001*
MV E (cm/sec), mean ± SD	101.2 ± 17.4	105.8 ±17	89.9 ± 13	<0.001*
MV A (cm/sec), mean ± SD	57.1 ± 12.6	58.1 ± 13.8	54.7 ± 8.9	0.08
MV DT (msec), mean ± SD	156.3 ± 27.5	155.2 ± 30.4	158.6 ± 19.6	0.42
IVRT (msec), mean ± SD	65.3 ± 9.9	68.7 ± 9.1	58.8 ± 7.8	<0.001*
E/A, mean ± SD	1.8 ± 0.5	1.9 ± 0.5	1.7 ± 0.3	<0.001*
Maximal TRv (m/sec), mean ± SD	2.1 ± 0.3	2.2 ± 0.2	2 ± 0.3	<0.001*
Lat E` Vel (cm/sec), mean ± SD	17.4 ± 4.4	17.59 ± 3.8	16.8 ± 2.5	0.19
Lat A` Vel (cm/sec , mean ± SD	7.4 ± 2.1	7.4 ± 2.3	7.2 ± 1.5	0.59
E/Lat E`, mean ± SD	6 ± 1.5	6.3 ± 1.6	5.5 ± 1	0.003*
E`/A` Lateral, mean ± SD	2.5 ± 0.7	2.6 ± 0.8	2.4 ± 0.5	0.12

Table 2. Echocardiographic parameters of the included patients. * indicates a statistically significant p-value. (SD, Standard deviation; LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDd, LV end-diastolic diameter; LVESd, LV end-systolic diameter; BSA, body surface area; IVSd, interventricular septal thickness in diastole; LVPWd, LV posterior wall thickness in diastole; MV, mitral valve; DT, deceleration time; IVRT, isovolumic relaxation time; E′, early diastolic tissue Doppler velocity; A′, late diastolic tissue Doppler velocity; LA, left atrium; TR, tricuspid regurgitation.)

	HbSB	HbSB0	HbSS	p-value
LV longitudinal strain (%)	-21.4 ± 1.3	-21.9 ± 1	-21.5 ± 1.4	0.57
LVEDd(mm)	45.8 ± 5.7	45 ± 5.8	46.8 ±7.8	0.68
LVEDd/BSA(mm/m^2)	38.5 ± 8.6	37.8 ± 11	40.6 ± 9.2	0.46
LVESd(mm)	30.6 ± 4.3	29.4 ± 4	30.9 ± 5.8	0.68
LVEF (%)	61.9 ± 3.5	63.7 ± 2.9	62.1 ± 3.4	0.28
IVSd(mm)	6.5 ± 1.8	6.4 ± 1.8	7.2 ± 2.1	0.27
LVPWd(mm)	5.5 ± 1.2	5.6 ± 1.4	6.1 ± 1.5	0.12
Indexes LV mass (g/m2)	65.4 ± 15.6	62.9 ± 17.2	78.7 ± 26.8	0.03*
LA volume index (mL/m2)	27.7 ± 5.8	26.4 ± 5.4	29 ± 7.3	0.40
MV E (cm/sec)	111.7 ± 13.6	102.1 ± 18	105.4 ± 17.7	0.22
MV A (cm/sec)	59.2 ± 12.5	55.1 ± 9.7	58.7 ± 15.1	0.73
MV DT (msec)	154.1 ± 26	166.2 ± 26	154.7 ± 32	0.53
IVRT (msec)	68.8 ± 10.2	70.6 ± 9.7	68.4 ± 9.1	0.82
E/A	2 ± 0.5	1.9 ± 0.4	1.9 ± 0.6	0.87
Maximal TRv (m/sec)	2.2 ± 0.2	2.1 ± 0.2	2.2 ± 0.3	0.29
Lat E` Vel (cm/sec)	18.9 ± 4.5	16.8 ± 4.2	17.4 ± 3.4	0.27
Lat A` Vel (cm/sec)	7.6 ± 1.7	7.2 ± 2	7.6 ± 2.6	0.90
E/Lat E`	6.2 ± 1.5	6.3 ± 1.6	6.1 ± 1.5	0.89
E`/A` Lateral	2.6 ± 0.7	2.6 ± 0.9	2.5 ± 0.8	0.81

Table 3. Comparative analysis of LV echocardiographic parameters in SCD patients by genotype. * indicates a statistically significant p-value. (LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDd, LV end-diastolic diameter; LVESd, LV end-systolic diameter; BSA, body surface area; IVSd, interventricular septal thickness in diastole; LVPWd, LV posterior wall thickness in diastole; MV, mitral valve; DT, deceleration time; IVRT, isovolumic relaxation time; E′, early diastolic tissue Doppler velocity; A′, late diastolic tissue Doppler velocity; LA, left atrium; TR, tricuspid regurgitation.)

Echocardiographic parameters	Pearson correlation	p-value
LVEDd/BSA	-0.38	<0.001*
LVESd	0.41	<0.001*
LVEF	-0.31	<0.001*
IVSd	0.28	0.002*
LVPWd	0.28	0.002*
Indexes LV mass	0.11	0.24
LA volume index	-0.07	0.43
MV E	-0.06	0.51
MV A	-0.10	0.32
MV DT	-0.08	0.44
IVRT	0.08	0.46
IVRT TD	-0.09	0.44
E/A	0.03	0.75
Maximal TRv	0.17	0.08
Lat E` Vel	0.09	0.42
Lat A` Vel	0.02	0.83
E/Lat E`	-0.15	0.15
E`/A` Lateral	-0.003	0.98
Clinical variables	**Pearson correlation**	P-value
Age	0.46	<0.001*
BSA	0.41	<0.001*
HR	0.003	0.98
Reticulocyte	0.02	0.81
Ferritin	-0.17	0.31
Vaso-occlusive Events	0.13	0.17
Bilirubin	0.10	0.39
SGPT	0.00	1.00
Lactate dehydrogenase	0.25	0.40
Creatinine	0.30	0.005*

Table 4. Correlations between LV strain and other echocardiographic parameters and clinical variables. * indicates a statistically significant p-value. (LV, left ventricle; LVEF, left ventricular ejection fraction; LVEDd, LV end-diastolic diameter; LVESd, LV end-systolic diameter; BSA, body surface area; IVSd, interventricular septal thickness in diastole; LVPWd, LV posterior wall thickness in diastole; MV, mitral valve; DT, deceleration time; IVRT, isovolumic relaxation time; E′, early diastolic tissue Doppler velocity; A′, late diastolic tissue Doppler velocity; LA, left atrium; TR, tricuspid regurgitation; HR, Heart rate; SGPT, Serum Glutamic Pyruvic Transaminase)

	First visit	Last visit
LV longitudinal strain (%)	-21.6 ± 1.5	-21.2 ± 1.3
Age, years	12.2 ± 5.2	15.9 ± 5.6
BSA, m^2	1.3 ± 0.4	1.5 ± 0.5
In males	**First visit**	**Last visit**
LV longitudinal strain (%)	-21.7 ± 1.7	-21 ± 1.4
Age, years	12.5 ± 5.2	16.7 ± 5.3
BSA, m^2	1.3 ± 0.4	1.5 ± 0.4
In Females	**First visit**	**Last visit**
LV longitudinal strain (%)	-21.5 ± 1.4	-21.3 ± 1.2
Age, years	11.9 ± 5.3	15 ± 5.9
BSA, m^2	1.2 ± 0.4	1.4 ± 0.4

Table 5. Longitudinal analysis of LV strain in SCD patients. (LV, left ventricle; BSA, body surface area)

Figure 1. Correlations of clinical characteristics with LV GLS. (LV, Left ventricle; GLS, Global longitudinal strain; ACS, Acute chest syndrome; AVN, avascular necrosis).

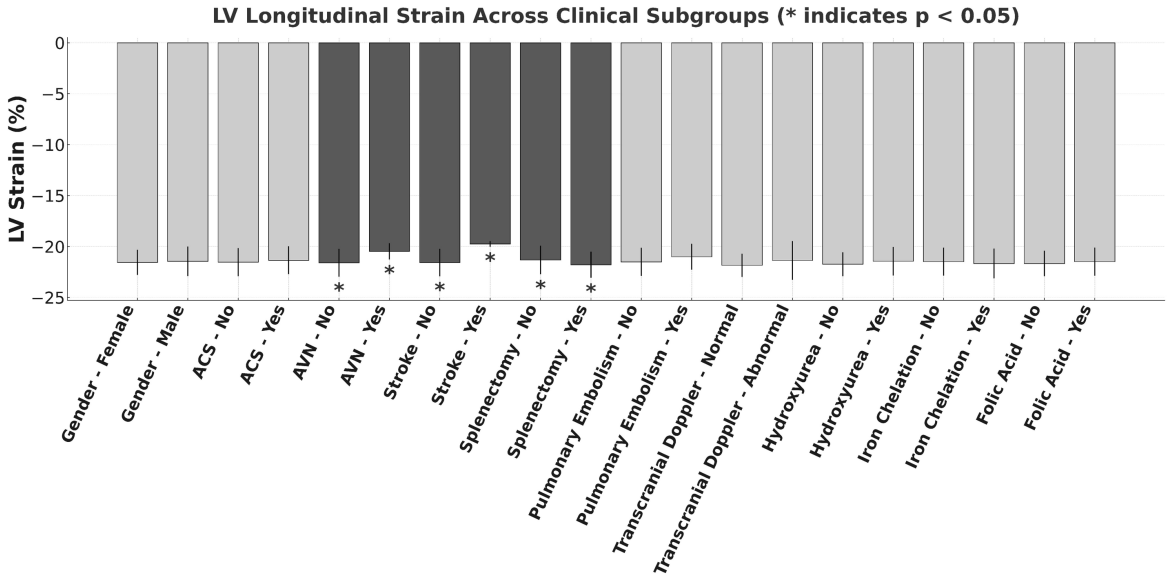
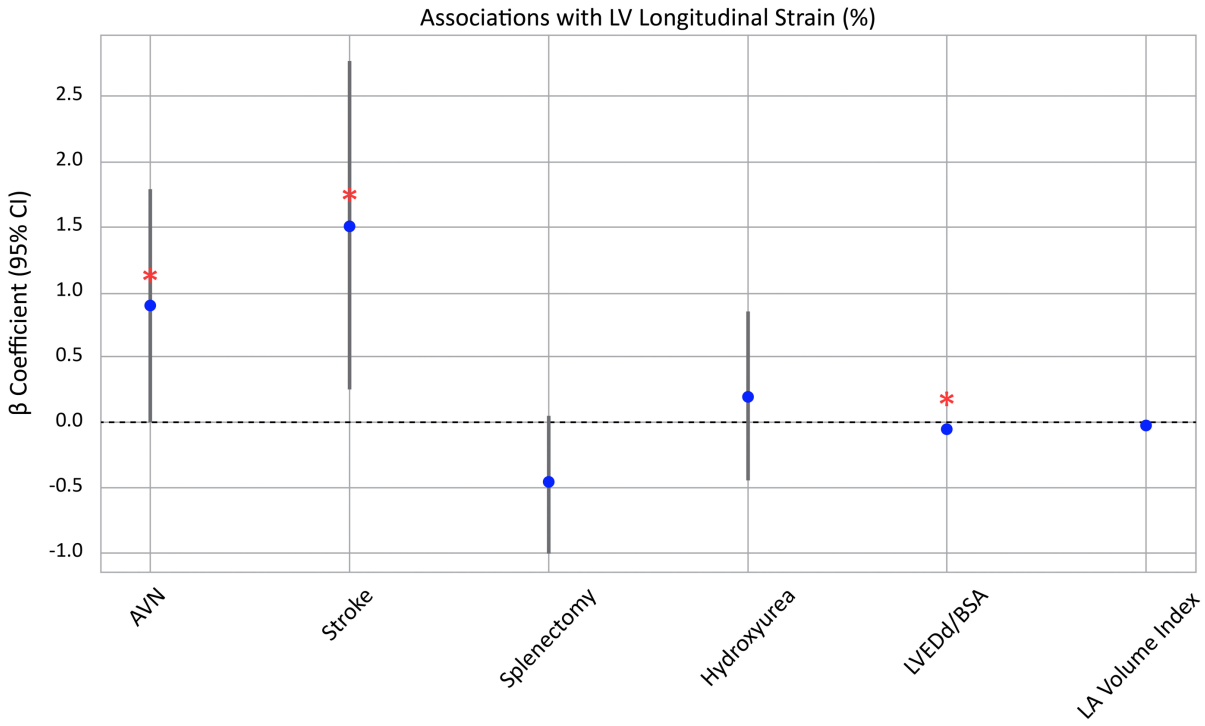


Figure 2. Multivariate analysis of the factors associated with LV strain (LV, Left ventricle; AVN, avascular necrosis; LVEDd, Left ventricular end diastolic diameter; BSA, Body surface area; LA, left atrium).



Category	Parameters	What They Measure	Clinical Relevance
Systolic function	- LV longitudinal strain - LVEF (%)	Strain: myocardial deformation. EF: traditional assessment of systolic function	Strain detects early dysfunction before EF drops. EF is conventional measure of systolic performance
Chamber size & remodeling	- LVEDd / LVESd - LVEDdi: LVEDd/BSA - IVSd / LVPWd - LV mass index	LV diameters, wall thickness, and indexed left ventricular size	Show effects of chronic anemia/volume overload which lead to dilation and/or hypertrophy
Diastolic function	- MV E and A velocities - E/A ratio - MV deceleration time (DT) - IVRT -Lat E′ / A′ velocities - E/E′ ratio - LA volume index	Mitral inflow, tissue Doppler; ventricular relaxation; LA size	Identify abnormal relaxation of the left ventricle, high filling pressures, and chronic diastolic burden
Pulmonary hemodynamics	- Maximal TR velocity	Peak regurgitant jet across tricuspid valve	Surrogate of pulmonary artery systolic pressure; elevated values suggest pulmonary hypertension

Supplementary table 1. Clinical significance of echocardiographic parameters. LV, left ventricle; LVEF, left ventricular ejection fraction; EF, ejection fraction; LVEDd, LV end-diastolic diameter; LVESd, LV end-systolic diameter; BSA, body surface area; IVSd, interventricular septal thickness in diastole; LVPWd, LV posterior wall thickness in diastole; MV, mitral valve; DT, deceleration time; IVRT, isovolumic relaxation time; E′, early diastolic tissue Doppler velocity; A′, late diastolic tissue Doppler velocity; LA, left atrium; TR, tricuspid regurgitation.