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1 **Subclinical Left Ventricular Systolic Impairment in Steady State Young Adult Patients**
2 **with Sickle-cell Anemia**

3
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13 This author takes responsibility for all aspects of the reliability and freedom from bias of the
14 data presented and their discussed interpretation ² This author drafted the article, revised it
15 and provided the final approval of the version to be published.

16
17 **Short title:** Systolic impairment in sickle-cell anemia

18
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1 **ABSTRACT**

2 **Purpose:** Chronic volume overload in sickle-cell anemia (SCA) is associated with left
3 ventricular (LV) enlargement and hypertrophy. The effect of the disease on LV systolic
4 function remains debated. The aim of our study was to investigate LV systolic function in
5 SCA patients using 2D speckle-tracking imaging.

6 **Methods:** We compared 30 steady state asymptomatic adult SCA patients (17 women, mean
7 age 24.7 ± 5.1 years) with 30 age and sex-matched healthy subjects (17 women, mean age
8 25.0 ± 4.9 years). In addition to conventional echocardiographic parameters including LV
9 ejection fraction (EF) and LV mass index (LVMI), global longitudinal strain (GLS) and strain
10 rate (GLSR) were measured.

11 **Results:** GLS ($-17.9 \pm 2.0\%$ vs. $-19.7 \pm 2.5\%$, $p=0.004$) and GLSR ($-0.92 \pm 0.09s^{-1}$ vs. -
12 $1.07 \pm 0.17s^{-1}$, $p<0.0001$) values were lower in SCA patients while LVEF values ($60.1 \pm 3.8\%$
13 vs. $61.7 \pm 4.7\%$, $p=0.30$) were not different. LVMI was increased in SCA patients
14 ($100.7 \pm 23.5g/m^2$ vs. $72.4 \pm 15.2g/m^2$, $p0.0001$) and GLSR was significantly lower in the
15 subgroup of patients with LV hypertrophy ($-0.88 \pm 0.09s^{-1}$ vs. $-0.96 \pm 0.08s^{-1}$, $p=0.02$). In SCA
16 patients LVMI was correlated to GLS ($r=0.58$, $p=0.001$) and GLSR ($r=0.45$, $p=0.015$)
17 pleading in favor of a pathological LV remodeling.

18 **Conclusions:** Asymptomatic SCA patients exhibited a subclinical alteration of LV systolic
19 function. Myocardial dysfunction appears to be linked to the degree of LV hypertrophy. 2D
20 speckle-tracking imaging might be useful for long-term follow-up and to study the natural
21 course of LV dysfunction in SCA patients.

22

23 **Keywords:** echocardiography, left ventricular function, speckle-tracking, strain, Sickle-cell
24 anemia

25

1 **BACKGROUND**

2 Sickle-cell disease is one of the most common inherited blood disorders worldwide [1].
3 Besides chronic anemia, many pathophysiological processes contribute to the complexity of
4 the disease including hemolysis and repeated vaso-occlusive events with ischemia-reperfusion
5 injury leading to endothelial cell dysfunction [1, 2]. Concomitantly to the life expectancy
6 improvement observed over the past years, the prevalence of heart disease in adult patients
7 has also increased representing now up to one fourth of all deaths [3].

8 In patients with homozygous sickle cell disease, also called sickle-cell anemia (SCA), a
9 diastolic dysfunction, as well as left ventricular (LV) remodelling, including dilation and
10 hypertrophy, have been previously described [4]. These modifications are best explained by
11 an adaptative response to the volume overload effect of chronic anemia [5, 6].

12 While chronic volume overload in valvular heart disease such as mitral or aortic regurgitation
13 [7] and prolonged anemia induced by iron deficiency in rat models [8] induce LV systolic
14 dysfunction, its' occurrence in SCA disease is still debated with conflicting results in past
15 studies [5, 6, 9–12]. Recently, ultrasound speckle-tracking imaging has emerged as a strong
16 and sensible tool that allows early diagnosis of LV systolic dysfunction [13].

17 We hypothesized that a systolic LV dysfunction that could be diagnosed by speckle-tracking
18 imaging may exist during steady-state SCA disease in adult patients.

19

20 **METHODS**

21 **Study population**

22 We enrolled 30 patients with SCA, aged 18 years and older, in stable condition and in sinus
23 rhythm. All these patients were referred to our echocardiography laboratory for routine
24 outpatient evaluation of cardiac function and/or systematic screening for pulmonary arterial
25 hypertension. The diagnosis of homozygous sickle-cell disease was based on molecular

1 genetic techniques. Patients who had developed acute chest syndrome, vaso-occlusive crisis
2 or an acute complication within the previous 4 months, including fever, surgery, blood
3 transfusion or hospital admission whatever the reason, were excluded in order to specifically
4 focus on a group of steady state patients free of confounding factors that could be linked to an
5 impaired LV function. The other exclusion criteria were the use of cardiovascular medication
6 at the time of enrollment, hypertension, history of heart failure, moderate or severe valvular
7 heart disease, atrial fibrillation, pregnancy and the presence of an associated comorbidity
8 including autoimmune diseases, HCV or HIV infections and kidney failure defined by a
9 glomerular filtration rate $<60\text{ml/mn}/1.73\text{m}^2$. Clinical and biological data were collected from
10 records of the reference centre for sickle-cell disease (Tenon Hospital, Paris, France). From
11 the general population, 30 age- and sex-matched healthy subjects without history of cardiac or
12 pulmonary disease and with normal electrocardiograms were recruited as control subjects.
13 Blood pressure was measured in patients and controls in supine position at the end of the
14 echocardiographic examination using a Dash 3000 monitor (GE Healthcare; Horten, Norway).
15 Informed consent was obtained from each patient. The study was approved by the institutional
16 committee on human research.

17

18 **Standard echocardiography**

19 Transthoracic echocardiography was performed in all patients with the use of the Vivid 7
20 system (GE Healthcare; Horten, Norway) and transferred to a workstation equipped with the
21 Echopac PC software (GE Vingmed Ultrasound; Horten, Norway) for offline analysis. All
22 exams were acquired and analyzed off-line blinded to the clinical data by a senior cardiologist
23 (NH). All measurements were averaged over 3 consecutive cardiac cycles. All projections
24 were obtained according to the recommendations of the American Society of
25 Echocardiography [14, 15]. From M-mode, the following measurements were made at end

1 diastole: LV internal diameter, inter-ventricular septal and posterior wall thicknesses. LV
2 mass was derived and indexed to body surface area (LVMI), relative wall thickness was also
3 calculated (posterior wall thicknesses $\times 2 /$ LV internal diameter) and LV remodeling was
4 categorized as recommended [15]. LV hypertrophy was defined by an LVMI $> 95\text{g/m}^2$ in
5 women and $>115\text{g/m}^2$ in men. Further classification as either concentric hypertrophy (relative
6 wall thickness > 0.42) or eccentric hypertrophy (relative wall thickness ≤ 0.42) was made.
7 From 2-dimensional mode, end systolic left and right atrial areas were measured, LV volumes
8 and ejection fraction (LVEF) were derived from Simpson's modified biplane method. From
9 pulsed wave Doppler mode, LV outflow tract time-velocity integral, early and late peak
10 diastolic velocities of the mitral (E and A) inflow and the E-wave deceleration time were
11 measured. LV ejection volume and output were calculated and indexed to body surface area
12 as recommended [14]. The peak e' velocity was used to calculate the E/e' ratio using pulsed
13 tissue Doppler imaging of the lateral mitral annulus [16]. Diastolic dysfunction was defined
14 by E/A ratio <1.0 and/or a deceleration time >240 ms; E/A ratio ≥ 1.0 and E/e' ratio >10 ; E/A
15 ratio higher than the 95th percentile for age or deceleration time <140 ms and E/e' >10 . This
16 classification of LV diastolic function has a prognostic value on mortality in patients with
17 SCA [17].

18 From continuous wave Doppler, peak tricuspid regurgitation was recorded in multiple views
19 and the highest level of velocity was selected. Elevated pulmonary systolic pressure was
20 defined by a peak tricuspid regurgitation jet velocity $\geq 2.5\text{m/s}$, severe elevation by a peak
21 tricuspid regurgitation jet velocity $\geq 2.9\text{m/s}$ [18].

22

23 **Speckle-tracking imaging**

24 For 2D speckle-tracking imaging, sector size and depth were adjusted to achieve optimal
25 visualization of all LV myocardium at the highest possible frame rate (mean value 87 ± 14

1 frames/s). Multiple consecutive cardiac cycles of the 3 standard apical views (4, 2 and 3
2 chambers views) were acquired during breath holding. In each view, the myocardium was
3 automatically divided by the software into 6 segments. The analyzed values within the middle
4 points for all resulting 18 segments were averaged to obtain the global longitudinal strain
5 (GLS) and the global longitudinal peak systolic strain rate (GLSR); in accordance with
6 current conventions GLS and GLSR values were presented as negative (segment shortening)
7 [13]. The adequacy of tracking was verified manually, and the region of interest was
8 readjusted to achieve optimal tracking. The segment was excluded if no acceptable border
9 was traced. GLS and GLSR values were not calculated if > 1 segment per view were
10 excluded.

11

12 **Statistical analysis**

13 All quantitative data are expressed as mean \pm standard deviation (SD); qualitative data are
14 expressed as number and as percentage. For case-control analysis, the Wilcoxon signed rank
15 test was used for univariate analysis of continuous variables and the McNemar's test was used
16 to compare categorical data.

17 Using the Mann-Whitney U test and the chi-square test a secondary analysis compared the
18 subgroup of patients with and without LV hypertrophy. The Pearson's correlation test was
19 used to assess the univariate relations between variables.

20 Intraobserver and interobserver variabilities for LV deformation parameters, LV volume,
21 LVEF and LVMI measurements were assessed in 20 studies by 2 independent observers (NH
22 and DA). Using the Bland-Altman approach, the 95% limit of agreement was calculated. In
23 addition, the coefficient of variation (CV) defined as the ratio of the SD of the difference of
24 paired samples to the average of the paired samples and the intra-class correlation coefficient
25 (ICC) were calculated. For intraobserver variability the CV and the ICC were respectively

1 4.1% and 0.93 for GLS, 4.3% and 0.92 for GLSR, 8.1% and 0.96 for LV end diastolic volume
2 index, 4% and 0.83 for LVEF and 5.5% and 0.99 for LVMI. The 95% limits of agreement
3 were -1.63 to 2.35% for GLS, -0.10 to 0.13 for GLSR, -17.1 to 14.7 ml/m² for LV end
4 diastolic volume index, -7.1 to 6.8% for LVEF and -15.4 to 12.2g/m² for LVMI. For
5 interobserver variability the CV and the ICC were respectively 6.6% and 0.88 for GLS, 6.2%
6 and 0.91 for GLSR, 7.6% and 0.96 for LV end diastolic volume index, 3.6% and 0.85 for
7 LVEF and 7.8% and 0.98 for LVMI. The 95% limits of agreement were -1.2 to 3.7% for GLS,
8 -0.05 to 0.18 for GLSR, -11.0 to 16.5 ml/m² for LV end diastolic volume index, -5.5 to 6.8%
9 for LVEF and -15.1 to 21.7 g/m² for LVMI.
10 SPSS software version 17.0 (SPSS, Inc, Chicago, IL) was used for calculation. A p<0.05
11 indicated statistical significance.

12

13 **RESULTS**

14 Patients' mean age was 24.7±5.1 years and 17 patients (57%) out of a total of 30 were women.
15 Percentages of patients with histories of thoracic vaso-occlusive events or cerebral
16 vasculopathy were 30% and 7% respectively. The mean hemoglobin level was 8.5±0.9 g/dl
17 and in 11 cases (36%) it was ≤ 8g/dl. Patients and controls were matched for age and gender
18 and there was no significant difference between the 2 groups for body surface area and body
19 mass index. Diastolic and mean blood pressures were significantly lower in patients than in
20 controls; the heart rate was not higher in patients (Table 1), only 3 patients had heart rates >
21 90/min and none >100/min.

22 Morphological and hemodynamic characteristics are summarized in Table 2. LV dimensions
23 and mass were greater in patients than in controls. In patients, the LV hypertrophy was mainly
24 eccentric; only 1 patient had concentric hypertrophy. The mean tricuspid regurgitant jet

1 velocity was higher in the patient group including 13 patients (43%) with elevated pulmonary
2 systolic pressures and none with severe elevation.

3 LVEF measurements were > 50% in all patients. Despite similar LVEF between the 2 groups,
4 the GLS and the GLSR values were significantly decreased in the SCA group (Table 2, Figure
5 1). LV speckle analysis was not feasible in 1 patient and 1 control subject, because of poor
6 image quality. Patients presented a diastolic dysfunction and had a higher E/e' ratio (Table 2).

7 In order to assess the potential impact of blood pressure or heart rate on the relationship
8 between GLS and SCA, 3 linear regression analyses including respectively, mean arterial
9 blood pressure, diastolic blood pressure and heart rate were done. The results of the 3 analyses
10 were similar and confirmed the independent link between GLS and SCA ($r^2=0.15$, $p=0.002$).

11 The GLSR was significantly lower in patients with LV hypertrophy (Table 3). A correlation
12 was found between LVMI and GLS ($r=0.58$, $p=0.001$) as well as with GLSR ($r=0.45$,
13 $p=0.015$). There was a significant inverse correlation between the hemoglobin level and
14 LVMI ($r=-0.43$, $p=0.017$) as well as LV end-diastolic diameter index ($r=-0.36$, $p=0.047$). The
15 hemoglobin level was not statistically correlated to LVEF ($r=-0.04$, $p=0.83$), E/e' ratio ($r=-$
16 0.28 , $p=0.13$), GLS ($r=0.15$, $p=0.44$) and GLSR ($r=0.28$, $p=0.14$).

17

18 **DISCUSSION**

19 In this study we found that in addition to morphological modifications including hypertrophy
20 and dilation, LV systolic function assessed by 2D speckle tracking imaging was impaired in a
21 population of steady state SCA young asymptomatic adult patients with preserved LVEF. The
22 severity of LV hypertrophy was linked to the impairment of global longitudinal LV
23 deformation parameters. The GLS was linked to SCA independently to blood pressure and to
24 heart rate. LV remodeling was inversely associated to the hemoglobin level.

1 Despite not being a pure form of anemia [19], the LV remodeling observed in homozygous
2 sickle-cell disease is commonly attributed to chronic anemia as reduced blood oxygen-
3 carrying capacity induces an increased cardiac output [4]. As described in this study and noted
4 previously by others, an important stroke volume increase associated with a relatively mild
5 heart rate elevation contribute to the cardiac output increase [12]. Modifications in LV
6 preload and afterload could explain the stroke volume increase; the significant reduction of
7 the mean arterial blood pressure while the cardiac index is increased underlines the decrease
8 in peripheral vascular resistances [20]. Volume overload contributes to the increased cardiac
9 output by inducing an increase in LV preload and a substantial LV enlargement[21, 22].
10 According to Laplace's Law, this volume overload increases the peak systolic wall stress
11 resulting in wall thickening to normalize the systolic stress. Wall thickening and fiber
12 elongation contribute to the pattern of eccentric hypertrophy in which the ratio of wall
13 thickness to chamber radius remains normal [23].
14 Regarding the LV systolic function assessment, conflicting results in previous studies are
15 partly explained by the multitude of different echocardiographic parameters used to assess
16 myocardial contractility including load-dependant measures such as the LVEF calculation [6,
17 12, 24–26]. In our study, deformation parameters were significantly reduced while the LVEF
18 was similar in both groups. Myocardial deformation assessed by strain and strain-rate is the
19 result of a complex interaction between the intrinsic contractile force and the extrinsic loading
20 conditions applied to a tissue with variable elastic properties [27]. Therefore, it could be
21 argued that the observed modifications of LV longitudinal deformation may not only be the
22 result of an alteration in contractility but may reflect modifications of loading conditions or in
23 myocardial stiffness. In our study the afterload was lower and the preload higher in the SCA
24 group and it is admitted that under these conditions deformation values should increase [28,
25 29]. This argument pleads in favor of the occurrence of a LV systolic impairment in young

1 adult SCA patients. Similarly, a recent meta-analysis reported an impairment of a relatively
2 load independent LV systolic function assessment parameter (end-systolic stress to end-
3 systolic volume index) despite preservation of load dependant parameters in SCA patients
4 [30].

5 An interesting parallel can be made concerning LV remodeling between patients suffering
6 from chronic anemia and endurance athletes in whom a comparable cardiac remodeling has
7 been reported [31]. In contrast with the results of our study, LV strain and strain rate values in
8 endurance athletes have been reported to be normal or increased [32, 33]. Besides, while
9 increased LV mass is associated with improved deformation indices in endurance athletes
10 [32], LV hypertrophy is associated with an impairment of LV function in our population
11 further supporting the hypothesis that a LV myocardial impairment exists in sickle-cell
12 disease patients. Similar findings have been reported in the course of hypertrophic
13 cardiomyopathy [32] and myocardial fibrosis is associated with depressed strain values in
14 these patients [34]. Moreover, as morphological and functional LV parameters are linked, LV
15 mass may be helpful in routine practice for the identification of a subgroup of SCA patients
16 at high risk of LV dysfunction.

17 In case of severe organic mitral regurgitation, prolonged burden due to volume overload
18 might result in LV dysfunction and irreversible myocardial damage. If a significant LV
19 myocardial morphological and/or functional involvement is/are identified, current guidelines
20 recommend the correction of the regurgitation in asymptomatic patients [7]. The LV
21 abnormalities observed in SCA patients are multifactorial including the combination of
22 chronic anemia and microvascular dysfunction[4]. In our study, LV deformation parameters
23 revealed a LV impairment in a population of young adult SCA patients with normal LVEF,
24 suggesting a promising role of these parameters for the detection of LV dysfunction at an
25 early stage before major and irreversible damage of the myocardium occurs. As

1 cardiovascular mortality in adult SCA patients is high[3] our findings may provide clinicians
2 a useful method of identification of a category of patients at high risk of developing long-
3 term congestive heart failure and/or premature death. Moreover these patients may benefit
4 from more regular follow up and more aggressive clinical interventions in order to improve
5 their prognosis.

6 A similar study using deformation imaging was recently conducted on a pediatric population
7 of sickle cell disease patients with contrasting results as deformation indices were not
8 modified [35]. It could be hypothesized that the LV systolic impairment, as found in our
9 population of adults, occurs later in the course of the disease. Age related deterioration of LV
10 systolic function was previously described [30]. Moreover, in a population of adult patients
11 presenting with sickle-cell crisis, the usefulness of deformation indices assessed by speckle
12 tracking for detecting LV systolic function impairment has already been reported [36]; our
13 study identified LV dysfunction in a population of steady-state patients. Contrastingly, no
14 impairment in LV systolic function was reported in a study based on 3-dimensional LV
15 speckle tracking echocardiography [37]. This promising new method performed on a pre-
16 commercial prototype software still suffers from technical limitations such as low temporal
17 resolution. Besides, in addition to SCA patients, hemoglobin sickle-cell (SC) patients were
18 also included in this study. It has already been described that SC patients have very different
19 clinical and biological characteristics [38]. Therefore, the results must be compared to ours
20 with caution.

21 Consistently with previous studies [10, 17, 39, 40], we also found a LV diastolic function
22 impairment. Diastolic dysfunction is known to be an independent risk factor for mortality in
23 SCA [17]. It is worth noting that the E/e' ratio is normal in healthy endurance athletes [32,
24 33].

1 Several limitations of our study need to be acknowledged. First, our population was relatively
2 small as we decided to focus on strict inclusion criteria in order to reduce any bias by
3 selecting only steady state homozygous sickle-cell disease patients free of confounding
4 factors that could be linked to LV systolic impairment. Despite this limitation, we found a
5 significant impairment of deformation indices. Second, we only evaluated the LV longitudinal
6 deformation parameters as they appear to be the most efficient and reproducible parameters in
7 speckle tracking technology [41]. Moreover, it has been earlier described that the natural
8 course of myocardial diseases is characterized by the impairment of the longitudinal function
9 that occurs before the onset of circumferential and radial alterations [42]. Finally, the
10 prognostic implications of LV deformation parameters were not assessed in this study and
11 need further investigations.

12 Steady state young adult patients suffering from homozygous sickle-cell anemia exhibited a
13 subclinical impairment of myocardial contractility. 2D speckle-tracking imaging might
14 constitute a useful tool for long-term follow-up and to study the natural course of LV
15 dysfunction in these patients. Additional studies are required to further understand the
16 prognostic implications of deformation parameters.

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2 The authors have no disclosures.

3

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6

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8 None

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1 **FIGURE LEGENDS**

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3 **Figure 1.** Comparison of LV global longitudinal strain measures between a sickle-cell anemia
4 patient and an age and sex-matched control subject. Despite similar LV ejection fractions, LV
5 peak global longitudinal strain value (white curve; arrow) is significantly decreased in the
6 sickle-cell anemia patients' measure.

7 GLS = Global longitudinal Strain; LVEF = Left ventricular ejection fraction; SCA = Sickle-
8 cell Anemia.

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1 **Table 1:** General characteristics of the study subjects

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	SCA patients (n=30)	Controls (n=30)	p value
Age (years)	24.7±5.1	25.0±4.9	0.08
Women	17 (57)	17 (57)	matched
Body Mass index (g/m ²)	21.0±3.2	22.0±2.9	0.23
Body surface area (m ²)	1.75±0.18	1.78±0.19	0.26
Systolic Blood Pressure (mmHg)	114.2±9.3	119.0±11.1	0.11
Diastolic Blood Pressure (mmHg)	65.5±8.6	70.8±7.0	0.008
Mean Blood Pressure (mmHg)	81.7±7.9	86.9±7.4	0.02
Heart rate (beats/min)	72.5±10.3	67.7±11.4	0.07

3 Data are expressed as mean ± SD or as number (%)

4 SCA = Sickle Cell Anemia

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1 **Table 2:** Echocardiographic measurements in patients and controls

	SCA patients (n=30)	Controls (n=30)	p value
LVEDD index (mm/m ²)	30.8±3.2	28.3±2.1	0.0009
LV mass index (g/m ²)	100.7±23.5	72.4±15.2	0.0001
LV mass index (g/m ²) in women (n=17)	98.6±19.2	66.6±13.4	0.0001
LV mass index (g/m ²) in men (n=13)	107.3±26.5	80.0±14.6	0.03
LV hypertrophy	14 (47)	1 (3)	< 0.0001
LV eccentric hypertrophy	13 (43)	1 (3)	0.0002
LVEDV index (ml/m ²)	80.9±16.0	59.5±13.0	< 0.0001
LV ejection volume index (ml/m ²)	56.4±9.6	47.3±7.6	0.0004
Cardiac index (L/min/m ²)	4.1±0.7	3.2±0.6	0.0001
TR velocity (m/s)	2.4±0.2	2.1±0.2*	< 0.0001
TR velocity > 2.5m/s n, %	13 (43.3)	1 (3.7)*	0.001
Left atrial area (cm ²)	23.8±3.8	18.0±3.9	< 0.0001
Right atrial area (cm ²)	17.7±2.9	14.4±3.5	0.0001
Diastolic function			
E (cm/s)	94.6±16.0	79.9±14.1	0.0003
A (cm/s)	49.5±11.7	46.2±11.0	0.33
E/A	2.0±0.5	1.8±0.4	0.04
E-wave deceleration time (ms)	169.5±34.6	153.3±30.7	0.02
e' (cm/s)	17.4±3.7**	19.0±3.5	0.11
E/e'	5.8±2.5**	4.5±2.1	0.0003
Diastolic dysfunction	6 (20)	0 (0)	0.03

Systolic function			
LVEF (%)	60.1±3.8	61.7±4.7	0.30
Global longitudinal strain (%)	-17.9±2.0**	-19.7±2.5**	0.004
Global longitudinal strain rate (s ⁻¹)	-0.92±0.09**	-1.07±0.17**	<0.0001

1 *n=27, **n=29

2 Data are expressed as mean ± SD or as number (%)

3 A= Late peak diastolic velocity of the mitral inflow; E = Early peak diastolic velocity of the
4 mitral inflow; e' = early diastolic mitral annular tissue Doppler velocity, E/e' = ratio between
5 peak velocities of mitral E wave and early-diastolic mitral annulus; LVEDD = Left
6 ventricular end-diastolic diameter; LVEDV = Left ventricular end-diastolic volume; LVEF =
7 left ventricular ejection fraction; TR velocity = tricuspid regurgitant maximal velocity; SCA =
8 Sickle Cell Anemia

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1 **Table 3:** Comparison of clinical and echocardiographic data according to LV Mass index in
 2 Sickle cell Anemia patients

	LV hypertrophy (n=14)	Normal LV morphology (n=16)	p value
Age (years)	24.3 ± 5.3	25.0 ± 5.1	0.80
Women	10 (71)	7 (44)	0.13
Systolic Blood Pressure (mmHg)	114.4 ± 10.0	113.9 ± 9.0	0.88
Diastolic Blood Pressure (mmHg)	64.1 ± 7.8	66.7 ± 9.3	0.51
Heart rate (beats/min)	70.9 ± 10.6	73.9 ± 10.1	0.37
Hemoglobin (g/dl)	8.3 ± 0.6	8.8 ± 1.1	0.21
LV mass index (g/m ²)	119.2±17.0	84.6±14.8	< 0.0001
Cardiac index (L/min/m ²)	4.2 ± 0.6	3.9 ± 0.8	0.13
TR velocity (m/s)	2.4 ± 0.2	2.4 ± 0.2	0.52
E (cm/s)	100.2 ± 13.3	89.6 ± 17.0	0.05
A (cm/s)	48.8 ± 13.0	50.1 ± 10.7	0.49
E/A	2.2 ± 0.5	1.9 ± 0.4	0.15
E-wave deceleration time (ms)	163.6 ± 21.9	174.6 ± 42.9	0.65
e' (cm/s)	16.6 ± 4.0*	18.0 ± 3.4	0.38
E/e'	6.7 ± 3.4*	5.1 ± 1.3	0.10
Diastolic dysfunction	5 (36)	1 (6)	0.04
LV Ejection Fraction (%)	59.4 ± 3.8	60.8 ± 3.8	0.42
Global longitudinal strain (%)	-17.1 ± 2.4*	-18.5 ± 1.5	0.07
Global longitudinal strain rate (s ⁻¹)	-0.88 ± 0.09*	-0.96 ± 0.08	0.02

3 *n=13.

- 1 Data are expressed as mean \pm SD or as number (%)
- 2 TR velocity = tricuspid regurgitant maximal velocity; E = Early peak diastolic velocity of the
- 3 mitral inflow; A= Late peak diastolic velocity of the mitral inflow; e' = early diastolic mitral
- 4 annular tissue Doppler velocity, E/e' = ratio between peak velocities of mitral E wave and
- 5 early-diastolic mitral annulus; SCA = Sickle Cell Anemia
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