Doppler Echocardiographic Study in Adolescents and Young Adults with Sickle Cell Anemia

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Objective – *Anatomical and functional assessment of the heart through Doppler and echocardiography in patients with cell anemia (SCA).*

Methods – *Twenty-five patients with SCA and ages ranging from 14 to 45 years were prospectively studied in a comparison with 25 healthy volunteers. All of them underwent clinical and laboratory evaluation and Doppler echocardiography as well.The measurements were converted into body surface indices.*

Results – *There were increases in all chamber diameters and left ventricle (LV) mass of the SCA patients. It was characterised an eccentric hypertrophy of the left ventricle. The preload was increased (left ventricle end-diastolic volume) and the afterload was decreased (diastolic blood pressure, peripheral vascular resistance and end-systolic parietal stress ESPS). The cardiac index was increased due to the stroke volume. The ejection fraction and the percentage of the systolic shortening , as well as the systolic time intervals of the LV were equivalent. The isovolumetric contraction period of the LV was increased. The mitral E-septum distance and the end-systolic volume index (ESVi) were increased. The ESPS/ESVi ratio,a loading independent parameter, was decreased in SCA, suggesting systolic dysfunction. No significant differences in the diastolic function or in the pulmonary pressure occurred.*

Conclusion – *Chamber dilations, eccentric hypertrophy and systolic dysfunction confirm the evidence of the literature in characterizing a sickle cell anemia cardiomyopathy.*

Key words: sickle cell anemia, echocardiography, cardiomyopathy

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It was certainly not casually but a result of the exuberating cardiovascular manifestations that sickle cell anemia (SCA) was first described by a cardiologist [1]. Due to the influence of African heritage on ethnic formation in Brazil, (SCA) the most prevalent hereditary disease [2-4]. SCA has a high morbidity and mortality [2,5,6] and its clinical course is more severe than those of the deficiency anemias, constituting a clinical and epidemiological problem.

Sickling of red cells reduces their flexibility resulting, therefore, in retardation of blood flow in microcirculation. The pathogenesis of the disorder is believed to be multifactorial but retardation of the blood flow with its consequent ischemia must be the major factor in the process of continuous and progressive aggression to the myocardium [8-10].

It is widely agreed that SCA leads to cardiomegaly [11-15] and to a state of high cardiac output secondary to increase in the preload and decrease in the afterload [15-18]. A hypothesis [19], later refuted [20], of a higher prevalence of mitral valve prolapse in patients with SCA was considered. Studies on pulmonary arterial pressure using Doppler echocardiography in these patients are scarce. Systolic and diastolic dysfunctions of the left ventricle are controversial [17-21]. This controversy is partially explained by the interferences of the alterations of the preload and afterload in the echocardiographic parameters of assessment.

Frequently, exuberance of cardiovascular alterations on physical examination and the complaints of dyspnea and fatigue have motivated the referral of the patients with SCA to the cardiologist. Despite the evolution of diagnostic methods in cardiology and the expressive number of individuals with SCA in high complexity care institutions, only a few careful studies on the adult population excluding the heterozygotes and other hemoglobinopathies of the group considered can be found.

Several doubts motivated this study, whose objective is an anatomical and functional assessment of the heart through Doppler echocardiography in adolescents and young adults with SCA.

Methods

For 12 months, 50 informed and agreeing volunteers were prospectively studied. They were divided into two groups as follows: the sickle cell group (individuals with sickle cell anemia) and the reference group (healthy volunteers). After excluding the individuals not fulfilling the requirements of the protocol, each group comprised 25 individuals with ages ranging from 14 to 45 years. The mean age for the group with SCAwas 26.56±9.19 years and, for the reference group, it was 26.76±7.62 years. There was statistical equivalence in regard to age (p=0.90), to sex (p=0.77), and to race (p=0.92). The sickle cell group comprised patients in ambulatory follow-up with clinical and electrophoretic diagnosis of the homozygous form of the S hemoglobinopathy (HbSS). Patients in painful or in hemolytic crisis or with infection in the previous 4 weeks were excluded from the study, as were those patients transfused in the previous 3 months. Individuals with other diseases were also excluded from the study, as were pregnant women and individuals on drugs with a cardiovascular effect.

The 50 volunteers underwent clinical examination, blood withdrawal for complete hemogram, hemoglobin electrophoresis in cellulose acetate, glycemia, creatinine, urea, sodium and potassium. They also underwent chest teleradiography in the posteroanterior and lateral positions and basal electrocardiography. All patients underwent Doppler echocardiography with the assessment of the blood pressure at a moment close to the obtainment of left ventricle diameters and flows. Blood pressure was taken in the right upper limb, with the patient lying down, through a mercury sphygmomanometer, exclusively used for this study. The left ventricle end-systolic pressure(ESP) was inferred through an equation of regression obtained in cardiac catheterization and validated in the literature [17,22-24], where the left ventricle end-systolic pressure was equal to the systolic pressure in sphygmomanometry multiplied by 0.66 and added to 13.55, a constant.

Doppler echocardiography was always performed by the same person with the same device, with a transducer of 3.5 MHz, concomitantly with basal electrocardiography. Arithmetical means of at least 3 consecutive cardiac cycles of all echocardiographic variables were used. The examinations were recorded and revised by 2 independent echocardiographers who ignored the precedent results and proceeded to the qualitative analysis of the examinations. Echocardiographic variables were corrected to the body surface of each patient and referred to as indices [25].

It is important to emphasize that some assessments were performed according to the following special criteria: 1) the left ventricular mass was estimated through the equation of Bennett and Evans [26], considering the determinations of the Penn's convention [27] for measurement acquisition. The equation of Bennett and Evans [26] determines that left ventricular mass = $[(2 \times DTPW + DD)^3 - DD^3] \times 1.05$, where DTPW = diastolic thickness of the posterior wall of the left ventricle and DD = diastolic diameter of the left ventricle; 2) the relative thickness of the septum (RTS) was calculated through a formula in which RTS is twice the diastolic thickness of the interventricular septum divided by the diastolic diameter of the left ventricle. A value <0.45 was considered normal [28]; 3) the stroke volume (SV) was calculated through the integral of the flow in the left ventricle outflow tract and the aortic area estimated through M-mode echocardiography [28-31]; 4) the total peripheral vascular resistance (TPVR) was estimated through the division of the mean blood pressure (MBP) by the cardiac output (CO) multiplied by the constant 80 [25]; 5) the systolic time intervals of the left ventricle were obtained through assessment of the intermediate flowchart between the transmitral and the left ventricle outflow tract compared with concomitant basal electrocardiography [32]. The criteria for diagnosing mitral valve prolapse were the following: systolic bulging of one or two leaflets into the left atrium in the longitudinal parasternal cross-section; the posterior meso- or end-systolic movement of the mitral valve or the excessive amplitude of the anterior leaflet in diastole (CE distance >25mm) [32]; 7) the left ventricle end-systolic thickening of the posterior wall (ESTPW) was calculated through a modification of the method proposed by Hugenholtz et al [33], in which $ESTPW = 0.5\,[(DD + 2DTPW)^3 - (DD)^3 + (SD)^3]^{1/3} - 0.5 \times SD$; 8) the end-systolic parietal stress (ESPS) was obtained through the following equation [17,22,34-36]:

$$ESPS = \frac{ESP \times SD}{4 \times ESTPW\left(1 + \frac{ESTPW}{SD}\right)}$$

9) the parietal stress/end-systolic volume index ratio was obtained by dividing the end-systolic parietal stress by the end-systolic volume index (ESVi) of the left ventricle [17]; 10) the pulmonary arterial pressure (PAP) was inferred from the flowchart of the right ventricle outflow tract through the equations proposed by Isobe et al [37].

The statistical analysis was performed through the Student *t* test or the Mann-Whitney's test for independent samples or through the chi-square test or the Fisher exact test for proportions. Pearson product moment correlation was used to measure the degree of association between two interval variables. The criterion for significance determination was 5%.

Results

The uni- and bidimensional studies and also the Doppler results did not show valvar lesions, structural defects or pericardial alterations in the 50 individuals, except one case of mitral valve prolapse with mild regurgitation, without myxomatous degeneration, in one patient with SCA.

All cavitary diameters were significantly increased, as were the muscle thickness and the estimated muscle mass of the left ventricle in the group of the patients with SCA. The left ventricle mass index was increased with preservation of the relative thickness of the septum within normal values, characterizing a pattern of eccentric hypertrophy in the patients with SCA (table I).

Patients with SCA had load alterations in the parameters of indirect evaluation. The end-diastolic volume index of the left ventricle (EDVi) (preload) was increased, contrasting with the expressive reduction in the diastolic blood pressure (DBP), in the total peripheral vascular

Table I - Comparison between cavitary diameters, muscle thickness and mass in the sickle cell anemia and reference groups

Variable	Sickle	Reference	p
Aoi (cm/m²)	1.81±0.21	1.45±0.19	<0.001
LAi (cm/m²)	2.81±0.33	1.94±0.24	<0.001
RVDD (cm/m²)	1.39±0.34	1.15±0.27	<0.009
LVDD (cm/m²)	3.47±0.40	2.81±0.21	<0.001
LVSD (cm/m²)	2.19±0.32	1.79±0.20	<0.001
IVSDi (cm/m²)	0.66±0.15	0.46±0.08	<0.001
IVSSi (cm/m²)	0.88±0.19	0.62±0.10	<0.001
LVDTPW (cm/m²)	0.66±0.15	0.41±0.06	<0.001
LVSTPW (cm/m²)	1.06±0.17	0.80±0.20	<0.001
Male Mi (g/m²)	178.80±66.61	91.25±15.71	<0.001
Female Mi (g/m²)	147.97±53.71	72.94±8.60	<0.001
RTS	0.38±0.09	0.33±0.06	0.013

AoI- aortic index; LAi- left atrium index; RVDDi- right ventricle diastolic diameter; LVDDi- left ventricle diastolic diameter; LVSDi- left ventricle systolic diameter; IVSDi- interventricular septum diastolic index; IVSSi- interventricular septum systolic index; LVDTPWi- left ventricle diastolic thickness of the posterior wall; LVSTPWi- left ventricle systolic thickness of the posterior wall; Mi- mass index; RTS- relative thickness of the septum.

resistance estimated (TPVR), and in the end-systolic parietal stress (afterload) (table II).

Heart rate was equivalent in both groups: group of patients with SCA (69.96±9.17 bpm) and reference group (66.88±9.48 bpm) (p=0.240).

Systolic time intervals of the left ventricle, such as electromechanical systole (EMS), preejection period (LVPEP), and ejection time (LVET) were statistically similar in both groups. Only the isovolumetric contraction period (IVCP) was increased in the patients with SCA (table III).

The indices of the ejection phase, such as ejection fraction (EF) and the percentage of systolic shortening (%SS), were equivalent. The stroke volume (SV) and the cardiac index (CI) were significantly increased in the group of patients with SCA (table IV).

The parameters of indirect assessment of the systolic function studied indicate the presence of dysfunction in the group of patients with SCA. The "the distance" between the mitral E point and the interventricular septum (mitral E-septum distance) was 7.29±3.44 mm in the group of patients with SCA and 5.37±3.22 mm in the reference group (p=0.048). The end-systolic volume index of the left ventricle (ESVi) was increased (29.55±10.48 ml/m²) in the group of patients with sicle cell anemia as compared with the reference group (22.07±5.68 ml/m²) (p=0.003).

The ratio between the end-systolic parietal stress and the end-systolic volume index , considered a parameter independent from load alterations and, therefore, more reliable in representing the myocardial intrinsic contractile function, indicated systolic dysfunction in the patients with SCA. In the patients with SCA, this ratio (1.30±0.35) was approximately half the value of the ratio in the reference group (2.57±0.47) (p<0.001).

Four parameters of diastolic function were studied: time of isovolumetric relaxation (TIVR), speed of the mitral EF slope (MEF), relation between the mitral E and A flow-charts (E/A), and the deceleration of the mitral A wave (\A). Out of these 4 parameters, 3 had a tendency to be different in the groups, without showing, however, statistical significance at the 5% level (table V).

The mean values of the systolic pulmonary arterial pressure (SPAP), the mean pulmonary arterial (MPAP), and the diastolic pulmonary arterial pressure (DPAP), inferred fraw the relation between right ventricle preejection period (RVPEP) and the acceleration time of the pulmonary flow (ATPF) did not differ between the two groups (table VI).

Table II – Comparison between the pre- and afterload parameters in the reference and sickle cell anemia groups

Variable	Sickle	Reference	p
Preload:			
- EDVi (ml/m²)	86.17±17.85	63.79±9.12	<0.001
Afterload:			
- DBP (mmHg)	62.00±12.46	73.60±7.30	<0.001
- TPVR (dyn/s/cm⁻²)	774.96±269.43	1.407.62±455.12	<0.001
- ESPS (10³ dyn/cm²)	37.63±11.20	55.93±15.91	<0.001

Table III – Comparison between the left ventricle systolic time intervals in the reference and sickle cell anemia groups

Variable	Sickle	Reference	p
EMS (s)	0.399±0.030	0.390±0.025	0.290 (ns)
PEP (s)	0.102±0.017	0.100±0.020	0.610 (ns)
ET (s)	0.296±0.027	0.287±0.033	0.290 (ns)
IVCP (s)	0.094±0.058	0.048±0.020	<0.001

ns- nonsignificant

Table IV – Comparison between the indices of the ejection phase in the reference and sickle cell anemia groups

Variable	Sickle	Reference	p
EF (%)	66.07±8.14	64.77±6.69	0.540 (ns)
%SS (%)	36.81±6.41	36.25±5.42	0.730 (ns)
SV (l)	0.125±0.036	0.081±0.020	<0.001
CI (l/min/m²)	5.90±1.77	3.14±0.91	<0.001

Table V – Comparison of the diastolic function parameters between the reference and sickle cell anemia groups

Variable	Sickle	Reference	p
TIVR (s)	0.087±0.025	0.075±0.018	0.063
MEF (mm/s)	114.23±21.67	131.19±38.58	0.062
E/A	1.902±0.453	2.266±0.780	0.052
\A (m/s²)	5.158±2.094	4.397±1.276	0.120

Table VI – Comparison of pulmonary arterial pressure between the reference and sickle cell anemia groups

Variable	Sickle	Reference	p
SPAP (mmHg)	18.38±9.88	17.72±6.04	0.810
MPAP (mmHg)	11.16±6.49	10.73±3.97	0.810
DPAP (mmHg)	6.73±4.79	6.41±2.93	0.810

Discussion

When comparing these results with those in the literature, one must pay attention to methodological errors often found. One of the most frequent errors is related to the heterogeneity of the groups studied. Patients are grouped without electrophoretic confirmation or with different sickle cell diseases, pediatric and adult populations are mixed, as are ambulatory patients and the decompensated ones, and patients being transfused and patients with recent hemolytic crises.

If, on the one hand, it is agreed in the literature that SCA leads to a chamber enlargement of the left atrium and ventricle [14,15,18,20,21,38-42], on the other hand, the enlargement of the right ventricle, when analyzed in absolute values, is considered controversial. Estrade et al [15] emphasize that the enlargement of the right ventricle occurs later than that of the left ventricle. Analysis of each case compared with the normal values of the literature shows that there is an increase in the right ventricle index in 28% of the patients with SCA contrasted to the increase in the left ventricle index in 80% of these same patients with SCA in our series. Some authors do not find an enlargement of the right ventricle in patients with sickle cell anemia probably because they work with absolute values. Patients with SCA are known to have a smaller body surface, influencing the chamber diameters of the heart [18,21,41]. The smaller frequency of right ventricle enlargement as compared with that of the left ventricle opposes the hypothesis that the alterations found in SCA are exclusively secondary to the volumetric overload common to chronic anemias. If the right ventricle enlargement were real, it would be proportional, or even more frequent, than enlargement of the left ventricle. Some factors might affect more specifically the left side of the heart, such as chronic ischemia acting upon the hypertrophied ventricular wall.

The literature shows an increase in the muscle mass of the left ventricle in patients with SCA, almost twice that which would be expected, either on Doppler echocardiography and on autopsy [7,18,21,40,41]. Both hypertrophy and dilation are known to progress with age [20,21], being found even in the pediatric population[14,15]. Hypertrophy may be a result of the compensatory mechanism to the volumetric overload, in an attempt to reduce parietal stress [34].

The hypothesis of a higher prevalence of mitral valve prolapse in SCA was formulated by Lippman et al [19] studying 57 patients with SCA and finding 25% with mitral valve prolapse. A possible mechanism would be ischemia of the papillary muscles during episodes of aggravation of the disease, because of their terminal localization in coronary circulation [43]. The cooperative study of sickle cell disease [20,44] reports a case of mitral valve prolapse in 225 patients studied. Our study, like others using bidimensional echocardiography [17,40,44], had statistically insufficient series for conclusions in regard to prevalence of mitral valve prolapse in patients with SCA.

Preload is increased due to increase in the plasmatic volume [16-18], while reduction in the afterload is due to intense peripheral vasodilation secondary to release of bradykinin and adenosine [45,46]. These load alterations assessed in the study through the end-diastolic volume index (EDVi), the diastolic slool pressure (DBP), the total peripheral vascular resistence(TPVR), and the end systolic parietal stress (ESPS) lead to the status of high cardiac output of the SCA. It is worth emphasizing that the high cardiac index is exclusively secondary to the increase in stroke volume, since the heart rate is normal in patients with SCA [16,39,47-50].

The normal values for systolic time intervals eletromecanical systole (EMS), tempo de ejeção (ET), and preejection perial (PEP) in patients with SCA in this study are in accordance with those in the literature [14,21,51]. Abdullah et al [52] emphasize that the systolic time intervals are influenced by load alterations found in chronic anemias, and a pseudonormalization of them may occur. the isovolumetria contraction perial (IVCP) is known to be increased in heart failure [32]. In our series, isovolumetria contraction perial (IVCP) is increased. Comparisons, however, were not possible due to the nonexistence of data in similar populations.

Denenberg et al [17] were the first to stress that dissonance between clinical and laboratory evidence of heart failure in SCA and echocardiography was due to a pseudonormalization of the indices of the ejection phase (EF and %SS) by load alterations. These indices were the only ones used to assess the systolic function in patients with SCA. Use of the end-systolic parietal stress/the end-systolic volume index (ESVi) ratio, considered independent from load alterations, was proposed. With a small series, results indicating the expected systolic dysfunction were obtained. In this study, we repeated that methodology with a larger and better-controlled series and we obtained similar results, but with a higher level of statistical significance. In addition to the increased end-systolic parietal stress/the end-systolic volume index (ESVi) ratio, increase in the mitral E-septum distance, in the the isovolumetria contraction perial (IVCP), and in the the end-systolic volume index (ESVi) confirmed the existence of systolic dysfunction in patients with SCA.

In the present study, a tendency suggesting a pattern of deficiency of relaxation in 3 out of the 4 parameters studied was found. This alteration could be attributed to myocardial hypoxia leading to kinetic alterations of calcium in the relaxation phase. Few studies analyzed the diastolic function in patients with SCA. One of these studies, grouped different hemoglobinopathies [53] and another study considered only one parameter [18]. However, the greatest limitation is technical. It is known that increased preload influences the parameters that assess the diastolic function on Doppler, leading to a pseudonormalization [54,55]. It is difficult, however, to know precisely what the effects of the combination of increased preload with decreased afterload would be upon the Doppler echocardiographic parameters. Study of the pulmonary vein flow and of the time of deceleration of the mitral flow, which was not performed in this study, might add some information. A further study is required to carefully evaluate the diastolic function in patients with SCA.

Estimation of the pulmonar artery pressure (PAP) on Doppler echocardiography through the tricuspid regurgita-

ting flow calculated with the Bernoulli's equation was considered the most accurate by Feigenbaum [56], and is certainly the most known. However, it has the limitation of not being able to be used in serial studies of comparison with normal individuals, in whom the maximum speed of tricuspid regurgitation cannot usually be obtained. The scarce studies assessing the pulmonar artery pressure (PAP) on Doppler echocardiography in sickle cell anemia used an inaccurate methodology, such as the grouping of different hemoglobinopathies, or were retrospective [57]. Isobe et al [37] concluded that the right ventricle preejection period (RVPEP)/ time of the pulmonary flow (ATPF) ratio was the best predictor of the the pulmonar artery pressure (PAP). However, no reference in regard to the probable influence of load alterations upon these parameters was found. In this study, many parameters proposed in the literature were calculated, such as the relationships between ATPF and the right ventricle ejection time; on average, all of them were normal. The load alterations that have influenced the left ventricle may have also influenced the right ventricle, interfering with and underestimating the pulmonary arterial pressure inferred on Doppler echocardiography.

Chamber dilations, the eccentric pattern of left ventricular hypertrophy, alterations in the pre- and afterload with their consequences, and the systolic dysfunction assessed by the mitral E-septum distance, by the isovolumetric contraction period (IVPC), by the end systolic volume index (ESVi) and by the end-systolic parietal stress/the end systolic volume index (ESVi) ratio observed on Doppler echocardiography confirm the clinical and histopathologic evidence of the literature, characterizing a sickle cell anemia cardiomyopathy.

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