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Left ventricular hypertrophy in children, adolescents and young adults with sickle cell anemia



Gustavo Baptista de Almeida Faro, Osvaldo Alves Menezes-Neto,
Geodete Santos Batista, Antônio Pereira Silva-Neto, Rosana Cipolotti*

Universidade Federal de Sergipe (UFS), Aracaju, SE, Brazil

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ABSTRACT

Objective: The aims of this study were to estimate the frequency of left ventricular hypertrophy and to identify variables associated with this condition in under 25-year-old patients with sickle cell anemia.

Methods: A cross-sectional study was performed of children, adolescents and young adults with sickle cell anemia submitted to a transthoracic Doppler echocardiography. The mass of the left ventricle was determined by the formula of Devereux et al. with correction for height, and the percentile curves of gender and age were applied. Individuals with rheumatic and congenital heart disease were excluded. The patients were divided into two groups according to the presence or absence of left ventricular hypertrophy and compared according to clinical, echocardiographic and laboratory variables.

Results: A total of 37.6% of the patients had left ventricular hypertrophy in this sample. There was no difference between the groups of patients with and without hypertrophy according to pathological history or clinical characteristics, except possibly for the use of hydroxyurea, more often used in the group without left ventricular hypertrophy. Patients with left ventricular hypertrophy presented larger left atria and lower hemoglobin and hematocrit levels, reticulocyte index and a higher albumin:creatinine ratio in urine.

Conclusion: Left ventricular hypertrophy was observed in more than one-third of the young patients with sickle cell anemia with this finding being inversely correlated to the hemoglobin and hematocrit levels, and reticulocyte index and directly associated to a higher albumin/creatinine ratio. It is possible that hydroxyurea had had a protective effect on the development of left ventricular hypertrophy.

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* Corresponding author at: Campus da Saúde, Hospital Universitário, Av. Cláudio Batista, s/n, Sanatório, 49000-000 Aracaju, SE, Brazil.

E-mail address: rosanaci@yahoo.com (R. Cipolotti).

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Introduction

Sickle cell anemia (SCA) is a multisystemic disease characterized by acute episodes of pain and progressive lesions of target organs. It is one of the most common and most severe monogenic disorders in the world. In Brazil, it is estimated that 3500 children are born with sickle cell anemia each year, that is 1:1000 live births, and is thus a serious public health problem.¹ Cardiovascular disease is a frequent clinical manifestation of people with sickle cell anemia.

Eccentric left ventricular hypertrophy (LVH), dilation of the chambers, biventricular dysfunction, pulmonary hypertension and myocardial ischemia are the principal findings.²⁻⁵ Patients with SCA frequently have severe anemia that results in increased cardiac output with minimal or no increase in cardiac frequency thereby causing dilatation of the left ventricle⁶ correlated to the hemoglobin (Hb) level.^{7,8} The dilated left ventricle adapts to the chronic volume overload by hypertrophy, thickening the heart muscle and stretching the myofibrils of the muscle. Hypertrophy allows the left ventricle to adapt to the chronic volume overload, initially preserving diastolic compliance and maintaining the filling pressure at normal levels.⁹ The literature shows that LVH is a common condition in sickle cell anemia after the second decade of life.¹⁰ Diagnosed by transthoracic Doppler echocardiography, the prevalence of LVH varies between 13 and 86%.^{7,10-14} In chronic cases, LVH presents with diastolic^{3,15,16} and systolic dysfunction.^{3,15}

Given the high morbimortality, the present article aimed to estimate the frequency of LVH in children, adolescents and young adults with sickle cell anemia and determine variables associated to this condition.

Method

Study design and population

A cross-sectional study was conducted of patients between the ages of 7 and 25 with SCA as confirmed by electrophoresis, regularly treated in a referral center. All patients were in steady state, and were submitted to outpatient transthoracic Doppler echocardiography. The exclusion criteria were the presence of rheumatic or congenital heart disease. Patients were consecutively enrolled and allocated in two groups according to the presence or absence of LVH.

Transthoracic Doppler echocardiography

Echocardiographic examinations were performed using a Nemio® XG (Toshiba) device by one experienced echocardiographer. Patients were placed in the left lateral decubitus position without sedation to perform the echocardiographic measurements in parasternal and apical acoustic windows following the recommendations of the American Society of Echocardiography.¹⁷ At least three cycles were analyzed for each variable. The electrocardiographic exam was performed concurrently with laboratory tests. The evaluation of the left ventricle was obtained using the variables: end diastolic thickness of the interventricular septum (IVS),

end-diastolic thickness of the posterior wall of the left ventricle (LVPW), left ventricular end-diastolic diameter (LVDD) and left ventricular end-systolic diameter (LVSD). The relative wall thickness (RWT) was obtained using the formula: $RWT = (IVS + LVPW)/LVDD$. The left ventricular mass index (LVMI) was calculated using the formula proposed by Devereux et al.¹⁸ in which:

$$LVMI(g) = 0.8\{1.04[(IVS + LVDD + LVPW)^3 - 3LVDD^3]\} + 0.6$$

Subsequently the result was corrected for the height^{18,19} and applied to specific percentile curves for gender and age.²⁰ LVH was diagnosed when the LVMI was higher than the 95th percentile for gender and age.²⁰

Demographic and clinical data

Data regarding the age, gender, anthropometry (weight, height), information regarding the diagnosis (age at diagnosis, electrophoresis results), previous use of hydroxyurea and pathological history (leg ulcers, gallstones, stroke, surgical splenectomy, priapism, acute chest syndrome, hospitalizations, transfusions and painful crises in the previous year) were collected through interviews and from medical charts.

Laboratory data

Data on the blood count, reticulocyte index (corrected by hematocrit), lactate dehydrogenase and total bilirubin levels, ferritin, serum creatinine and urea, albumin:creatinine ratio in urine and 24-hour creatinine clearance were collected during the week prior to the echocardiography in order to correlate them with LVH.

Ethical considerations

This study is part of clinical research in sickle cell anemia approved by the Research Ethics Committee of the Universidade Federal de Sergipe (number 0173.0.107.000-09). Patients over 18 years old and the guardians of under 18-year-old patients signed informed consent forms.

Data analysis

The results were analyzed using the Statistical Package for the Social Sciences for Windows version 17.0 (SPSS, Chicago IL). Categorical variables were analyzed using the chi-squared distribution or Fisher's exact test. The Student's t-test or Mann-Whitney test were used to compare numerical variables between the groups. A logistical regression model was used to evaluate the protective effect of hydroxyurea after the elimination of possible confusing variables. The level of significance was set for p -values <0.05 .

Results

One hundred and nine patients with SCA were studied; 56 (51.4%) were male. SCA was diagnosed at a mean age of 69.28 ± 46.09 months and LVH was present in 41 (37.6%)

Table 1 – Demographic and clinical characteristics of sickle cell anemia patients with and without left ventricular hypertrophy.

	Left ventricular hypertrophy		Total	p-value
	Yes	No		
Age (years)	14.07 ± 5.55	15.60 ± 5.70	15.03 ± 5.67	0.17
Gender – n (%)				
Male	23 (41.1)	33 (58.9)	56 (51.4)	0.57
Female	18 (34)	35 (66)	53 (48.6)	
Age at diagnosis (months)	61.42 ± 41.18	74.46 ± 48.76	69.28 ± 46.09	0.21
Hemoglobin S (%)	80.52 ± 15.33	83.93 ± 11.27	82.56 ± 13.06	0.27
Hemoglobin F (%)	5.52 ± 6.62	4.90 ± 5.87	5.15 ± 6.15	1.00
Ulcers – n (%)	3 (7.5)	13 (19.7)	16 (15.1)	0.07
Cholelithiasis – n (%)	9 (22.5)	27 (40.9)	36 (34)	0.08
Stroke – n (%)	4 (10)	12 (18.2)	16 (15.1)	0.20
Splenectomy – n (%)	6 (15)	7 (10.6)	13 (12.3)	0.72
Priapism – n (%)	1 (4.5)	2 (6.3)	3 (5.6)	0.64
ACS – n (%)	23 (59)	49 (75.4)	72 (69.2)	0.12
Hydroxyurea (yes) – n (%)	3 (7.5)	16 (24.2)	19 (17.6)	0.02
Hydroxyurea (months of use)	34.67 ± 3.21	32.50 ± 16.01	32.84 ± 14.68	0.82
Hospitalizations/year	0.72 ± 1.23	0.91 ± 1.36	0.84 ± 1.31	0.47
Pain crises/year	0.51 ± 0.91	0.74 ± 1.23	0.66 ± 1.13	0.44
Transfusions/year	0.77 ± 1.25	1.48 ± 2.74	1.22 ± 2.32	0.31

ACS: acute chest syndrome.

patients. The mean age, and the proportions of Hb S and Hb F were similar between patients with or without LVH. The main complications resulting from SCA were acute chest syndrome (69.2%), cholelithiasis (34%), stroke (15.1%) and leg ulcers (15.1%). Patients presented on average 0.84 ± 1.31 episodes of hospitalization/year and 0.66 ± 1.13 pain crises that required hospitalization/year and received 1.22 ± 2.32 units of packed red blood cells/year; there were no significant differences in respect to these variables between the two groups. Hydroxyurea was continuously used by 17.6% of the 109 patients, 7.5% in the group with LVH and 24.2% in the group without LVH (p -value = 0.02). The duration of hydroxyurea use was similar between the two groups (Table 1).

Patients with LVH presented greater LVDD, LVSD, end diastolic thickness of the IVS, end-diastolic thickness of the LVPW and larger diameters of the aortic root and of the left atria. End-diastolic volume, ejection fraction and the systolic shortening fraction were similar between the two groups (Table 2).

The group with LVH presented lower Hb levels (7.65 ± 1.39 g/dL vs. 8.46 ± 1.70 g/dL; p -value = 0.01), hematocrit concentrations ($21.94 \pm 3.41\%$ vs. $25.26 \pm 5.49\%$; p -value = 0.001), reticulocyte index (1.23 ± 0.75 vs. 1.97 ± 1.52 ; p -value = 0.02) and a higher 24-h albumin:creatinine ratio in urine (97.92 ± 217.83 mg/dL vs. 27.60 ± 43.51 mg/dL; p -value = 0.01). Hemolysis markers (lactate dehydrogenase, indirect bilirubin and ferritin) and creatinine clearance were statistically similar in both groups (Table 3). The logistic regression model did not confirm any protective effect of hydroxyurea in this sample.

Discussion

LVH was present in 37.6% of the patients included in the study. There was no difference between groups with respect to

clinical, demographic or pathological aspects, with a possible exception for the use of hydroxyurea. Patients with LVH had a larger left atria index for body surface and lower hemoglobin and hematocrit levels, and reticulocyte index and higher 24-h albumin:creatinine ratio in urine. Markers of hemolysis (lactic dehydrogenase, indirect bilirubin and ferritin) and creatinine clearance were uniformly high in both groups. Using echocardiography, previous studies have shown that LVH is a common condition of SCA adults^{8,9} with a prevalence that ranges between 13 and 86%, a variation related to the different criteria used in the studies.^{7,10-14} Anatomopathological studies show frequencies for LVH of 20–100% in SCA patients.²¹ Sickle cell disease patients have higher rates of left ventricular mass when compared to Hb S heterozygotes, patients with iron deficiency anemia and healthy patients.^{2,8}

In this study, no significant difference was identified between the groups with respect to age and age at diagnosis. Several authors have shown that LVH is directly related to the age^{3,7,8,15} whereas another study¹⁰ showed that LVH is much more common in young people. Moreover, other authors did not find any difference in age among patients with or without hypertrophy.¹² There was no statistical difference regarding the percentage of Hb S and Hb F at diagnosis between the groups in this study. A previous study showed a directly proportional relationship between left ventricular mass and Hb S levels,⁷ but not with Hb F.^{11,22}

The continued use of hydroxyurea was a protector against LVH in the bivariate analysis, but the logistic regression model did not confirm this finding, which may be related to the sample size. There is no reference in previous studies regarding association between LVH and leg ulcers, cholelithiasis, stroke, priapism or acute chest syndrome. Although statistically similar between groups, the numerical difference can be considered, as these were the most common morbidities in patients without LVH, perhaps because of a 'shield'

Table 2 – Echocardiographic parameters of sickle cell anemia patients with and without left ventricular hypertrophy.

	Left ventricular hypertrophy		p-value
	Yes	No	
LV mass index (g/m ²) ^a	49.40 ± 9.65	32.94 ± 4.43	<0.001
Aortic root (mm/m ²) ^a	21.9 ± 3	19.7 ± 2.6	<0.001
Left atrium (mm/m ²) ^a	25.5 ± 3.9	22 ± 3.4	<0.001
LV diastolic diameter (mm/m ²) ^a	44.6 ± 7.7	36.7 ± 5.3	<0.001
LV systolic diameter (mm/m ²) ^a	27 ± 5.1	22.2 ± 3.9	<0.001
Interventricular septum (mm/m ²) ^a	6.5 ± 1.2	5.2 ± 0.7	<0.001
LV posterior wall (mm/m ²) ^a	6.6 ± 1.3	5.3 ± 0.8	<0.001
End-diastolic volume (mm ³ /m ²) ^a	34.77 ± 26.32	26.25 ± 11.93	0.09
Relative wall thickness (mm)	0.30 ± 0.05	0.29 ± 0.04	0.63
Systolic shortening fraction (%)	0.39 ± 0.05	0.39 ± 0.07	0.73
Ejection fraction (%)	0.69 ± 0.64	0.69 ± 0.64	0.99
SPAP (mmHg)	17.89 ± 7.72	20.60 ± 8.75	0.15

LV: left ventricle; SPAP: systolic pulmonary artery pressure.
^a Adjusted for body surface.

Table 3 – Laboratory variables of sickle cell anemia patients with and without left ventricular hypertrophy.

	LVH		p-value
	Yes	No	
Hemoglobin (g/dL)	7.65 ± 1.39	8.46 ± 1.70	0.01
Hemoglobin (%)	21.94 ± 3.41	25.26 ± 5.49	0.001
Leukocytes (mm ³)	12,954.00 ± 3460.78	12,007.71 ± 4500.11	0.26
Reticulocyte index	1.23 ± 0.75	1.97 ± 1.52	0.02
Lactate dehydrogenase (U/L)	1576.89 ± 789.76	1310.14 ± 701.96	0.10
Total bilirubin (mg/dL)	4.93 ± 2.93	4.14 ± 3.44	0.25
Indirect bilirubin (mg/dL)	4.11 ± 2.73	3.39 ± 3.23	0.27
Ferritin (ng/mL)	651.57 ± 1313.11	857.95 ± 1271.80	0.46
Creatinine (mg/dL)	0.39 ± 0.14	0.42 ± 0.12	0.22
Urea (mg/dL)	16.17 ± 6.66	15.37 ± 6.05	0.55
Albumin:creatinine (mg/g)	97.92 ± 217.83	27.60 ± 43.51	0.01
CC (mL/min/1.73m ²)	162.31 ± 68.13	160.80 ± 46.76	0.85

CC: creatinine clearance.

effect given by a possible higher frequency of blood transfusions. Likewise, patients with histories of stroke, priapism and acute chest syndrome constitute the group with classical indication for the use of hydroxyurea, which also contributes to increased levels of hemoglobin and a proportionate decrease in Hb S, previously demonstrated as being directly related to increases in left ventricular mass in SCA patients. The left atrium, a potential marker of diastolic dysfunction, was significantly larger in patients with LVH, a result consistent with previous studies.^{13,14} Systolic pulmonary artery pressure was similar between the groups in this study, thereby disagreeing with the literature.^{14,23}

LVH is inversely related to the hemoglobin concentration, which is consistent with previous studies.^{7,8,12} The reticulocyte index, lower in patients with LVH, may signal bone marrow exhaustion. Markers of hemolysis (lactic dehydrogenase, indirect bilirubin and ferritin) and creatinine clearance were uniformly high in both groups, possibly due to the predominant haplotype in Brazil, Bantu, which is associated with the most severe disease.²⁴ Previous studies showed that patients who more often received red blood cell transfusions had lower left ventricular masses,^{12,25} similar to data found in the present study, in which numerical, albeit non-significant,

differences were observed. LVH was not associated to ferritin levels, similar to a previous study.¹² In one study patients with LVH had a higher mean 24-h albumin:creatinine ratio in urine, with similar glomerular filtration rates between the two groups.¹² Patients were described as chronically anemic, with established renal impairment, dilation of the left ventricle and LVH in another study,²⁶ reinforcing the difference found in the albumin:creatinine ratio, although there was no relation to the glomerular filtration rate. This is possibly due to the state of hyperfiltration, characteristic of early renal injury in SCA patients. In one study cardiac remodeling was prevented with the use of enalapril in nine SCA patients.²⁷ Although the association of increased left ventricular mass and diastolic dysfunction is related to hypertension in the general population, in SCA patients this association is due to a combination of compensatory hypertrophy of the left ventricle, secondary anemia and left ventricular dilatation along with systemic vasculopathy. Direct myocardial injury and microvascular disease by iron deposition have been postulated as possible etiologies for cardiac abnormalities.¹⁷ The dilated left ventricle allows an adaptation to chronic volume overload, initially preserving diastolic compliance and maintaining filling pressures normal.²⁸ Chronic LVH evolves to left

ventricular diastolic^{3,15,17} and systolic dysfunction^{3,15} and has been described as a cause of sudden death in SCA patients.¹⁰

This study presents limitations. The criteria used to define LVH are designed for more ethnically homogeneous populations. Moreover, arterial blood pressures were not evaluated. The low number of patients using hydroxyurea may have interfered in the adequate analysis of a possible protective role.

Conclusion

Young SCA patients in this study had a high prevalence of LVH (37.6%); this was associated with lower hemoglobin and hematocrit levels and reticulocyte index and a higher albumin:creatinine ratio.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

- Cançado RD, Jesus JA. Sick cell disease in Brazil. *Rev Bras Hematol Hemoter.* 2007;29(3):203-6.
- Souza-Júnior JL, Rodrigues AC, Buck PC, Guallandro SF, Mady C. Coronary flow reserve in sickle cell anemia. *Arq Bras Cardiol.* 2007;88(5):552-8.
- Martins WA, Mesquita ET, Cunha DM, Ferrari AH, Pinheiro LA, Romeo-Filho LJ, et al. Cardiovascular changes in sickle cell anemia. *Arq Bras Cardiol.* 1998;70(5):365-70.
- Gualandro SF, Fonseca GH, Gualandro DM. Cardiopulmonary complications of sickle cell disease. *Rev Bras Hematol Hemoter.* 2007;29(3):291-8.
- Cipolotti R, Costa GB, Lima WH, Franco RP, Mello EV, Dal Fabbro AL, et al. Echocardiographic characteristics of patients with sickle cell anemia in Sergipe, Brazil. *J Trop Pediatr.* 2001;47(2):73-6.
- Varat MA, Adolph RJ, Fowler NO. Cardiovascular effects of anemia. *Am Heart J.* 1972;83(3):415-26.
- Lester LA, Sodt PC, Hutcheon N, Arcilla RA. Cardiac abnormalities in children with sickle cell anemia. *Chest.* 1990;98(5):1169-74.
- Poludasu S, Ramkissoon K, Saliccioli L, Kamran H, Lazar JM. Left ventricular systolic function in sickle cell anemia: a meta-analysis. *J Card Fail.* 2013;19(5):333-41.
- Grossman W, Jones D, McLaurin LP. Wall stress and patterns of hypertrophy in the human left ventricle. *J Clin Invest.* 1975;56(1):56-64.
- Johnson MC, Kirkham FJ, Redline S, Rosen CL, Yan Y, Roberts I, et al. Left ventricular hypertrophy and diastolic dysfunction in children with sickle cell disease are related to asleep and waking oxygen desaturation. *Blood.* 2010;116(1):16-21.
- Ahmed S, Siddiqui AK, Sadiq A, Shahid RK, Patel DV, Russo LA. Echocardiographic abnormalities in sickle cell disease. *Am J Hematol.* 2004;76(3):195-8.
- Zilberman MV, Du W, Das S, Sarnaik SA. Evaluation of left ventricular diastolic function in pediatric sickle cell disease patients. *Am J Hematol.* 2007;82(6):433-8.
- Naoman SG, Nouraie M, Castro OL, Nwokolo C, Fadojutimi-Akinsiku M, Diaz S, et al. Echocardiographic findings in patients with sickle cell disease. *Ann Hematol.* 2010;89(1):61-6.
- Blanc J, Stos B, De Montalembert M, Bonnet D, Boudjemline Y. Right ventricular systolic strain is altered in children with sickle cell disease. *J Am Soc Echocardiogr.* 2012;25(5):511-7.
- Denenberg BS, Criner G, Jones R, Spann JF. Cardiac function in sickle cell anemia. *Am J Cardiol.* 1983;51(10):1674-8.
- Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr.* 2009;22(2):107-33.
- Gordeuk VR, Sachdev V, Taylor JG, Gladwin MT, Kato G, Castro OL. Relative systemic hypertension in patients with sickle cell disease is associated with risk of pulmonary hypertension and renal insufficiency. *Am J Hematol.* 2008;83(1):15-8.
- Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol.* 1986;57(6):450-8.
- Hassell KL. Population estimates of sickle cell disease in the U.S. *Am J Prev Med.* 2010;38 Suppl. 4:S512-21.
- Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. *Lancet.* 2010;376(9757):2018-31.
- Martin C, Cobb C, Johnson C, Tatter D, Haywood LJ. Cardiovascular pathology in sickle cell disease. *Clin Res.* 1983;31:13A.
- Tidake A, Gangurde P, Taksande A, Mahajan A, Nathani P. Left ventricular function by echocardiogram in children with sickle cell anaemia in Mumbai, Western India. *Cardiol Young.* 2014;18:1-7.
- Ribera MC, Ribera RB, Koifman RJ, Koifman S. Echocardiography in sickle cell anaemia patients under 20 years of age: a descriptive study in the Brazilian Western Amazon. *Cardiol Young.* 2015;25(1):63-9.
- Galiza-Neto GC, Pitombeira MS. Molecular aspects for sickle cell anemia. *J Bras Patol Med Lab.* 2003;39(1):51-6.
- Batra AS, Acherman RJ, Wong WY, Wood JC, Chan LS, Ramicone E, et al. Cardiac abnormalities in children with sickle cell anemia. *Am J Hematol.* 2002;70(4):306-12.
- Goldberg N, Lundin AP, Delano B, Friedman EA, Stein RA. Changes in left ventricular size, wall thickness, and function in anemic patients treated with recombinant human erythropoietin. *Am Heart J.* 1992;124(2):424-7.
- Lima CS, Ueti OM, Ueti AA, Franchini KG, Costa FF, Saad ST. Enalapril therapy and cardiac remodelling in sickle cell disease patients. *Acta Cardiol.* 2008;63(5):599-602.
- Gladwin MT, Sachdev V. Cardiovascular abnormalities in sickle cell disease. *J Am Coll Cardiol.* 2012;59(13):1123-33.