Assessment of Ventricular Function in Adults with Sickle Cell Disease: Role of Two-Dimensional Speckle-Tracking Strain

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Background: Sickle cell disease (SCD) is a hemoglobinopathy that is common worldwide. It usually presents with cardiac involvement, although data on systolic function are somewhat controversial. The aim of this study was to investigate the value of speckle-tracking strain, a deformation index, in detecting ventricular dysfunction in SCD.

Methods: Ninety adult patients with SCD were compared with 20 healthy controls. Doppler echocardiography with Doppler tissue imaging was performed in all, and the left and right ventricles were analyzed by the use of two-dimensional speckle-tracking strain.

Results: The mean age of the patients with SCD was 26 years, and 43% were men. Left ventricular (LV) dimensions and mass were higher in patients with SCD, whereas LV ejection fraction did not differ from the controls. E and A waves, as well as E/e′ ratio, were also higher in patients with SCD. Two-dimensional speckle-tracking strain of both ventricles in the patients with SCD was not different from that of controls. The factors independently associated with LV longitudinal strain were age (P = .009), oximetry (P = .001), lactate dehydrogenase (P = .014), LV ejection fraction (P < .001), and right ventricular systolic annular velocity (P = .010).

Conclusions: Ventricular enlargement with normal ventricular function was a frequent finding in SCD. Two-dimensional speckle-tracking strain of both ventricles was similar in patients and controls, suggesting normal myocardial contractility in patients with SCD. LV global longitudinal strain was associated with age, intensity of hemolysis, and ventricular function. (J Am Soc Echocardiogr 2014;27:1216-22.)

Keywords: Sickle cell disease, Two-dimensional speckle-tracking strain, Ventricular function, Echocardiography

Sickle cell disease (SCD) is a frequent inherited hemoglobinopathy that affects approximately 100,000 individuals in the United States, with a prevalence of 1 in 365 African Americans.[1] Cardiovascular complications are increasingly identified in patients with SCD and have been associated with mortality.[2-6] Several mechanisms have been proposed to explain cardiac involvement in SCD, including chronic anemia,[7,8] progressive dysplasia or thrombotic occlusion of coronary vessels,[7] intrinsic cardiomyopathy,[9] and pulmonary hypertension.[10-12]

Pulmonary hypertension represents a serious complication of SCD associated with increased morbidity and mortality.[13-15] Both left ventricular (LV) systolic and diastolic dysfunction may occur in adults and children with SCD, but LV systolic dysfunction is not common and is usually observed in older patients and in those with associated disorders such as systemic hypertension and renal failure.[13,16] Although most studies in adults show abnormalities of LV diastolic function,[3,17-19] LV ejection fraction (LVEF) and/or other conventional indices of systolic function have usually been reported to remain normal.[20] It is well known that conventional indices of LV systolic function are limited in identifying and measuring early ventricular dysfunction because of the volume-expanded high–cardiac output state present in chronic anemia. Strain, a parameter that seems to be independent of ventricular geometry and, to a lesser extent, of ventricular loading conditions,[21] has been used to detect incipient LV and right ventricular (RV) systolic dysfunction in several heart diseases. However, only a few studies, with small numbers of patients, have addressed the role of strain in detecting subclinical changes in ventricular function in SCD, and their results are somewhat controversial.[22-24]

Thus, the purpose of the present study was to use two-dimensional (2D) speckle-tracking strain to evaluate RV and LV function to determine if incipient ventricular systolic dysfunction in SCD can be detected, despite a normal LVEF. In addition, we investigated the associations between demographic, clinical, laboratory, and echocardiographic parameters and LV longitudinal strain.

METHODS

Study Group

Adult outpatients ranging from 18 to 40 years of age, homozygous for hemoglobin S (HbSS) or who had Sβ⁰ thalassemia attended at Hemominas Foundation, a referral center for SCD in Belo Horizonte, Brazil, were included. Patients were prospectively enrolled if the diagnosis of SCD had been previously documented by hemoglobin electrophoresis on cellulose acetate and on acid citrate agar showing an absence of hemoglobin A and positive results for sickling. Individuals with HbSS and hemoglobin Sβ⁰ were selected because they present a very similar clinical course.[25,26] The control group consisted of patients without any histories of cardiac disease who were seen at the echocardiography laboratory and had normal results on Doppler echocardiography.

Patients outside the age range or who presented with associated conditions (hypertension, diabetes, alcohol or drug abuse, pregnancy, chronic obstructive lung disease, rheumatic heart disease, and other cardiomyopathies) were excluded.

The study was approved by the institutional research ethics committee of the Hemominas Foundation and Universidade Federal de Minas Gerais, and written informed consent was obtained from all patients.

Clinical Evaluation

At entry, a complete clinical evaluation and routine laboratory examinations were carried out on all patients. Only patients clinically stable for ≥4 weeks were included, and functional status was determined using the New York Heart Association classification on the basis of functional capacity and dyspnea.

Electrocardiography and comprehensive Doppler echocardiography, with color flow mapping, tissue Doppler imaging, and speckle-tracking (2D strain) of both left and right ventricles, were also performed in all patients.

Doppler Echocardiography

Doppler echocardiography with color flow mapping was performed using a Vivid 7 system (GE Healthcare, Milwaukee, WI) with multifrequency transducers. M-mode measurements were performed according to the American Society of Echocardiography recommendations.[27] LV mass was calculated using Devereux's formula.[28]

LV diastolic function was assessed by pulsed Doppler of the mitral inflow and by tissue Doppler imaging measurements, obtained at the medial and lateral border of the mitral annulus in the apical four-chamber view. Systolic tissue Doppler velocity (S′) and early (e′) and late (A′) diastolic tissue velocities were acquired, and the ratio of the mitral E velocity to the mean e′ was calculated (E/e′). Measurements were averaged over three beats.[29]

Right atrial area was measured in end-systole in the apical four-chamber view.[27] RV areas at end-systole and end-diastole were obtained in the apical four-chamber view, and fractional area change was calculated as (RV end-diastolic area − RV end-systolic area)/RV end-diastolic area × 100. RV tissue Doppler imaging was performed at the lateral tricuspid annulus in the apical four-chamber view, where peak systolic (S′) and early (e′) and late (A′) diastolic velocities were measured.

The presence and severity of valvular regurgitation was evaluated by integrating several parameters, as recommended.[30] Maximal tricuspid regurgitation velocity (TRv) was obtained in the four-chamber or parasternal view.

RV and LV 2D Strain

Images of the left ventricle in the apical four-, two-, and three-chamber views were obtained for analysis, as previously described.[21] The left ventricle was divided into 18 segments and, by using a dedicated software package (EchoPAC PC version 7.0.X; GE Healthcare, Fairfield, CT), 2D LV longitudinal strain was obtained for each segment. Longitudinal strain was assessed in all six LV walls in the three apical views, and the average value of each wall on each view was used for comparisons with the controls (Figure 1). RV longitudinal strain was also measured in a modified four-chamber view, aiming at the right ventricle and using the same software provided for the left ventricle (Figure 2). Both septal and free RV walls were measured and the mean value of the six segments was used to calculate RV global longitudinal strain.[31]

Radial and circumferential strain were assessed in the six LV walls in the parasternal LV short-axis view at the levels of the papillary muscles and mitral valve, and their average values were used for comparison with the controls. Global longitudinal, radial, and circumferential strains were obtained by dividing the sum of the strain from all LV walls segments by the number of segments.

Statistical Analysis

Categorical data are presented as numbers and percentages and continuous data as mean ± SD or median (interquartile range). The variables of patients with SCD and controls were compared using χ^2 tests, unpaired Student's t tests, or Mann-Whitney tests as appropriate. A multivariate linear regression model was performed to estimate the association between clinical, demographic, laboratory, and echocardiographic variables with LV global longitudinal strain. The reproducibility of three types of LV strain and RV strain was assessed by the intraclass correlation coefficients for repeated measures in a random sample of 15 patients. P values < .05 were considered significant. SPSS version 18 (SPSS, Inc, Chicago, IL) was used for all analyses.

RESULTS

Study Group

A total of 106 patients with SCD who were referred to the Hemominas Foundation were initially considered for the study. On the basis of exclusion criteria, 16 patients (15%) were not eligible for the study. A total of 90 adults with SCD, genotype HbSS (86 patients) or Sβ⁰ thalassemia (four patients), ranging from 18 to 40 years of age, were included. The control group consisted of 20 age- and gender-balanced control patients. Their clinical and demographic characteristics, as well as Doppler echocardiographic data, are presented in Table 1.

Forty-two patients with SCD (47%) were on hydroxyurea, and 16 individuals (18%) with the genotype HbSS who had histories of stroke were under hypertransfusion (i.e., periodic transfusion at regularly
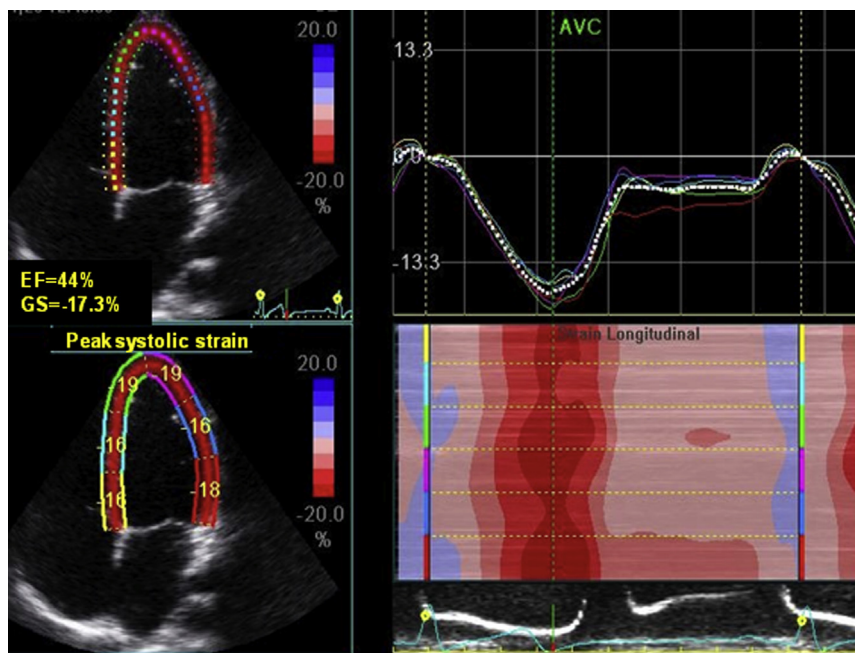
Figure 1 Two-dimensional longitudinal strain imaging showing segmental peak systolic longitudinal strain of the left ventricle in the apical four-chamber view.

scheduled intervals to maintain the percentage HbSS < 30% of total hemoglobin). The patients on hydroxyurea or on hypertransfusion regimen had higher hemoglobin values (9.5 ± 1.7 vs 8.2 ± 1.2 g/dL, P < .001), lower reticulocyte counts (0.8 ± 0.6% vs 1.4 ± 0.5%, P < .01), and better oxygen saturation (95% vs. 92%, P = .010) than those not undergoing these treatment modalities. Body surface area was lower in the patients, while both blood pressure and heart rate were similar to those of the controls. LV dimensions and indexed mass were higher in patients with SCD, and LVEFs was equal in patients and controls (Table 1). Both septal and lateral mitral annular velocities were similar between patients with SCD and control subjects.

Ventricular Function

Mitral E and A waves were higher in patients with SCD, while septal and lateral e′ were similar to those of the controls. As a consequence, E/e′ ratios were also higher in patients, but they still remained within the normal range. Left atrial (LA) diameter and indexed volume were higher in patients with SCD (Table 2).

Diastolic and systolic RV areas were both higher in patients with SCD, while RV fractional area change remained normal and similar to that of the controls (Table 3), as well as RV strain. The other conventional RV function indices were similar between the groups.

Because patients with primary heart valve disease were excluded, all patients had no or mild mitral regurgitation, and four patients had moderate tricuspid regurgitation. RV S′ was higher in the patients than in the controls. In patients with SCD, maximal TRv ranged from 2.1 to 3.3 m/sec and was ≥2.8 m/sec in 10 of them (9%), with only one patient presenting a TRv >3.0 m/sec.

Two-Dimensional Speckle-Tracking Strain

The three modalities of LV strain did not differ between patients with SCD and controls, as shown in Table 2. RV longitudinal strain in pa-

tients with SCD was also normal and similar to that in controls, even when the subgroup of patients with elevated pulmonary pressure was compared with the controls (Table 3).

In the multivariate linear regression analysis adjusted for age, blood pressures, body surface area, hydroxyurea treatment, oximetry laboratory markers of hemolysis, and echocardiographic variables including LA mass, LVEF, RV fractional area change, RV systolic annular velocity, TRv, and E/e′ ratio, the factors that remained independently associated with LV longitudinal strain were age (P = .009), oximetry (P = .001), lactate dehydrogenase (P = .014), LVEF (P < .001), and RV systolic annular velocity (P = .010) (Table 4).

Reproducibility

The intraclass correlation coefficients for LV global longitudinal, radial, and circumferential strain were 0.97, 0.93, and 0.59, respectively, for interobserver, and 0.97, 0.96, and 0.75, respectively, for intraobserver variability. For RV global strain, the intraclass correlation coefficients were 0.92 for interobserver variability and 0.93 for intraobserver variability.

DISCUSSION

The present study showed no difference in LV and RV systolic function, evaluated by 2D speckle-tracking strain between adults with SCD and healthy controls. LV global longitudinal strain was associated with age, oximetry, intensity of hemolysis assessed by lactate dehydrogenase, and LV and RV systolic function.

Left Chambers Structure and Function

In our study, conventional Doppler echocardiographic parameters demonstrated increased LV and LA diameters, as well as LV mass, similar to what has been extensively shown in both adults[3,16,32] and children.[18] Larger left and right chambers in individuals with SCD
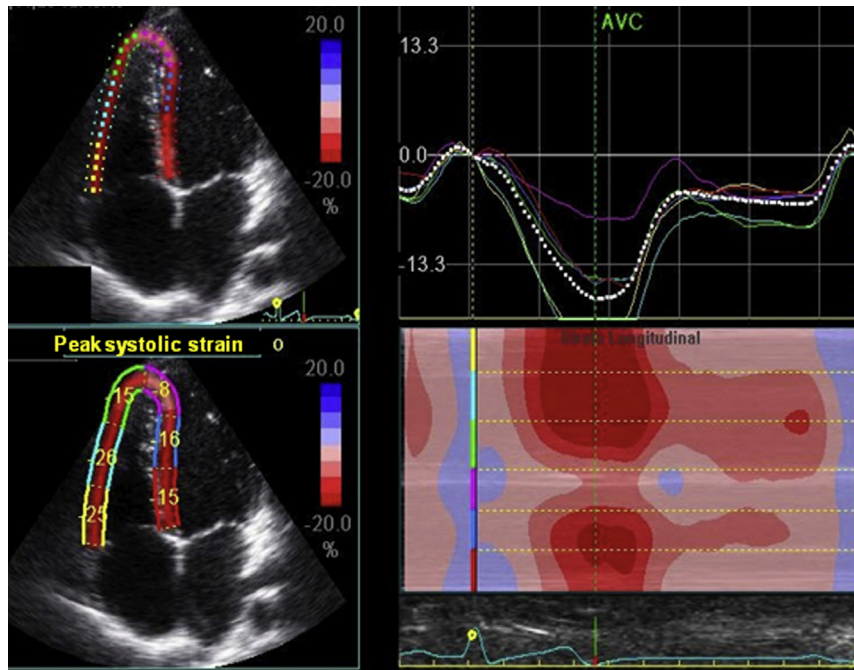
Figure 2 Two-dimensional longitudinal strain imaging of the right ventricle in the apical four-chamber view.

Table 1 Clinical and LV echocardiographic data in patients with SCD compared with controls

Variable	Patients	Controls	P
Age (yrs)	26.5 (22–33)	27.5 (24–35)	.162
Men	39 (43%)	9 (45%)	.542
BSA (m²)	1.6 ± 0.2	1.8 ± 0.2	.017
Heart rate (beats/min)	72 (63–78)	65 (60–70)	.122
Systolic pressure (mm Hg)	110 (105–120)	110 (110–120)	.680
Diastolic pressure (mm Hg)	70 (60–80)	70 (70–80)	.166
LVEDd (mm)	52 (49–57)	46 (41–49)	<.001
LVEDd/BSA (mm)	33 (30–36)	26 (24–28)	<.001
LVESd (mm)	34 (31–37)	30 (26–32)	<.001
LVEF (%)	63 (59–66)	63 (60–65)	.928
VS (mm)	11 (10–12)	9.5 (8–10)	<.001
PW (mm)	11 (10–12)	9 (8–10)	<.001
Indexed LV mass (g/m²)	147.9 ± 42.7	79.9 ± 17.8	<.001

BSA, Body surface area; *LVEDd*, LV end-diastolic diameter; *LVESd*, LV end-systolic diameter; *PW*, posterior wall; *VS*, ventricular septum. Data are expressed as mean ± SD, as median (interquartile range), or as number (percentage) of patients.

Table 2 Doppler echocardiographic diastolic parameters in patients with SCD compared with controls

Variable	Patients	Controls	P
E (cm/sec)	109.4 ± 20.8	89.1 ± 14.0	<.001
A (cm/sec)	60.8 ± 15.3	49.6 ± 9.7	.002
DT (cm/sec)	224.0 ± 37.9	236.9 ± 43.0	.186
IVRT (msec)	75.2 ± 9.5	76.2 ± 9.5	.656
E/A	1.9 ± 0.5	1.9 ± 0.5	.872
Septal e′ (cm/sec)	12.3 ± 2.2	12.7 ± 2.1	.452
Lateral e′ (cm/sec)	16.8 ± 2.7	16.3 ± 2.6	.374
E/e− ratio	5.4 ± 1.3	4.3 ± 0.7	<.001
LAd (mm)	38 (36–44)	32 (30–36.5)	<.001
LA volume index (mL/m²)	35.8 ± 12.1	18.7 ± 5.2	<.001
LV longitudinal strain (%)	−19.4 ± 2.2	−18.9 ± 2.0	.377
LV radial strain (%)	35.5 ± 11.1	38.2 ± 13.8	.427
LV circumferential strain (%)	−18.4 ± 4.0	−18.1 ± 2.4	.772

DT, Deceleration time of the E wave of the mitral valve; *IVRT*, isovolumic relaxation time; *LAd*, LA diameter. Data are expressed as mean ± SD or as median (interquartile range).

are probably an adaptive response to the increased stroke volume present in SCD[20] that can gradually cause ventricular enlargement. Although the mechanism of heart failure in anemia is not completely understood, some factors have been reported to contribute to high-output heart failure, including activation of the renin-angiotensin-aldosterone system and hyperactivity of the sympathetic nervous system. However, these conditions are rarely the sole cause of heart failure; in most such patients, the high cardiac output provokes heart failure in the setting of reduced ventricular reserve from some underlying cardiac disorder.[32,33]

Available data evaluating strain in the assessment of ventricular function in patients with SCD are limited. In the present study, no incipient LV systolic dysfunction was detected, and in both patients and controls, strain was within the normal limits, which is in agreement with a recently published meta-analysis.[34] This finding is also similar to what was observed by Sengupta *et al.*[23] who showed, in a study with a much smaller number of patients, no difference in LV strain between patients with SCD and controls.

The hyperdynamic state due to the volume overload present in SCD may mask incipient LV dysfunction. Strain might potentially be influenced by patient (age, gender, ethnicity, anthropometria),

Table 3 RV measurements in patients with SCD compared with controls

Variable	Patients	Controls	P
RV end-diastolic area (cm^2)	14.1 ± 3.5	11.2 ± 3.2	<.001
RV end-systolic area (cm^2)	7.9 ± 2.1	6.1 ± 2.0	.001
RV FAC (%)	44.2 ± 10.2	45.1 ± 8.6	.722
Maximal TRv (m/sec)*	2.51 ± 0.23	2.15 ± 0.21	<.001
TAPSE (mm)	23.7 ± 3.8	22.9 ± 2.0	.286
RV e′ (cm/sec)	15.9 ± 3.0	14.7 ± 3.0	.096
RV A′ (cm/sec)	12.2 ± 3.3	12.3 ± 3.6	.954
RV S (cm/sec)	15.8 ± 2.8	14.2 ± 2.3	.024
RV e′/A ratio	1.4 ± 0.4	1.3 ± 0.4	.271
RV global longitudinal strain (%)	21.6 ± 3.1	22.0 ± 4.1	.679

FAC, Fractional area change; *TAPSE*, tricuspid annular plane systolic excursion.
Data are expressed as mean ± SD.
*Measured in 79 patients with SCD (88%).

Table 4 Multivariate analysis of the factors associated with LV global longitudinal strain

Variable	β	P
Age	0.104	.009
Oximetry	−0.191	.001
Lactate dehydrogenase	−0.001	.014
RV systolic annular velocity	0.218	.010
LV ejection fraction	0.254	<.001

The R^2 value for the final multivariate model was 0.53.

hemodynamic (heart rate, blood pressure), and cardiac (ventricular size and wall thickness) factors.[35] Deformation is related not only to contractility but also to ventricular size and geometry (Hooke's law). Detecting subclinical dysfunction in a volume overloaded ventricle may require the correction of the deformation parameters for LV volume and loading conditions[36]; however, current guidelines do not establish the necessity of adjusting speckle-tracking strain for gender or LV morphology.[36] Strain increases with increased preload and decreases with increased afterload.[21] Thus, the high preload present in patients with SCD may have masked the detection of incipient ventricular dysfunction by strain in this group of patients. In fact, in another study, in which 28 patients with SCD underwent three-dimensional strain assessment,[24] even higher LV longitudinal strain was found in the patients compared with the controls. The authors suggested that this finding could be due to a cardiovascular system compensatory mechanism to keep adequate oxygenation in anemic patients.

Transfusion-related excessive iron stores is a cause of significant morbidity in patients with hemolytic anemia who receive frequent blood transfusions, and myocardial hemochromatosis is another factor that can affect strain. However, patients with SCD accumulate cardiac iron at a lower rate than patients with thalassemia major, which is frequently associated with myocardial iron deposition and iron-mediated cardiomyopathy.[37] Moreover, in our study, an iron chelator was prescribed to the patients at risk for hemosiderosis to minimize iron deposition in organs such as the liver and the heart.[38] Although a few patients with S-β^0 thalassemia were included in our investigation, this fact did not influence our results, as the clinical course of S-β^0 thalassemia is identical to that of SCD, which is different from the course of β-thalassemia major.[25]

Furthermore, 47% of our patients were on hydroxyurea, which is known to improve the overall course of the disease, decreasing hemolysis and its consequences.[37] Therefore, the use of hydroxyurea and hypertransfusion in a subset of the patients with SCD could be another factor preventing the development of ventricular dysfunction and consequent detection of abnormal strain in these patients. However, LV and RV 2D strain were similar among patients on hydroxyurea and/or hypertransfusion and patients without treatment and controls.

Both the E and A waves were higher in patients with SCD, which is probably a result of increased preload. LA and indexed LA volume were significantly higher in patients with SCD, probably reflecting increased preload but also indicating some degree of diastolic dysfunction. Higher E/e′ ratios were observed in patients with SCD. However, E/e′ ratios remained within the normal range, suggesting that these patients, although presenting higher E/e′ ratios, do not have elevated filling pressures.[29] Our results support the observations that LV enlargement can occur, but with normal LV filling pressures and without overt heart failure.

RV Function and Pulmonary Pressure in SCD

RV adaptation to disease is complex and depends on many factors. There are some possible explanations for RV dysfunction in SCD, including LV diastolic dysfunction[3,39] and elevation of pulmonary pressure due to increased cardiac output, rather than to increased pulmonary vascular resistance.[22,32,40] Airway hyperactivity and sleep-disordered breathing have also been mentioned as etiologic factors.[3,41] In the present study, no RV dysfunction was detected using conventional echocardiographic methods, including M-mode-derived tricuspid annular motion, RV fractional area change, and tissue Doppler imaging, and speckle-tracking strain for additional information beyond standard measurements.

A previous study from Blanc *et al.*[22] including 28 children with SCD showed lower RV longitudinal strain in the patients compared with the controls. However, global RV longitudinal strain was still within the normal range in the individuals with SCD. Global RV longitudinal strain was higher in that study than in ours (28.5 ± 5.6 vs 21.6 ± 3.1, respectively), which may be related to the ages of the populations included in the studies. Additionally, other conventional RV function indices were similar between patients and controls, which are in agreement with our findings.

Similarly to what has been previously proposed,[32] patients with SCD without pulmonary hypertension showed dilated right heart chambers without RV dysfunction. Furthermore, increased RV preload due to anemia may have prevented the detection of lower 2D strain, masking the identification of any incipient RV dysfunction that could be present. The fact that RV systolic annular velocity was higher in the patients with SCD than in the controls corroborates this hypothesis. Akgul *et al.*,[42] studying 48 young adults with SCD, also found higher RV systolic annular velocity values in patients with SCD than in controls. In contrast, Knight-Perry *et al.*[32] found lower RV systolic annular velocity in patients with SCD compared with controls. A higher S′ wave may be an expression of the relative "hyperdynamic" response of the right ventricle to the increased preload due to anemia.

In the setting of SCD, recent studies have shown that the prevalence of pulmonary hypertension is not as high as previously thought. A previous study showed that among subjects with SCD, pulmonary

hypertension assessed by echocardiography (TRv $\geq$ 2.5 m/sec) was present in 40% of them.[32] However, pulmonary hypertension confirmed by right-heart catheterization and defined as a mean pulmonary artery pressure $\geq$ 25 mm Hg occurred in 6.2%[12] to 10%[10] of patients with SCD. In our study, only one patient had tricuspid regurgitation maximum velocity >3.0 m/sec. Therefore, we believe that RV function in patients with SCD is determined mainly by ventricular afterload. This is corroborated by the fact that during acute chest syndrome, pulmonary pressures increase, leading to RV dysfunction. In a series of 84 consecutive hospital admissions, cor pulmonale was seen in 13% of patients with SCD during acute chest syndrome, and all these patients had TRv $\geq$ 3 m/sec during the acute event.[43]

The present study of patients with SCD in steady state without pulmonary hypertension is in agreement with previous studies that have shown dilated right heart chambers without significant RV dysfunction. RV global strain in SCD being similar to controls supports the fact that strain decreases with increased afterload but appears not to be significantly affected by the high flow state of anemia.

Limitations

Because there is no specific software for the analysis of 2D RV strain, the longitudinal strain in this chamber was assessed by the use of LV software.

Assessment of RV function using 2D speckle-tracking longitudinal deformation strain is rapidly evolving in the investigational field. However, several factors should be considered before implementing this method in the clinical setting. Compared with the left ventricle, RV strain is more difficult to measure and to interpret. We measured global RV strain including the free wall and the septum, because septal contraction contributes to both RV and LV function. However, currently, there is no consensus on the best approach to assess RV strain. Inclusion of interventricular septal strain as a component of global RV strain varies among prior studies.[44-47] Despite the limitations, previous studies have shown that 2D speckle-tracking strain permits the accurate assessment of RV function in many conditions, especially pulmonary hypertension.[46,47]

Although strain is considered relatively load independent, systolic strain is largely an ejection phase index, which is substantially dependent on preload and afterload. The impact of loading conditions and ventricular contractile state on strain parameters remains unclear. Advances in LV image-based evaluation in different loading conditions will permit meaningful assessment contractility using strain.

Our findings were obtained from a relatively young adult population and may not apply to an older population of patients with SCD. Another limitation is related to the fact that the patients were not submitted to right-heart catheterization for a more accurate measurement of pulmonary pressure.

CONCLUSIONS

Adults with SCD presented with ventricular enlargement but normal 2D speckle-tracking strain of both ventricles, reflecting normal myocardial function. LV global longitudinal strain was associated with age, oximetry, intensity of hemolysis, and LV and RV systolic function.

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