Original Article

Tissue Doppler Echocardiographic Findings of Left Ventricle in Children with Sickle-Cell Anemia

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Abstract

Background: *Sickle-cell disease (SCD) is an inherited hemoglobin childhood disorder, frequently complicated by pulmonary hypertension and cardiac involvement. Cardiovascular events and complications are the leading cause of mortality and morbidity in patients with SCD. Tissue Doppler imaging and the myocardial performance index (Tei index), are simple indices for the assessment of the cardiac function. The purpose of this study was to assess the left ventricular function in children with SCD.*

Methods: *Sixty-four patients with SCD (mean age = 11.7 ± 5.5 years) were compared with 50 age matched healthy controls (mean age = 11.2 ± 5.20 years). Myocardial wall motion velocities at the lateral mitral annulus and the junction between the medial mitral annulus and the interventricular septum were assessed during systole (Sa), early diastole (Ea), and late diastole (Aa) through a four-chamber view using pulsed Doppler echocardiography. The ejection fraction and shortening fraction were estimated. The Tei index was estimated via tissue Doppler echocardiography.*

Results: *The results showed that Ea and Aa velocity in the mitral annulus and interventricular septum had no difference between the patients and controls (p value > 0.05), and nor was there any difference between the two groups as regards the Tei index, Ea/Aa, ejection fraction, and shortening fraction (p value > 0.05). Sa_m wave velocity, however, had a significant difference between the two groups (p value < 0.038).*

Conclusion: *The Tei index is a sensitive indicator for the cardiac function in chronic diseases and the right ventricular function in some disorders such as SCD.*

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Keywords: *Elasticity imaging techniques • Anemia, sickle cell • Heart function tests*

Introduction

Hemoglobin S (Hb S) results from an exchange, thymine for adenine, at the 6th codon of the beta-globin gene. This change encodes valine instead of glutamine in the beta-globin molecule. In sickle-cell disease (SCD), Hb S accounts for over 50% of all hemoglobin; and in sickle-cell anemia, Hb S is commonly as high as 80-90% of the total hemoglobin.[1]

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SCD is the most common genetic disease identified through the screening program in the United States and is very common in the south-western Iranian province of Khuzestan. The main presentations of this disorder are abnormal immune function, bacterial sepsis, dactylitis, acute splenic sequestration, vaso-occlusive episode, priapism, neurologic complications, pulmonary hypertension, renal disease, retinopathy, delayed onset of puberty, avascular necrosis of the femoral head and humerus, and leg ulcers. A major risk factor for death in adults with sickle-cell anemia is pulmonary hypertension.[1]

The cardiac manifestations of sickle-cell anemia are those seen in patients who have developed chronic anemia and compensatory increased cardiac output and left ventricular (LV) hypertrophy: cardiovascular events and complications are the leading cause of mortality and morbidity in patients with SCD. Be that as it may, myocardial infarction, arrhythmia, and cardiomyopathy are uncommon in patients with sickle-cell anemia.[2]

The cardiac function is evaluated using such echocardiographic modalities as two-dimensional, M-mode, Doppler, and tissue Doppler imaging (TDI).[3, 4] In TDI, the myocardial motion can be displayed via both color Doppler velocity maps and pulsed Doppler spectral display,[4] and myocardial velocities are assessed during a cardiac cycle. Pulsed wave spectral Doppler display of the tissue velocity is required for the quantitative assessment of the diastolic function. For the evaluation of the LV function, it is conventional to utilize pulsed wave Doppler of the lateral mitral valve annulus to obtain the spectral display, which is necessary for the assessment of the diastolic function. TDI can be used at any point of the ventricular myocardium to give information on the regional wall motion. TDI can also be drawn upon in the assessment of ventricular dyssynchrony in biventricular pacing.[5]

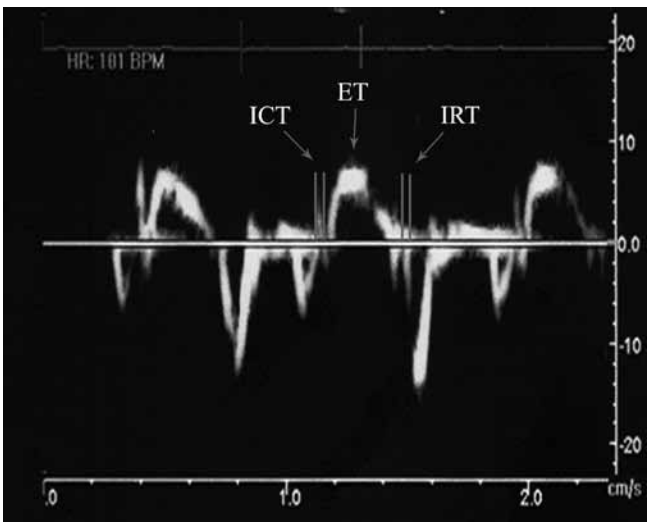

Figure 1. The Tei index is estimated by adding the isovolumic relaxation time (IRT) and isovolumic contraction time (ICT) and dividing the sum by the ejection time (ET)

The measurement of both systolic and diastolic components can be made simultaneously via the myocardial performance index (MPI) or the Tei index, which is estimated with the aid of TDI.[4, 6, 7] The Tei index is the isovolumic contraction time (ICT) plus the isovolumic relaxation time (IRT) divided by the ejection time (ET) (Figure 1) and affords a simultaneous measurement of the atrioventricular inflow and ipsilateral semi-lunar outflow Doppler velocities. Furthermore, this index is used for the evaluation of the systolic and diastolic functions and is correlated with the index of the cardiac function in cardiac catheterization and magnetic resonance-derived right ventricular (RV) ejection fraction. [8-14]

Reports of echocardiographic examinations in children with sickle-cell anemia are scarcely available. Therefore, the purpose of this study was to assess the left heart function via echocardiography in children with sickle-cell anemia and to compare the data with those of a sample of normal children.

Methods

Sixty-four patients, admitted to Shafa Hospital due to at least one of the SCD symptoms and with hemoglobin S > 50% according to hemoglobin electrophoresis, were included in this study. Fifty age- and sex- matched healthy children without any underlying or cardiac disease, underwent echocardiographic evaluation as controls. The study protocol was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, and the study was conducted during a period of 15 months between July 2010 and November 2011.

The inclusion criteria were comprised of: (a) the diagnosis of SCD, made via the solubility screening test and confirmed using hemoglobin electrophoresis; (b) hemoglobin > 8 g/dl; and (c) a symptom or complication of the disease in at least a two-month period prior to commencement of the study. The exclusion criteria consisted of: (a) a history of regular or frequent transfusion; (b) history of hepatic dysfunction or ascites because of non-cardiac causes; and (c) presence of other hemoglobinopathies such as thalassemia.

Each patient underwent an echocardiographic study, including M-mode, two-dimensional, color Doppler, and TDI using a GE Vivid 3 echocardiographic machine at least two weeks after hospitalization. The standard technique was used to obtain the measurements in a quiet, wakeful, and non-sedated state, and all the measurements were made by only one pediatric cardiologist in Golestan Hospital, which is adjacent to Shafa Hospital.

The ejection fraction was estimated using M-mode and Simpson in the parasternal long- and short-axis views as well as in the apical four-chamber view, with two-dimensional and Color Doppler being used in all the views. The TDI program was set using the pulsed wave Doppler mode and filtering for high frequency signals.

TDI was performed in the apical four-chamber view by placing a two-mm sample volume at the lateral mitral valve annulus and medial mitral valve annulus, at the junction with the interventricular septum, in order to obtain myocardial velocities. The peak myocardial velocities during early diastolic (Ea_m), late diastolic (Aa_m), and systolic wave (Sa_m) were measured at the lateral corner, and the ratio of the early to late diastolic (Ea_m/Aa_m) velocities was calculated from the lateral corner. Similar measurements were made for the medial mitral corner, at the junction with the interventricular septum (Ea_s, Aa_s, Sa_s, respectively). The ICT was measured from the end of Aa to the beginning of Sa wave, and the IRT was measured from the end of Sa to the beginning of Ea wave. The duration of the systolic time (ST) was estimated from the beginning to the end of Sa wave.

The TDI-Tei index was determined for the lateral mitral annulus corner. Each measurement was obtained for three to five cardiac cycles. Finally, pulsed Doppler studies of the pulmonary artery were carried out to assess the presence and degree of pulmonary regurgitation.

All the data are expressed as mean ± standard deviation (SD). The differences in the variables were compared between the patients and controls using the t-test or Mann-Whitney U test when appropriate. Statistical significance was defined as a p value < 0.05.

Results

The results of the TDI study in the patients and controls are depicted in Table 1.

The mean age of the patients was 11.7 ± 5.5 years, as opposed to 11.2 ± 5.20 years in the controls.

Sa_m, Ea_m, Aa_m , and Ea_m/Aa_m as well as E/Ea_m ratio at the lateral border of the mitral annulus in the patients were statistically similar to those of the controls. Maximum difference was seen in Sa_m between the patients and controls (p value < 0.038). By TDI, at the medial border of the mitral annulus at the junction with the interventricular septum, Sa_s, Ea_s, Aa_s and Ea_s/Aa_s had similar findings in both groups. The ejection fraction and shortening fraction were lower in the patients, but the difference was within the normal range. The isovolumic relaxation time (IVRT), isovolumic contraction time (IVCT), and Tei index were equal in both groups.

Two patients had mild pulmonary regurgitation without a significant pressure gradient between the RV outflow tract and the pulmonary artery. Three patients had mild mitral regurgitation, one patient had previously undergone splenectomy, and another one had previously undergone surgery for hip joint complications. One of the patients had severe coarctation of the aorta. In two families, we had two patients.

Discussion

SCD is frequently complicated by pulmonary hypertension and cardiac involvement. Most of the reports in the existing literature on the Tei index are related to the RV diastolic function, especially in the tetralogy of Fallot[15] in patients

Table 1. Echocardiographic parameters in patients and controls

Parameter	Patients n=64	Controls n=50	P value
TDI inter ventricular septum Sa_s (cm/s)	8.2±1.7	7.5±1.0	0.96
TDI inter ventricular septum Ea_s (cm/s)	12.5±1.6	12.9±1.5	0.38
TDI inter ventricular septum Aa_s (cm/s)	5.6±1.7	5.2±1.2	0.37
TDI inter ventricular septum Ea_s/Aa_s	2.4±0.7	2.6±0.6	0.29
TDI lateral mitral annulus Sa_m (cm/s)	10.7±3.4	8.2±1.4	0.03
TDI lateral mitral annulus Ea_m (cm/s)	18.7±3.4	17.8±2.9	0.34
TDI lateral mitral annulus Aa_m (cm/s)	7.0±2.1	6.1±1.4	0.12
TDI lateral mitral annulus Ea_m/Aa_m	2.8±0.8	3.1±0.9	0.36
LV isovolumic relaxation time (msec)	44.9±12.9	41.7±8.0	0.37
LV isovolumic contraction time (msec)	52±15.1	51.1±9.1	0.74
Tei- index	0.4±0.1	0.3±0.1	0.26
E/Ea_m	5.4±1.7	5.2±1.3	0.49
EF (%)	50.2±9.3	56.0±5.0	0.28
SF (%)	28.2±6.1	29.0±3.7	0.37
HR (beat/min)	89.9±14.9	87.4±11.2	0.54

TDI, Tissue Doppler Imaging; Sa_s, Peak systolic tissue Doppler velocity at medial corner of mitral valve and interventricular septum; Ea_s, Peak early diastolic tissue Doppler velocity at medial corner of mitral valve and interventricular septum; Aa_s, Peak late diastolic tissue Doppler velocity at medial corner of mitral valve and interventricular septum; Sa_m, Peak systolic tissue Doppler velocity at lateral corner of mitral annulus; Ea_m, Peak early diastolic tissue Doppler velocity at lateral corner of mitral annulus; Aa_m, Peak late diastolic tissue Doppler velocity at lateral corner of mitral mitral annulus; EF, Ejection fraction; SF, Shortening fraction; HR, Heart rate

with the transposition of the great arteries remote from the atrial switch operation and after bidirectional cavopulmonary anastomosis.[16, 17]

Previous studies have reported RV failure in SCD patients, and there are only a few reports on the LV diastolic function in SCD patients.[18-20] Most of these reports seem to contain different ideas because of the restrictive or constrictive pattern of the trans-mitral flow. Ferit Akgu et al. showed that the LV systolic and diastolic functions were preserved in all SCD patients with or without pulmonary hypertension and the RV diastolic function was disturbed only in SCD patients with pulmonary hypertension.[21] Our study yielded similar results, with the difference that Sa_m wave velocity was higher in the patients than in the controls. The RV abnormal diastolic pattern may be in consequence of a rise in the RV afterload, secondary to pulmonary hypertension. Myocardial micro emboli may be caused by an ischemic area and diastolic abnormalities in patients with SCD, and these abnormalities are progressive with age. It should also be taken into account that anemia and tachycardia may worsen the cardiac disease in these patients. Hemolysis may be a risk factor for the development of pulmonary hypertension, and various markers of hemolysis have been correlated with hemolysis in these patients.[22]

Studies having thus far been performed in adults show that cardiac involvement in sickle β-thalassemia concerns biventricular dilatation and dysfunction along with pulmonary hypertension, leading to congestive heart failure and cardiac involvement.[23-26]

TDI is an effective method for the evaluation of the cardiac function and myocardial velocities through the cardiac cycle. The Tei index is a simple parameter for the evaluation of the RV and LV functions and is correlated with the invasive measurements of the cardiac systolic and diastolic functions. TDI can record systolic and diastolic velocities during the same beat.

Our TDI velocities revealed normal ranges of IRT, ICT, and Ea together with increased Sa_m velocity. In patients with SCD, a chronic volume overload from prolonged anemia along with or without micro vasculopathy and myopathy, which affect all patients, may explain such abnormalities in echocardiographic examinations. We tend to think that this sign might be the first sign when evaluating an SCD patient for the cardiac function.

Our patient group had a normal Tei index. Prolongation of the ICT and IRT occurs in prolonged and chronic pathologic conditions such as increased LV load or an intrinsic LV myocardial dysfunction. A higher than normal Tei index is indicative of a reduced LV function. Endothelial dysfunction and increased arterial stiffness have been encountered in these patients at an older age. High-output state, which is seen in anemia, can also lead to heart failure. Myocardial iron load seems to be of less importance in the sickling syndrome. Furthermore, the sickling process could directly affect the heart and induce myocardial ischemia and heart failure. Chronic LV dysfunction in such patients maybe a significant determinant of the clinical outcome in acute states such as sickling crisis. It is worthy of note that the ejection fraction was within the normal limits in our patients, but it was significantly lower than that of our control group.

First and foremost amongst the limitations of the present study is that it evaluated the patients in a short period of time (15 months). This limitation could explain why there were no significant differences between our two groups in terms of the majority of the obtained echocardiographic data. In addition, our study sample size and power were limited, and this shortcoming should be considered in the interpretation of the results. Prospective research is required to assess the long-term monitoring of the cardiopulmonary function in patients with SCD.

Conclusion

The results of the present study confirmed the presence of normal LV systolic and diastolic functions and the Tei index in children with SCD. Our patients were children with a mildly progressing restrictive or constrictive pattern in their hearts; they are, therefore, likely to develop cardiac involvement in the future. Our findings also showed that the TDI-Tei index could be a useful tool in the evaluation of the diastolic and systolic functions both for basic studies and for planning the prevention and treatment of cardiac failure in the long term in this group of patients. We would advise that increased Sa_m wave velocity on echocardiography be further followed up through frequent examinations. Another finding of note in the current study was that a decreased cardiac function was a chronic and progressive process: in comparison with other similar studies, our patients had a low age and had normal indices in their evaluations; nevertheless, increased Sa_m wave velocity could be a marker for evaluation in the future. The results presented herein could provide basic echocardiographic measures in children with SCD at early stages of the disease and could, therefore, be drawn upon in future research.

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