Original Research

Evaluation of Cardiac Sequelae in Patients with Sickle Cell Anemia

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Introduction: The aim of this study was aim to evaluate cardiac function by means of echocardiography in patients with sickle cell anemia.

Methods: This was a case control study that evaluated a total of 44 patients with sickle cell anemia, who were on regular follow up, and 44 age/sex-matched normal healthy control subjects. M-mode, two-dimensional, Doppler and pulse tissue-Doppler echocardiographic measurements were performed in both groups.

Results: The mean age was 14.06 ± 6.4 years (55% female, 45% male). The mean hemoglobin, hemoglobin F, and serum ferritin levels were 9.4 ± 1.20 g/dL, 22.7 ± 12.9 g/dL, and 391 ± 590 ng/dL respectively. Pulsed Doppler echocardiography showed that the early diastolic trans-tricuspid peak flow velocity was greater in the patients than in the control subjects. Assessment of the lateral mitral and tricuspid annulus peak velocities by pulsed tissue Doppler imaging showed that the patients had significantly greater systolic, and early and late diastolic velocities than the controls. The left ventricular diameter, interventricular septum diameter, and posterior wall diameter were statistically significantly greater in the patients compared with the control group, whereas there was no difference in ejection fraction.

Conclusion: Sickle cell anemia in children results in a volume-overloaded heart with a significant increase in left ventricular dimensions. However, left ventricular systolic dysfunction and pulmonary hypertension were not frequent findings in our patients.

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Sickle cell anemia (SCA) is one of the most common inherited hemoglobinopathies and is associated with high morbidity and mortality, particularly in the early childhood of the most affected population.[1] Children who have only hemoglobin S usually have severe intermittent illness during life, with painful vaso-occlusive episodes and complications of their sickle cell disease. A few children will have a less severe course, owing to higher levels of Hb F.[2,3]

Patients with SCA are living longer with better medical management, and what were previously uncommon sequelae are frequently being recognized, including those involving the cardiovascular system.[4,5]

The cardiac manifestations of SCA are a significant feature of the disease but there is a paucity of information about the cardiovascular involvement in these patients.[1]

Pulmonary hypertension has been identified as a major risk factor for death in adults with sickle cell anemia. The natural history of pulmonary hypertension in children with SCA is unknown, and therefore the optimal diagnostic and therapeutic strategy for pulmonary hypertension has not been identified.[6]

Conventional 2-dimensional, M-mode, and spectral Doppler echocardiographic imaging have documented abnormal ventricular function in adults with sickle cell disease.[7] Tissue Doppler echo-

cardiography provides additional information about myocardial function[8].

This study aimed to evaluate myocardial function in patients with SCA using M-mode, conventional and tissue Doppler imaging.

Methods

This case-control study was conducted at an outpatient clinic affiliated with Shiraz University of Medical Sciences in Shiraz, Southern Iran, from June 2011 to June 2012. The investigation was approved by the ethics committee of the university, and written informed consent was obtained from the patients or their parents.

The criteria for enrollment in this study were fulfilled by 44 patients with SCA who were on follow up in hematologic centers. The diagnosis was established based on complete blood count (CBC), hemoglobin electrophoresis, solubility test, and clinical status. The exclusion criteria were hypothyroidism, diabetes mellitus, any congenital cardiac disease, hemoglobinopathies other than sickle cell homozygous (SS), and pregnancy or lactation. The patients' medical histories were recorded, including drug history or transfusion. All of the patients had homozygous SCA. All of their parents were anemia heterozygous, a sickle cell trait which was confirmed by the CBC, solubility test, and hemoglobin electrophoresis.

The study also included 44 age/sex-matched normal healthy subjects. They were randomly selected from people who were coming to our general pediatric clinic for a routine checkup. These subjects had no personal or family history of cardiac or hematologic disease.

Fasting blood sample was taken for complete blood count and measurement of serum ferritin (mini-VIDAS, Japan).

Echocardiographic methods

Echocardiography was performed using a GE Vivid 3 echocardiographic machine (GE Vingmed, Horten, Norway) with a 3-MHz probe and pulsed-Doppler tissue imaging software. All M-mode, two-dimensional, Doppler, and tissue Doppler echocardiographic measurements were performed by the same qualified cardiologist with the patient in the left lateral decubitus position. Ejection fraction, shortening fraction, and septal and posterior wall thickness in systole and diastole were measured in the left parasternal long-axis view.

The pulsed Doppler sample volume was placed at the mitral valve and tricuspid tips, and three cardiac cycles were recorded from the apical window. Early (E) and late (A) peak velocities (m/s) and their ratio were determined for evaluation of diastolic function. Acceleration and ejection time of pulmonary flow and its ratio were measured in the parasternal short-axis view.

In the case of pulmonary or tricuspid regurgitation, the gradients (mmHg) were measured for the estimation of pulmonary artery pressure. Pulsed tissue Doppler imaging was performed with the sample volume placed at the lateral mitral annulus, subsequently on the medial (or septal) and lateral tricuspid annulus in the apical four-chamber view, and then at the anterior and posterior wall in the parasternal short-axis view. In each region, peak systolic (S) wave, peak early (Ea) and peak late (Aa) diastolic velocities and ejection time were recorded.

Statistical analysis

The numeric data are presented as mean ± standard deviation. The independent samples t-test was used to compare echocardiographic data between patients and controls. Pearson correlation was used to evaluate correlations between echocardiographic parameters and hematologic parameters. A p-value <0.05 was considered significant for all the statistical tests.

Results

A total of 44 patients with SCA were included in this study. The demographic data, clinical and laboratory variables of the patients and controls are shown in Table 1. Only three patients had a significant increase in serum ferritin levels (ferritin >1000). All patients were transfusion-independent, except for three who had been on irregular transfusion (3-4 times per year) for a period of 3-20 years. Forty-five percent of the patients were on hydroxyurea (10-20 mg/kg/day). No patient had clinical signs of heart failure and none had a decreased ejection fraction (<55%). In this study, one patient demonstrated pulmonary artery hypertension, defined as a peak trans-tricuspid regurgitation gradient exceeding 36 mmHg, or a peak pulmonary regurgitation gradient exceeding 25 mmHg.

The M-mode and Doppler echocardiographic findings are summarized in Table 2. The ejection fraction was 72 ± 12% in sickle cell patients and 75 ± 5% in the control group (p=0.4). End-diastolic and end-systolic left ventricular diameter, left ventricular volume, left

Table 1. Demographic, clinical and laboratory variables of the patients and control groups.

	Patients	Controls	p
Sex (M/F)	45%/55%	45%/55%	
Mean age	14.06 ± 6.41	14.04 ± 5.68	0.24
Mean hemoglobin (g/dL)	9.4 ± 1.20	15.3 ± 2.21	0.13
Median ferritin (ng/dL) (range)	200 (30-3000)	-	
Mean hemoglobin S (g/dL)	66.4 ± 13.3	-	
Mean hemoglobin F (g/dL)	22.7 ± 12.9	-	
Mean New York Heart Association classification	0.7 ± 0.42	-	

Table 2. M-mode and Doppler echocardiographic measurements in patients with sickle cell anemia (SCA) and control subjects.

	SCA patients	Controls	p
EF (%)	72 ± 12	75 ± 5	0.4
IVSd (mm)	0.90 ± 0.20	0.67 ± 0.15	<0.001
IVSs (mm)	1.2 ± 0.26	0.8 ± 0.18	<0.001
LVIDd (mm)	4.2 ± .0.60	3 ± 0.5	<0.001
LVIDs (mm)	2.4 ± 0.50	1.7 ± 0.3	<0.001
LVPWd (mm)	0.77 ± 0.18	0.67 ± 0.15	<0.001
LVPWs (mm)	0.90 ± 0.19	0.7 ± 0.14	<0.001
Et (cm.s)	0.70 ± 0.39	0.18 ± 0.1	0.040
At (cm.s)	0.50 ± 0.15	0.4 ± 0.17	0.120
Et/At	1.80 ± 1.10	1.5 ± 0.5	0.501
Em (cm.s)	1.10 ± 0.26	1.05 ± 0.17	0.150
Am (cm.s)	0.69 ± 0.28	0.57 ± 0.12	0.081
Em/Am	1.5 ± 0.9	1.8 ± 1.3	0.140

EF – ejection fraction; IVSd – interventricular septum diastolic dimension; IVSs – interventricular septum systolic dimension; LVIDd – left ventricular diastolic internal diameter; LVIDs – left ventricular systolic internal diameter; LVPWd – left ventricular posterior wall diastolic thickness; LVPWs – left ventricular posterior wall systolic thickness; Et – tricuspid E wave peak velocity; At – tricuspid A wave peak velocity; Em – mitral E wave peak velocity; Am – mitral A wave peak velocity.

Table 3. Pulsed tissue Doppler measurements in patients with sickle cell anemia (SCA) and control subjects.

	SCA patients	Controls	p
Septum			
S (m/s)	0.09 ± 0.02	0.06 ± 0.02	0.001
Ea (m/s)	0.14 ± 0.02	0.12 ± 0.03	0.008
Aa (m/s)	0.08 ± 0.02	0.07 ± 0.02	0.039
Mitral valve			
S (m/s)	0.09 ± 0.01	0.06 ± 0.02	<0.001
Ea (m/s)	0.19 ± 0.04	0.14 ± 0.04	<0.001
Aa (m/s)	0.08 ± 0.01	0.06 ± 0.02	0.030
E/Ea	6.14 ± 1.90	7.6 ± 2.70	0.010
Tricuspid valve			
S (m/s)	0.20 ± 0.04	0.11 ± 0.03	0.210
Ea (m/s)	0.17 ± 0.03	0.14 ± 0.04	0.006
Aa (m/s)	0.14 ± 0.04	0.11 ± 0.03	0.010
E/Ea	1.80 ± 1.50	1.5 ± 0.52	0.501

S – peak systolic velocity by tissue Doppler; Ea – peak early diastolic velocity by tissue Doppler; Aa – peak atrial velocity by tissue Doppler.

ventricular posterior wall diameter, and interventricular septum thickness were significantly greater in the patients than in controls (p<0.01). The early and late diastolic velocities of the tricuspid and mitral valves did not differ significantly between the groups (p>0.05).

The pulsed Doppler tissue imaging data are presented in Table 3. The peak systolic velocity, peak early diastolic velocity, peak atrial velocity of the lateral mitral annulus and septum were all significantly greater in patients than in controls (p<0.05). The peak systolic velocity of the lateral tricuspid annulus was not significantly different, but the peak early diastolic velocity and the peak atrial velocity of the lateral tricuspid annulus were significantly greater in patients compared to controls (p<0.05).

The serum ferritin level had a statistically significant positive correlation with the tricuspid E/A peak velocity ratio (r=0.75, p=0.01) and the end-systolic left ventricular posterior wall diameter (r=0.40, p=0.03).

The percentage of hemoglobin S had a correlation with the systolic velocity of the lateral tricuspid annulus (r=0.35, p=0.04), the systolic velocity of the lateral mitral annulus (r=0.47, p=0.006) and the early diastolic velocity of the tricuspid valve (r=0.46, p=0.007).

The percentage of hemoglobin F had a correlation with the tissue-Doppler–derived systolic velocity of the lateral tricuspid annulus (r=-0.35, p=0.04), the systolic velocity of the lateral mitral annulus (r=-0.35, p=0.035), and the early diastolic velocity of the tricuspid valve (r=-0.4, p=0.019).

Discussion

In this study, there was a statistically significant correlation between the serum ferritin level and the E/A

ratio of tricuspid peak velocity. This correlation indicates that diastolic dysfunction is associated with an increased ferritin level.

The percentage of hemoglobin S had a correlation with the systolic velocity of the lateral tricuspid annulus, the systolic velocity of the lateral mitral annulus, and the early diastolic velocity of the tricuspid valve. Increased velocities can be an indicator of increased heart function (hyperdynamic state) with increased hemoglobin S.[9]

The percentage of hemoglobin F had an inverse correlation with the systolic velocity of the lateral tricuspid annulus, the systolic velocity of the lateral mitral annulus, and the early diastolic velocity of the tricuspid valve. This reverse correlation may show a protective effect of hemoglobin F, attenuating the hyperkinetic state due to SCA.

This study showed that only three patients had a significant increase in ferritin levels (ferritin >1000), which could be an indicator of an iron overload in the studied population. It is important to mention that serum ferritin levels cannot show the exact status of an iron overload in SCA.[6] The mean percentage of hemoglobin F was 22.7 ± 12.9%. In similar studies that evaluated heart function and pulmonary hypertension in patients with SCA, the range of hemoglobin F levels was 5-8%.[10] The higher hemoglobin F in our patients may explain the lower incidence of pulmonary hypertension and better heart function compared with other studies.

A study in Howard University, USA, using an echocardiographic assessment of tricuspid valve regurgitant jet velocity of ≥2.5 m/s as a diagnostic criterion, demonstrated pulmonary hypertension in 32% of adult sickle cell patients, and the prevalence appeared to increase with the patients' age.[11] In patients between 40 and 49 years of age, the prevalence was 40%, but it increased to 55-60% by age 50 and above. Other studies have documented prevalence rates between 20% and 40%.[11-13] In our study, just one patient had pulmonary hypertension—a lower rate than in previous published retrospective studies. This difference could be due to a younger age range or a milder form of the disease in our region, or higher hemoglobin F in the patients evaluated, which may have had a protective effect.

Pulsed Doppler tissue imaging is an established technique as a component of a diagnostic ultrasound examination. This technique permits the assessment of regional left ventricular function, myocardial velocity, and time intervals throughout the cardiac cycle. Findings have demonstrated that pulsed Doppler tissue imaging gives additional information compared with other echocardiography techniques, detecting even minor diastolic changes in several diseases and thereby aiding in the determination of the prognosis.[8-14]

In our study, systolic function was also in the normal range, but there was a statistically significant increase in left ventricular volume and tissue Doppler velocities. In a study by Lewis et al, which aimed to determine whether left ventricular diastolic abnormalities are an early feature of SCA, indexes of diastolic filling were obtained with pulsed Doppler echocardiography. The results demonstrated that left ventricular diastolic filling patterns are altered in patients with SCA and that these diastolic abnormalities may be present in the absence of symptoms of heart failure.[15] In another study by Moyssakis et al, which included middle aged patients with sickle beta thalassaemia, diastolic function was abnormal in both ventricles but still higher in the right ventricle, whereas systolic function remained unchanged.[16] In a study by Sachdev et al, diastolic dysfunction and pulmonary hypertension each contributed independently to mortality in patients with SCA. Patients with both risk factors had an extremely poor prognosis. Diastolic function was assessed using pulsed Doppler peak E and A velocities, E/A ratio, deceleration time and tissue Doppler echocardiography. Their study showed an increased prevalence of diastolic dysfunction alone in SCA patients and pulmonary hypertension alone in younger patients.[17]

The early trans-tricuspid peak flow velocities in the patients were higher than those of the control subjects. There was also a difference in mitral E/Ea (p=0.01), which was lower in the patients. The filling pattern observed in our patients may have resulted from an increased volume overload (hyperdynamic state) caused by chronic anemia.

Assessment of the mitral and tricuspid valve systolic and diastolic function with pulsed Doppler tissue imaging showed significant differences for all measured parameters between the patient group and the control subjects, with velocities being higher in the patient group.

In a study by Kilinc Y et al, M-mode echocardiographic findings were compared between sickle cell anemic and healthy children. Their findings showed a greater left ventricular end-diastolic dimension in sickle cell patients compared to their controls. The difference could be due to the patients' anemia. Left

ventricular contraction was good and systolic function was normal, while there was no correlation between the echocardiographic findings and hematological indices.[18] Another study found that SCA in children results in a volume-overloaded heart with a significant increase in left ventricular dimensions and mass, both proportional to the degree of anemia.[19]

In our study, the M-mode echocardiographic findings, including left ventricular internal diastolic dimension, left ventricular internal systolic dimension, left ventricular posterior wall diastolic diameter, left ventricular posterior wall systolic diameter, interventricular septum diastolic dimension, and interventricular septum systolic dimension, showed a statistically significant difference compared with the control group, whereas ejection fraction showed no such difference.

Conclusions

Sickle cell patients exhibit statistically significant changes in left ventricular volume and pulsed tissue Doppler imaging parameters. Sickle cell anemia in children results in a volume-overloaded heart with a significant increase in left ventricular dimensions and mass. However, left ventricular systolic dysfunction and pulmonary hypertension were not frequent findings in our patients with SCA. This could be due to higher levels of hemoglobin F in our region compared to other populations.

Acknowledgement

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