



Original article

Echocardiographic abnormalities in patients with sickle cell/ β -thalassemia do not depend on the β -thalassemia phenotype



Bruno Deltreggia Benites*, Ianara Silva Cisneiros, Stephany Oliveira Bastos, Ana Paula Beppler Lazaro Lino, Fernando Ferreira Costa, Simone Cristina Olenscki Gilli, Sara Teresinha Olalla Saad

Universidade Estadual de Campinas (UNICAMP), Campinas, SP, Brazil

ARTICLE INFO

Article history:

Received 3 January 2018

Accepted 11 September 2018

Available online 31 December 2018

Keywords:

Sickle cell disease

Beta-thalassemia

Echocardiography

ABSTRACT

Objectives and methods: We evaluated possible relationships between echocardiographic findings and clinical and laboratory parameters, in a cohort of Brazilian patients diagnosed with sickle cell/ β -thalassemia, to better understand the cardiac involvement in this disease.

Results: Left atrial (LA) and left ventricular (LV) dilation were found in 19.5 and 11% of patients, respectively; systolic left ventricular dysfunction was present in a single patient. There were no differences in masses and volumes of cardiac chambers comparing $S\beta^0$ with $S\beta^+$ patients, and no relationship between these parameters and specific complications of the disease. However, parameters of altered ventricular geometry were significantly correlated with serum creatinine, hepatic transaminases and bilirubin levels. Moreover, 3 patients presented stroke; they were significantly older [53 (41–56) $\times$ 37.5 (18–70), $p=0.048$], had higher values of LV posterior wall diastolic thickness [10 (10–11) $\times$ 8 (6–14), $p=0.03$], LV mass [226 (194–260) $\times$ 147 (69–537), $p=0.039$] and LA/aortic ratio [1.545 (1.48–1.61) $\times$ 1.26 (0.9–1.48), $p=0.032$].

Conclusions: Cardiac involvement in this disease does not appear to depend on the thalassemia phenotype. The presence of signs of myocardial remodeling in this group of patients was related to multi-organ impairment and rendered a higher propensity for stroke in older patients, suggesting the need for greater vigilance and control of associated factors.

© 2018 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author at: Hematology and Transfusion Medicine Center, University of Campinas (UNICAMP), Rua Carlos Chagas, 480, CEP: 13083-970, Campinas, SP, Brazil. Tel.: +55 19 3521 8603.

E-mail address: benites@unicamp.br (B.D. Benites).

<https://doi.org/10.1016/j.htct.2018.09.003>

2531-1379/© 2018 Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The double heterozygosity of sickle cell disease (SCD) and beta-thalassemia (sickle cell/ β -thalassemia or HbS/ β -thal) leads to the clinical expression of a variant form of SCD, with multiple acute and chronic complications, such as painful vaso occlusive events, cerebral vasculopathy, priapism, renal and lung disease, among others.¹ Disease severity varies among patients, even between individuals with a similar genotype, but depends highly on the degree of the beta-thalassemia mutation: decreased (β^+) or absent (β^0) beta-globin synthesis.²

This condition has a considerable prevalence in Brazil, due to the intense miscegenation of this population, including Mediterranean Caucasians and Afro-descendants, among other ethnic groups, creating a very peculiar genetic profile. However, although much is known regarding the organic involvement in SCD and beta-thalassemia, there are few studies specifically evaluating sickle cell/ β -thalassemia patients.

Our group has previously identified significant differences among sickle cell/ β -thalassemia patients according to the beta globin mutation.³ The S β^+ individuals are more prone to acute chest syndrome, and S β^0 patients presented with a lower body mass index (BMI) and bone mineral density. The degree of bone damage correlates to lower BMI and hemoglobin levels, as well as plaquetosis, monocytosis and elevated lactate dehydrogenase (LDH), possibly reflecting the effects of hemolysis and inflammation on bone metabolism and body constitution.³

Heart disease represents an important cause of mortality and morbidity in sickle cell disease and beta-thalassemia patients.⁴ However, the knowledge on the involvement of cardiac function in this specific group of compound heterozygotes is scarce. Two studies evaluated the register of repercussions on this organ, both performed in Greece. Moysakis et al. evaluated 43 patients with sickle β -thalassemia and 55 healthy controls and demonstrated that in the anemic group, the diastolic function was abnormal in both ventricles, whereas the systolic function remained unchanged.⁵ Aessopoulos et al. also showed biventricular dilatation and dysfunction in sickle beta-thalassemia patients, along with pulmonary hypertension, leading to congestive heart failure.⁶

Therefore, the objective of this study was to evaluate the relationship of echocardiographic findings with clinical and laboratory parameters in a cohort of Brazilian patients diagnosed with sickle cell/ β -thalassemia, to better understand the cardiac involvement in this disease in our particular ethnic background.

Patients and methods

Patients and data collection

A retrospective chart review was made for patients with a diagnosis of sickle cell/ β -thalassemia, regularly followed at the outpatient clinic of the Hematology and Transfusion Medicine Center of the University of Campinas, Brazil, from 1998 to 2016, comprising a total of forty-one patients (27 S β^0 and 14 S β^+). Patients were evaluated at steady-state

disease and were transfused sporadically. All patients were informed regarding the purpose and procedures of the study and provided written consent. The medical records of these 41 patients were reviewed for laboratory and clinical data comprising age, gender, weight, height, body mass index ($BMI = \text{weight (kg)} / \text{height}^2 \text{ (m}^2\text{)}$), white blood cell (WBC) counts, hemoglobin levels, reticulocyte counts, mean cell volume (MCV), mean corpuscular hemoglobin concentration (MCHC), platelet counts, lactate dehydrogenase (LDH) level, hepatic enzymes and aspartate aminotransferase (AST); alanine aminotransferase (ALT); alkaline phosphatase (ALP) and gamma-glutamyltransferase (GGT), serum ferritin, serum iron, total iron-binding capacity (TIBC), haptoglobin, conjugated and unconjugated bilirubin levels, microalbuminuria, creatinine and glomerular filtration rate estimated by 51Cr-EDTA clearance. Hospital admissions were recorded for all sickle related organ involvements, especially acute chest syndrome (ACS), which was recorded according to the current criteria: new infiltrate visible on chest radiograph associated with one or more symptoms, such as fever, cough, tachypnea, breathing difficulties or new hypoxia onset; retinopathy as the presence of a dense capillary bed up to the margin of perfusion, with abrupt termination of small or medium caliber vessels and irregular appearance of the border; avascular bone necrosis defined by a history of osteonecrosis of the femoral head or joint replacement; stroke defined by patient reported cerebrovascular disease (when treated in other emergency services) or documented by CT or MRI at our center. Episodes of priapism, leg ulcers and venous thromboembolism (VTE) were also carefully recorded. Laboratory tests were performed as part of a routine evaluation during the steady-state condition.

Echocardiographic evaluation

Echocardiographic evaluation was performed on all patients at rest, in steady-state disease, with pulsed, continuous, and color Doppler, with Hewlett Packard Sonos 1000 ultrasound System, using a 2.5 MHz transducer. All studies were done by two observers unaware of the subject's status. A complete M-mode, two-dimensional examination was used to assess: LV systolic and diastolic wall thickness (SWTh and DWTh, respectively), LV end diastolic and systolic diameters (EDD and ESD) and end systolic volumes (ESV). The following indexes were calculated: LV percent fractional shortening (%FS), and LV percent ejection fraction (%EF). All parameters were normalized per m^2 body surface area (BSA). A continuous wave Doppler echocardiogram was used to estimate the peak systolic pressure gradient across the tricuspid valve as an indicator of pulmonary hypertension.

Statistical analysis

Exploratory data analyses were used to investigate the distribution of variables. The means and standard deviations (SD) or median and range were used to summarize data, when applicable. The relationships among variables were tested for significance using Spearman's rank correlation and Wilcoxon/Kruskal-Wallis Rank Sum tests. Fisher's Exact Test was used for categorical variables. The Wilcoxon/Kruskal-Wallis Rank Sum and Fisher's Exact tests

Table 1 – Patients' clinical and laboratory data.

Parameters	S β ⁺ (n = 14)	S β ⁰ (n = 27)	p-value
Age (y)	37 (27–70)	38 (18–57)	p = 0.762
Weight (kg)	69.4 (50–124.3)	55 (35.3–78)	p = 0.025
Stature (m)	1.63 (1.52–1.82)	1.69 (1.41–1.87)	p = 1
Body mass index (BMI) (kg/m ²)	25.1 (19.5–37.5)	21.1 (17.7–29)	p < 0.001
Body surface area (BSA) (m ²)	1.81 (1.46–2.18)	1.54 (1.34–1.93)	p = 0.1502
Hemoglobin (g/L)	9.9 (7.6–13.7)	8.7 (5.7–13.9)	p = 0.002
MCV (fL)	72.3 (65.9–94.1)	76.7 (55.9–97.1)	p = 0.518
MCHC (pg)	31.5 (30.5–36.7)	33.3 (30.2–37.7)	p = 0.165
Reticulocyte counts ($\times 10^9$ /L)	187.5 (66.78–561.1)	258 (67.5–540)	p = 0.460
HbS (%)	68.2 (25.5–82.4)	79.7 (24.2–93.7)	p = 0.048
HbF (%)	2.75 (0.3–10.2)	7.5 (1.3–24.9)	p = 0.001
Leukocytes count ($\times 10^9$ /L)	7.36 (3.01–16.01)	9.29 (3.99–15.07)	p = 0.320
Neutrophils	3.67 (0.84–9.89)	5.09 (2.03–9.36)	p = 0.182
Lymphocytes	1.96 (0.99–4.73)	2.59 (0.96–5.97)	p = 0.322
Platelets count ($\times 10^9$ /L)	167.5 (74–644)	358 (98–818)	p = 0.039
MPV	7.00 (6.1–13.5)	7.60 (6–11.6)	p = 0.074
Serum creatinin	0.8 (0.5–1.6)	0.6 (0.3–2.6)	p = 0.182
GFR	106.65 (54.6–157)	105 (74–151)	p = 0.951
Serum ferritin (ng/L)	316.1 (22.8–1955)	423 (64.5–7576)	p = 1
Serum iron (μ g/dL)	70.5 (39–201)	125 (44–363)	p = 0.026
TIBC (μ g/dL)	273 (214–325)	228 (172–538)	p = 0.149
Transferrin saturation (%)	27.03 (13.13–67)	48.64 (16.54–95.34)	p = 0.004
Lactate dehydrogenase U/L	469.5 (260–1974)	639 (328–1455)	p = 0.080
AST (IU/L)	26 (14–102)	32 (16–104)	p = 0.570
ALT (IU/L)	23 (12–135)	22 (8–161)	p = 0.419
Conjugated bilirubin (mg/dL)	0.66 (0.38–4.4)	0.60 (0.25–2.9)	p = 0.906
Unconjugated bilirubin (mg/dL)	0.9 (0.73–5.1)	1.2 (0.7–8)	p = 0.830
Diabetes (N)	1	0	n/a
Hypertension (N)	6	4	n/a
Smoking (N)	1	1	n/a
Transfusion (RBC units/patient)	7.45 (0–81)	9 (0–39)	p = 0.110
Genotype (N)	IVS1-110 (4) IVS1-6 (2) Cd39 (1)	Cd39 (9)	n/a
Hydroxyurea treatment (N)	8	14	n/a

Abbreviations: MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, MPV: mean platelet volume, TIBC: total iron binding capacity, AST: aspartate aminotransferase, ALT: alanine aminotransferase, GFR: glomerular filtration rate (estimated by 51Cr-EDTA clearance), RBC: packed red blood cells.

were used for comparisons between the two groups (S β ⁰ and S β ⁺) and Spearman's rank correlation test were used to evaluate relationships among variables in the whole group of patients. Results were considered significant at $p < 0.05$. Statistical analysis was performed using the R software version 3.3.0 (2016-05-03) Copyright (C) 2016, The R Foundation for Statistical Computing.

Results

Demographic findings and clinical features

Among the studied population, 23 (56%) were women and 18 (44%) were men. The median age was 38 years, with a range of 18–70 years; 27 (65%) patients were diagnosed as S β ⁰, and 14 (35%) as S β ⁺. The patients' clinical and laboratory characteristics described in this study are detailed in Table 1.

Considering the S β -thalassemia phenotype, as expected, the two groups of patients differed significantly. Hemoglobin levels were significantly lower in S β ⁰ patients, who also presented a higher proportion of HbS and HbF. In addition, these

patients showed higher index levels of transferrin saturation and serum iron, probably reflecting a higher degree of ineffective hematopoiesis and/or hemolysis, despite the fact that other hemolysis parameters did not differ significantly between the two groups. Moreover, S β ⁰ patients had a significantly lower body mass index and weight and a higher number of platelets, emphasizing the disease severity in this group of patients.

Of the S β ⁺ patients, 42.8% had a previous diagnosis of Systemic Arterial Hypertension, as opposed to 14.8% of the S β ⁰ patients. However, all of these patients were treated with antihypertensive medications, presenting satisfactory blood pressure control according to the means of blood pressure measurements in the last 3 visits: median systolic blood pressure of 113.5 mmHg (88–129) in S β ⁺ and 118 (102–128) in S β ⁰ patients and median diastolic blood pressure: 66.5 mmHg (52–80) in S β ⁺ and 75 (59–91) in S β ⁰ patients.

When we evaluated the median number of packed red blood cells (RBCs) transfused per patient in each group, we observed, as expected, a higher number of transfused RBCs per patient in the S β ⁰ group (9 vs 7.45); however, this difference was not significant ($p = 0.11$).

Table 2 – Comparison of echocardiographic parameters according to the S β -thalassemia phenotype.

Echocardiographic parameters	S β ⁺	S β ⁰	p-value
Aortic diameter (mm)	32 (27–44)	29.5 (20–35)	<i>p</i> = 0.026
Left atrium diameter (mm)	38 (33–45)	36.5 (28–72)	<i>p</i> = 0.289
Left atrium/aortic ratio	1.21 (0.75–1.38)	1.295 (0.9–1.61)	<i>p</i> = 0.363
Right ventricular diameter (mm)	22 (19–34)	23 (18–38)	<i>p</i> = 0.874
Left ventricular end diastolic diameter (mm)	50 (45–54)	50.5 (42–67)	<i>p</i> = 0.711
Left ventricular end systolic diameter (mm)	31.5 (26.35)	32 (24–41)	<i>p</i> = 0.958
Left ventricular end diastolic volume (mm)	118 (92–141)	124 (79–231.3)	<i>p</i> = 0.499
Left ventricular end systolic volume (mL)	39.5 (25–51)	41 (20–74.2)	<i>p</i> = 1
Septum diastolic thickness (mm)	9 (7–10)	8 (6–13)	<i>p</i> = 0.85
Left ventricular posterior wall diastolic thickness (mm)	9 (7–11)	8.5 (6–14)	<i>p</i> = 0.918
Left ventricular mass (g)	152.5 (106–240)	159 (69–537.41)	<i>p</i> = 0.765
Left ventricular percent ejection fraction (Teicholz) (%)	65.5 (59–77)	68 (58–79)	<i>p</i> = 0.338
Left ventricular percent fractional shortening (%)	36 (31–46)	38 (31–48)	<i>p</i> = 0.441

Evaluation of echocardiographic parameters in the cohort of patients with S β -thalassemia

Except for the aorta diameter, which was higher in the S β ⁰ patients [32 (27–44) $\times$ 29.5 (20–35), *p* = 0.026], there were no significant differences in cardiac parameters (ejection fraction, diameters, thicknesses, masses and volumes of cardiac chambers), comparing both groups of patients (Table 2).

The left atrial (LA) and left ventricular (LV) dilation were found in 19.5 and 11% of patients, respectively. Systolic LV dysfunction (defined as LV ejection fraction <55%) was present in a single patient of our cohort. Thus, we can observe a group of patients with LA enlargement and LV remodeling, but cardiac involvement in S β -thalassemia patients does not appear to be dependent on the thalassemia phenotype.

Association between ventricular geometry, dysfunction of target organs and stroke

We found no relationship between the echocardiographic parameters analyzed and the occurrence of specific

complications of the disease (acute thoracic syndrome, leg ulcers, retinopathy, splenic sequestration, venous thromboembolism and avascular necrosis of the hip (Table 3).

However, a significant correlation was found regarding parameters of ventricular geometry with serum creatinine, hepatic transaminases, bilirubin levels and LDH. This fact may indicate a progressive systemic dysfunction in this group of patients, involving a multi-organ involvement. These associations are shown in Table 4.

Among the 41 patients studied, 3 of them presented stroke (1 S β ⁺ and 2 S β ⁰). These patients were significantly older than the others (median 53 years $\times$ 37.5 years, *p* = 0.048), which may reflect a longer time of exposure to the organic damage caused by the disease. Patients affected by stroke had higher values of left ventricular posterior wall diastolic thickness [10 (10–11) $\times$ 8 (6–14), *p* = 0.03] and greater left ventricular mass [226 (194–260) $\times$ 147 (69–537), *p* = 0.039]. In addition, S β ⁰ patients affected by stroke also presented a significantly higher left atrium/aortic ratio [1.545 (1.48–1.61) $\times$ 1.26 (0.9–1.48), *p* = 0.032].

Table 3 – Relationship between echocardiographic findings and specific complications of the disease (Wilcoxon rank sum test with continuity correction).

	Leg Ulcer	ACS	Retinopathy	Splenic Sequestration	VTE	Avascular necrosis
Aortic diameter	W = 48, <i>p</i> = 0.301	W = 147.5 <i>p</i> = 0.546	W = 88.5 <i>p</i> = 0.966	W = 44 <i>p</i> = 0.51	W = 9.5 <i>p</i> = 0.207	W = 27 <i>p</i> = 0.725
Left atrium diameter	W = 39.5 <i>p</i> = 0.669	W = 118 <i>p</i> = 0.684	W = 74.5 <i>p</i> = 0.523	W = 39.5 <i>p</i> = 0.729	W = 43 <i>p</i> = 0.731	W = 103.5 <i>p</i> = 0.58
LV EDD	W = 31, <i>p</i> = 0.915	W = 154 <i>p</i> = 0.405	W = 96.5 <i>p</i> = 0.798	W = 45 <i>p</i> = 0.467	W = 35.5 <i>p</i> = 0.572	W = 82.5 <i>p</i> = 0.766
S-DWTh	W = 23.5 <i>p</i> = 0.512	W = 113 <i>p</i> = 0.55	W = 75.5 <i>p</i> = 0.542	W = 36.5 <i>p</i> = 0.887	W = 33.5 <i>p</i> = 0.362	W = 88 <i>p</i> = 0.948
LV-DWTh	W = 28 <i>p</i> = 0.743	W = 94 <i>p</i> = 0.199	W = 83 <i>p</i> = 0.777	W = 53 <i>p</i> = 0.588	W = 26 <i>p</i> = 0.177	W = 77.5 <i>p</i> = 0.602
LV mass	W = 27 <i>p</i> = 0.846	W = 119.5 <i>p</i> = 0.875	W = 87.5 <i>p</i> = 0.779	W = 38 <i>p</i> = 0.624	W = 33.5 <i>p</i> = 0.491	W = 80.5 <i>p</i> = 1
LV mass/volume ratio	W = 40 <i>p</i> = 0.398	W = 129 <i>p</i> = 0.451	W = 8 <i>p</i> = 0.906	W = 30.5 <i>p</i> = 1	W = 58 <i>p</i> = 0.365	W = 70 <i>p</i> = 0.717

Abbreviations: ACS: acute chest syndrome, VTE: venous thromboembolism, LV EDD: left ventricular end diastolic diameter, S-DWTh: septum diastolic thickness, LV-DWTh: LV diastolic wall thickness.

Table 4 – Relationship between echocardiographic findings and serum creatinine, AST, ALT and bilirubin levels (“r” values for Spearman correlation results, significant at $p < 0.05$).

	Creatinine	AST	ALT	CB	UB	LDH
Aortic diameter	$r = 0.367$ $p = 0.028$	$r = 0.097$ NS	$r = 0.352$ $p = 0.038$	$r = 0.326$ NS	$r = -0.22$ NS	$r = -0.146$ NS
Left atrium diameter	$r = 0.488$ $p = 0.003$	$r = 0.418$ $p = 0.012$	$r = 0.625$ $p < 0.001$	$r = 0.534$ $p = 0.002$	$r = -0.18$ NS	$r = 0.044$ NS
LV EDD	$r = 0.341$ $p = 0.042$	$r = 0.226$ NS	$r = 0.245$ NS	$r = 0.221$ NS	$r = -0.172$ NS	$r = 0.167$ NS
S-DWTh	$r = 0.468$ $p = 0.004$	$r = 0.26$ NS	$r = 0.43$ $p < 0.001$	$r = 0.435$ $p = 0.016$	$r = 0.353$ NS	$r = 0.263$ NS
LV-DWTh	$r = 0.442$ left ventricular	$r = 0.24$ NS	$r = 0.428$ $p = 0.010$	$r = 0.378$ $p = 0.039$	$r = 0.289$ NS	$r = 0.236$ NS
LV mass	$r = 0.358$ $p = 0.041$	$r = 0.312$ NS	$r = 0.363$ $p = 0.041$	$r = 0.403$ $p = 0.037$	$r = 0.238$ NS	$r = 0.421$ $p = 0.026$
LV mass/volume ratio	$r = 0.17$ NS	$r = -0.206$ NS	$r = -0.22$ NS	$r = -0.299$ NS	$r = -0.431$ $p = 0.028$	$r = -0.327$ NS

Abbreviations: AST: aspartate aminotransferase, ALT: alanine aminotransferase, CB: conjugated bilirubin, UB: unconjugated bilirubin, LV EDD: left ventricle end diastolic diameter, S-DWTh: septum diastolic thickness, LV-DWTh: LV diastolic wall thickness, NS: statistically not significant.

Evaluation of pulmonary hypertension

No significant differences were found in pulmonary artery systolic pressure values between $S\beta^+$ and $S\beta^0$ patients. In this small sample, we found no relationship between PASP and the occurrence of acute or chronic complications (acute chest syndrome, thromboembolism, stroke, retinopathy, splenic sequestration and avascular hip necrosis).

Discussion

Improvement in the care of patients with hemoglobinopathies during the last decades has increased their life expectancy, creating new challenges in the clinical management of these individuals. These include the possibility of deterioration of the cardiac function, which can add considerable morbidity to the clinical picture of the disease. Less common variants, such as sickle cell/beta-thalassemia, still lack better characterization in this topic, and the objective of this study was to evaluate the echocardiographic findings in this group of patients, seeking correlations with laboratory data and other complications.

Except for the aorta diameters (higher in the $S\beta^0$ group), there were no significant differences in the other parameters (diameters, thicknesses, masses and volumes of cardiac chambers) between $S\beta^0$ and $S\beta^+$ patients. We therefore consider that the cardiac involvement in this disease does not depend so much on the thalassemia phenotype, unlike other clinical parameters, such as the body mass index and bone mineral density, which differ significantly between $S\beta^0$ and $S\beta^+$ patients.³ Cardiac involvement seems to occur more homogeneously in this group of individuals.

The prevalence of the left atrial and left ventricular dilation in our cohort was 19.5 and 11%, respectively. This prevalence is considerably lower than that reported for homozygous SS patients (78 and 35%, respectively),⁷ and is in agreement with the data found in $S\beta$ -thalassemia patients of Greek origin.⁶ Although we do not have a more accurate evaluation of the occurrence of diastolic dysfunction in our group of patients,

the dilation of chambers (mainly the LA) can be considered an indirect parameter of diastolic dysfunction.⁸ Previous studies have demonstrated a significant relation between the LA remodeling and echocardiographic indices of diastolic function⁹ and a higher LA volume index has shown to be an independent predictor of death, heart failure, atrial fibrillation, and ischemic stroke.¹⁰

New insights into the pathophysiology of heart disease in patients with sickle cell anemia demonstrate the association between myocardial fibrosis and the occurrence of diastolic dysfunction.¹¹ Despite this mechanism not having been evaluated in sickle cell/ β -thalassemia patients, this event may also be responsible for the alterations found in this group of compound heterozygotes. In fact, one limitation in our study was the unavailability of methods that can accurately evaluate the presence of still incipient cardiac lesions. An example would be the assessment of the global longitudinal strain (GLS), assessed by 2-dimensional speckle tracking echocardiography, a method able to recognize the cardiac involvement in early stages of disease.¹² The GLS is altered despite preserved LV function, as assessed by the ejection fraction and seems to be helpful in the prediction of cardiovascular outcomes in the general population.¹³ These methods have already been evaluated specifically in patients with β -thalassemia, demonstrating an important correlation even with cardiac damage secondary to iron overload.¹⁴ They also present a better prognostic value for diastolic dysfunction in this group of patients than parameters evaluated in traditional echocardiography.¹⁵ The use of these new techniques in heterozygous patients still needs to be evaluated in future studies.

Systolic LV dysfunction (defined as LV ejection fraction $< 59\%$) was present in only one patient of our cohort, and it is also uncommon in SS patients (8.5% in the study of Damy et al.).⁷ Interestingly, a significant correlation was found regarding altered parameters of ventricular geometry with markers of systemic disease (serum creatinine, hepatic transaminases and bilirubin levels). Moreover, 3 of the 41 patients studied presented stroke (1 $S\beta^+$ and 2 $S\beta^0$), and these patients presented significantly higher values of left ventricular posterior wall diastolic thickness and greater left

ventricular mass, and the 2 S β^0 patients affected by stroke also presented a significantly higher left atrium/aortic ratio. These results may suggest a higher propensity for stroke in older patients with signs of ventricular hypertrophy.

Thus, in the case of Brazilian patients diagnosed with sickle cell/ β -thalassemia, we can observe a higher prevalence of left atrial and left ventricular dilation with little systolic function impairment. In addition, the comparison between the two groups of patients reveals that cardiac involvement in this disease does not appear to depend on the thalassemia phenotype. The presence of signs of myocardial remodeling in this group of patients was related to multi-organ impairment, rendering a higher propensity for stroke in older patients, suggesting the need for greater vigilance and control of associated factors, such as hypertension, dyslipidemia and diabetes.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Zago MA, Costa FF, Freitas TC, Bottura C. Clinical, hematological and genetic features of sickle-cell anemia and sickle cell-beta thalassemia in a Brazilian population. *Clin Genet*. 1980;18(1):58–64.
2. Daniel Y, Hill K, Inusa B, Thein SL, Howard J. Sickle cell/ β -thalassemia associated with the 1393bp deletion can be associated with a severe phenotype. *Hemoglobin*. 2011;35(4):406–10.
3. Benites BD, Bastos SO, Baldanzi G, dos Santos AO, Ramos CD, Costa FF, et al. Sickle cell/ β -thalassemia: comparison of S β 0 and S β + Brazilian patients followed at a single institution. *Hematology*. 2016;21(10):623–9.
4. Farmakis D, Triposkiadis F, Lekakis J, Parissis J. Heart failure in haemoglobinopathies: pathophysiology, clinical phenotypes, and management. *Eur J Heart Fail*. 2017;19(4):479–89.
5. Moyssakis I, Tzanetea R, Tsaftaridis P, Rombos I, Papadopoulos DP, Kalotychou V, et al. Systolic and diastolic function in middle aged patients with sickle beta thalassaemia. An echocardiographic study. *Postgrad Med J*. 2005;81(961):711–4.
6. Aessopos A, Farmakis D, Trompoukis C, Tsironi M, Moyssakis I, Tsaftaridis P, et al. Cardiac involvement in sickle beta-thalassemia. *Ann Hematol*. 2009;88(6):557–64.
7. Damy T, Bodez D, Habibi A, Guellich A, Rappeneau S, Inamo J, et al. Haematological determinants of cardiac involvement in adults with sickle cell disease. *Eur Heart J*. 2016;37(14):1158–67.
8. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by Echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17(12):1321–60.
9. Tsang TS, Barnes ME, Gersh BJ, Bailey KR, Seward JB. Left atrial volume as a morphophysiological expression of left ventricular diastolic dysfunction and relation to cardiovascular risk burden. *Am J Cardiol*. 2002;90:1284–9.
10. Abhayaratna WP, Seward JB, Appleton CP, Douglas PS, Oh JK, Tajik AJ, et al. Left atrial size: physiologic determinants and clinical applications. *J Am Coll Cardiol*. 2006;47(12):2357–63.
11. Niss O, Fleck R, Makue F, Alsaied T, Desai P, Towbin JA, et al. Association between diffuse myocardial fibrosis and diastolic dysfunction in sickle cell anemia. *Blood*. 2017;130(2):205–13.
12. Parsaee M, Saedi S, Joghataei P, Azarkeivan A, Alizadeh Sani Z. Value of speckle tracking echocardiography for detection of clinically silent left ventricular dysfunction in patients with β -thalassemia. *Hematology*. 2017;22(9):554–8.
13. Biering-Sørensen T, Biering-Sørensen SR, Olsen FJ, Sengeløv M, Jørgensen PG, Mogelvang R, et al. Global longitudinal strain by echocardiography predicts long-term risk of cardiovascular morbidity and mortality in a low-risk general population: the copenhagen city heart study. *Circ Cardiovasc Imaging*. 2017;10(3), pii:e005521.
14. Parsaee M, Akiash N, Azarkeivan A, Alizadeh Sani Z, Amin A, Pazoki M, et al. The correlation between cardiac magnetic resonance T2* and left ventricular global longitudinal strain in people with β -thalassemia. *Echocardiography*. 2018;35(April (4)):438–44.
15. Karamanou AG, Hamodraka ES, Vrakas SC, Paraskevaidis I, Lekakis I, Kremastinos DT. Assessment of left ventricular and atrial diastolic function using two-dimensional (2D) strain imaging in patients with β -thalassemia major. *Eur J Haematol*. 2014;92(1):59–65.