

# Cardiac Structural and Functional Changes Evaluated by Transthoracic and Tissue Doppler Echocardiography in Adult Patients with Sickle Cell Disease

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doi: 10.5455/aim.2017.25.9-13

ACTA INFORM MED. 2017 MAR; 25(1):9-13

Received: Jan 17, 2017 • Accepted: Mar 09, 2017

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## ABSTRACT

One of the most common genetic blood disorders, resulting from inherited red blood cell disorders, is sickle cell disease (SCD) which is responsible for high death in adult patients with left ventricular diastolic dysfunction and pulmonary hypertension. Tissue Doppler Echocardiography (TDE) and transthoracic echocardiography (TTE) are two useful tools to assess the risk of SCD. The present study was conducted to evaluate the cardiac functions and structure using TDE and TTE among adult patients suffering from sickle cell anemia compare to normal samples. Methods: The current study was performed on 30 SCD patients with a mean age 18-40 years and healthy cases at Mazandaran Heart Center, Iran. The left and right ventricular functions were assessed using M-mode, two-dimensional (2D), and tricuspid regurgitation jet velocity (TRJV) data and TDE derived myocardial velocity measurements in SCD patients compared to control. Results: According to the findings, SCD group showed significantly higher E and E' waves of left ventricle inflow compare to the control group ( $p < 0.03$  and  $p < 0.01$ , respectively). No significant difference was observed for E/ E' ratio between two groups: case and control, but there was significant differences between the groups in E and E' waves respectively equal to 8.55 and 8.14 cm/s. We obtained significant differences for peak early and late LV diastolic velocity between two groups and other indicators showed no significant differences. Conclusion: The evaluation of LV systolic and diastolic function via TDE did not indicate significant differences between SCD patients compared to healthy subjects. High E and E' waves in these patients, could indicate progression towards cardiac disorders and pulmonary hypertension in future.

**Keywords:** Ventricular structure, Ventricular function, Transthoracic echocardiography, Sickle cell disease, Tissue Doppler echocardiography.

## 1. INTRODUCTION

The word sickle cell disease (SCD) describes inherited hemoglobin disorders. The SCD patients have abnormal hemoglobin in the RBCs, called hemoglobin S or sickle hemoglobin, because of adenine-to-thymine substitution in the sixth codon in the beta globin gene, replacing glutamic acid with valine in the beta-globin chain (1). Roughly, 80-90% of the total hemoglobin (Hb) is sickle hemoglobin (HbS) in these patients (2). Some parts of the world including tropical regions like sub-Saharan Africa, India and the Middle East as well as the Northern provinces of Iran have the most incidence rate of the sickle cell disease (3).

The disease is characterized by complications such as anemia, pulmonary hypertension, lungs, kidneys, spleen, and brain injuries due to de-

prived tissues and organs from oxygen-rich blood. The left ventricular hypertrophy (LVH) is the main clinical symptoms of SCD. This occurs because of high cardiac output caused by developed chronic anemia in patients with SCD; particularly the adult SCD cases experience abnormal systolic and diastolic ventricular functions (4). The major reasons for death in SCD patients are cardiovascular disorders and the relevant complications. The most common impairments observed in such adult patients are diastolic dysfunction in the left ventricle and pulmonary hypertension (5, 6). There are also unusual but more likely complications in the adult SCD patients, such as myocardial infarction, arrhythmia and cardiomyopathy (7).

The echocardiographic modalities such as two-dimensional, M-mode,

Doppler and tissue Doppler echocardiography (TDE) are employed to assess the cardiac function (8), so that the device display the myocardial motion as color Doppler velocity maps and pulsed Doppler spectral display as well as provides the possibility of checking myocardial velocities within heart cycle (2). The diastolic function can be assessed quantitatively due to the pulsed-wave spectral Doppler display of the tissue velocity. In addition, pulsed-wave Doppler of the lateral mitral valve annulus is commonly recruited to investigate the function of left ventricle, resulting in the spectral display required to evaluate the diastolic function (2). The regional wall motion at any point of the ventricular myocardium can be achieved via the TDE. Also subclinical myocardial dysfunction can be found by TDE often not evident on M-mode, two-dimensional (2D) or spectral Doppler studies. The ventricular function in myocardial disease can be evaluated using TDE via LV filling pressures (9). Preload changes influence the TDE outcomes with low probability like in chronic anemia (10). The MPI (myocardial performance index) or the Tei-index estimated by TDE can be used to measure at the same time the systolic and diastolic components (2). The isovolumic contraction time (ICT) along with the isovolumic relaxation time (IRT) resulting from the ejection time (ET) is Tei-index to calculate simultaneously the atrioventricular inflow and ipsilateral semi-lunar outflow Doppler velocities, as well as to assess the systolic and diastolic functions. The cardiac function index in cardiac catheterization and magnetic resonance derived right ventricular ejection fraction is also associated with the Tei-index (11, 12).

There is limited information on echocardiographic findings in the SCD patients including among the population in Iran. In the SCD patients also, one of the sensitive ventricular function markers to complement conventional echocardiography can be the tissue Doppler echocardiography. According to the mentioned issues, the present study was therefore conducted to evaluate the cardiac functions and structure using TTE and TDE among adult patients suffering from SCD compare to normal samples.

## 2. MATERIALS AND METHODS

### *The Design of Research*

The present study using Hb electrophoresis was carried out 30 stable patients with more than 50% HbS. In addition, the control group consisted of 32 healthy volunteers homogenized for age and gender that underwent echocardiographic assessments, those who had no underlying or cardiac and hematological diseases. The Ethics Committee of Mazandaran University of Medical Sciences, Iran, approved the study protocol performed within three-month period in 2013. The objectives of the project and the study design were explained completely to the participants and then informed written consent was obtained from them, as well as they were ensured that the data would remain private.

The participants aged between 18 and 40 years confirmed by Hb electrophoresis and Hb more than 8 g/dl were included in the study. The exclusion criteria were history of regular or frequent transfusion, history of hospital admission due to heart disease within the past year, history of kidney failure, high blood pressure, diabetes mellitus, history of coronary artery disease and other hemoglobinopathies such as thalassemia.

Only one cardiologist blinded to groups carried out the echocardiographic assessment in the two case and control groups within the study period using the standard technique in a quiet, wakeful, and non-sedated state at Mazandaran Heart Center in Northern of Iran. On the day of echocardiographic examination, the parameters including demographics data, blood pressures and heart rate values were recorded for the participants.

### *Echocardiography*

For the subjects, the transthoracic Echocardiography (TTE), M-mode, 2D, color Doppler (made in USA) was applied to prepare the echocardiograms and GE Vivid S5 echocardiographic machine for TDE at rest and in the left lateral decubitus position based on the American Society of Echocardiography (13, 14).

### *Measurements of M-mode*

The measurements of M-mode parasternal short-axis were conducted at end-diastole for interventricular septal thickness, LV posterior wall thickness and left ventricular diameter in diastole and systole. Devereux formula was employed to measure the LV mass index corrected for body surface area.

### *Mitral flow velocities*

The pulsed wave Doppler with the sample volume placed at the tip of the mitral valve from the apical four-chamber view was used to calculate the mitral flow velocities curve for measuring the parameters, including peak E-wave velocity and its DT, peak A-wave velocity, and the isovolumic relaxation time measured from aortic valve closure to the mitral valve opening.

### *Tissue Doppler Echocardiography*

The pulsed wave Doppler mode and filtering for high frequency signals and a standard pulse-wave Doppler technique were recruited to adjust the TDE program. Concerning the mitral annular segments, predefined two consecutive cardiac cycles to achieve color-coded tissue Doppler images that were tested to customized image visualization, processing, and analysis using software package on PC.

The sample volume of 2 mm was put at the lateral and medial mitral valve annulus at the junction with the interventricular septum for the measurements of myocardial velocities from the apical 4-chamber view. In the lateral corner, the maximum myocardial velocities were obtained within early diastolic ( $E_m$ ), late diastolic ( $A_m$ ), systolic wave ( $S_m$ ) and early to late diastolic ratio ( $E_m/A_m$ ). Normal LV filling pressure and normal LV diastolic function are predicted according to the ratios  $\leq 8$ , as well as elevated LV filling pressure and diastolic dysfunction are determined by the ratios  $> 8$ , in the adults (15). Accordingly, in the medial mitral corner, the same records respectively as  $E_s$ ,  $A_s$ ,  $S_s$ , were reported at the junction with the interventricular septum (10). The mean four sites were indicated through the final value. Using three consecutive heartbeats, the mean values were calculated for tissue Doppler measurements and spectral Doppler velocities.

Regarding the lateral mitral annulus corner, the TDE-Tei index was obtained for 3-5 cardiac cycles. The existence and degree of pulmonary regurgitation were determined via pulsed Doppler studies of the pulmonary artery. The biplane Simpson technique was employed to assess the left ventricular ejection fraction (LVEF). The time taken from the maximum E point to baseline, deceleration time (DT), was ap-

plied as a diastolic dysfunction index.

### Statistical analysis

Mean  $\pm$  SD was used to describe the continuous variables with a normal distribution assessed by the K-S test. The independent samples t-test analyzed the differences for the mean continuous data between the two study groups. Qualitative data were compared using the Chi-squared test or the Fisher's exact test. Statistical analysis was performed using the Software SPSS 16. Our results were statistically significant at the p-value  $\leq$ 0.05.

## 3. RESULTS

The present study was conducted totally on 62 subjects within two case or the SCD patients (n=30) and control or healthy groups (n=32). Table 1 shows the demographic and clinical information of these two groups.

Variables	Healthy subjects (control) (n=32) (mean $\pm$ SD)	SCD patients (case) (n=30) (mean $\pm$ SD)	P-value
Gender (Female/Male)	19/13	18/12	*0.5<
Age (year)	27 $\pm$ 7.9	26.9 $\pm$ 8.7	0.9<
HR (beat/min)	77.6 $\pm$ 7.3	78.2 $\pm$ 12.6	0.9<
SBP (mmHg)	118.12 $\pm$ 11.05	112.68 $\pm$ 12.65	0.8<
DBP (mmHg)	71.72 $\pm$ 9.12	68.70 $\pm$ 8.78	0.2<

Table 1. Demographic and clinical information of the two case and control groups. HR: Heart rate, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, \* P-value calculated from Chi-square test between the two groups, P-value calculated from independent t-test between the two groups

There were no significant difference for age, gender, systolic and diastolic blood pressure and heart rate between the two case and control groups. Table 2 presents the Tissue Doppler echocardiographic and conventional echocardiographic findings in the two case and control groups.

According to the results, there was only significant differences for the peak early (p<0.03) and late (p<0.01) diastolic velocity of left ventricular (E and E' waves) between the case and control groups. However, no significant differences were founded for the other indicators between the case and control groups. The E' wave had the highest difference was seen in between the SCD and healthy subjects. The E/E' ratio showed no significant difference between the two groups, but the differences between the two groups were 8.55 cm/s in E wave and 8.14 cm/s in E' wave, respectively. Non-significant difference was obtained for RVS (right ventricular size) though it was slightly higher in SCD patients. The TDE indicated the same findings between the two groups for S<sub>m</sub>, E<sub>s</sub>, A<sub>s</sub> and E<sub>m</sub>/E<sub>s</sub> at the medial border of the mitral annulus at the junction with the interventricular septum. Although, the ejection fraction was lower in SCD patients, the difference was within the normal range. The results were similar for Tei-index in both SCD patients and healthy volunteers.

## 4. DISCUSSION

The sickle-cell disease (SCD) as an inherited hemoglobin disorder is often associated with pulmonary hypertension and cardiac impairments (16). In this regard, one of the approaches to assess cardiac function and myocardial velocities during the cardiac cycle is TDE. LV relaxation is measured using Mitral valve annular velocities that are able to predict

Indexes (unit)	Healthy subjects (control) (n=32) (mean $\pm$ SD)	SCD patients (case) (n=30) (mean $\pm$ SD)	P-value
LVESD (cm)	3.06 $\pm$ 0.32	3.13 $\pm$ 0.36	0.4
LVEDD (cm)	4.77 $\pm$ 0.44	4.88 $\pm$ 0.41	0.3
IVSD (cm)	0.75 $\pm$ 0.08	0.72 $\pm$ 0.11	0.2
LVPW (cm)	0.75 $\pm$ 0.09	0.74 $\pm$ 0.11	0.7
LVEF (%)	65.25 $\pm$ 5.81	64.93 $\pm$ 6.02	0.8
TRJV (m/s)	1.86 $\pm$ 0.43	1.96 $\pm$ 0.43	0.6
PAP (mmHg)	18.71 $\pm$ 6.77	21.19 $\pm$ 6.61	0.3
E wave (cm/s)	84.66 $\pm$ 16.55	93.21 $\pm$ 13.99	0.03
E' wave (cm/s)	54.97 $\pm$ 9.94	63.11 $\pm$ 14.94	0.01
E/E' ratio	1.58 $\pm$ 0.39	1.54 $\pm$ 0.41	0.7
TAPSE (cm)	2.27 $\pm$ 0.33	2.35 $\pm$ 0.24	0.2
Tei-index	56.31 $\pm$ 12.15	55.81 $\pm$ 13.54	0.8
FAC	32.07 $\pm$ 9.98	36.34 $\pm$ 11.71	0.1
RVS (cm)	2.51 $\pm$ 0.09	2.67 $\pm$ 0.13	0.3
S <sub>m</sub> (cm/s)	9.78 $\pm$ 2.03	10.11 $\pm$ 3.17	0.7
E <sub>m</sub> (cm/s)	17.34 $\pm$ 3.75	18.21 $\pm$ 3.22	0.3
A <sub>m</sub> (cm/s)	8.48 $\pm$ 1.91	8.43 $\pm$ 3.39	0.9
S <sub>s</sub> (cm/s)	8.44 $\pm$ 1.95	8.61 $\pm$ 1.51	0.7
E <sub>s</sub> (cm/s)	12.88 $\pm$ 2.87	13.21 $\pm$ 2.72	0.6
A <sub>s</sub> (cm/s)	9.03 $\pm$ 2.72	8.33 $\pm$ 2.71	0.3
S <sub>t</sub> (cm/s)	14.78 $\pm$ 1.66	15.86 $\pm$ 2.17	0.3
DT (milisec)	152.5 $\pm$ 32.3	143.4 $\pm$ 30.1	0.2
E <sub>m</sub> /E <sub>s</sub>	6.78 $\pm$ 1.48	7.33 $\pm$ 1.74	0.1

Table 2. Echocardiography indexes in the two case and control groups. P-value calculated from independent t-test between the two groups - LVESD: Left ventricular end systolic diameter; LVEDD: Left ventricular end diastolic diameter; IVSD: Interventricular septal diameter; LVPW: Left ventricular posterior wall thickness; LVEF: Left ventricular ejection fraction; TRJV: Tricuspid regurgitation jet velocity; PAP: Systolic pulmonary artery pressure; E wave: Peak early diastolic velocity of left ventricular inflow Doppler; E' wave: Peak late diastolic velocity of left ventricular inflow Doppler; E/e' ratio: Peak early diastolic velocity of left ventricular inflow Doppler/ peak late diastolic velocity of left ventricular inflow Doppler; TAPSE: Tricuspid annular plane systolic excursion; FAC: Fractional area change; RVS: Right ventricular size; S<sub>m</sub>: Peak systolic velocity at lateral mitral valve annulus; E<sub>m</sub>: Peak early diastolic velocity at lateral mitral valve annulus; A<sub>m</sub>: Peak late diastolic velocity at lateral mitral valve annulus; S<sub>s</sub>: Peak systolic velocity at interventricular septum; E<sub>s</sub>: Peak early diastolic velocity at interventricular septum; A<sub>s</sub>: Peak late diastolic velocity at interventricular septum; S<sub>t</sub>: Peak systolic velocity at lateral tricuspid valve annulus; DT: Deceleration time of early diastolic velocity of left ventricular inflow Doppler; E<sub>m</sub>/E<sub>s</sub>: Peak early diastolic velocity at lateral mitral valve annulus/ peak early diastolic velocity at interventricular septum.

LV filling pressure along with mitral peak E velocity, E/E' ratio (17). LV systolic and diastolic functions have been investigated among the Iranian SCD patients during the present case-control research using the echocardiographic findings. Despite finding similar results in the indexes, we observed significant elevation for the peak early and late diastolic velocity in left ventricles among the SCD adult patients. Heart disorders and pulmonary hypertension could be predicted through high E and E' waves in such patients and the moderate increase in E and E' wave accounts for prediction of high LV filling pressure (17). This can be the first sign of assessing cardiac function in SCD patient. In our SCD patients, the LV systolic function (LV ejection fraction, tricuspid annular plane systolic excursion, peak systolic velocity at lateral

mitral valve annulus and interventricular septum and lateral tricuspid valve annulus), and spectral Doppler measurements of LV and right ventricular diastolic functions (peak early/late diastolic velocity of LV and right ventricular inflows and pulmonary) were found normal according to the echocardiographic findings.

There are several conflicting results on SCD patients in previous investigations indicating LV diastolic dysfunction (18, 19), elevated interventricular septal thickness, LVPW, LV end-diastolic diameter, LV end-systolic diameter and LV mass. It should be noted that non-significant differences were seen for these parameters in the current research. Based on these outcomes, it can be concluded that the cardiac output is enhanced with slightly increase in heart rate due to progressive LV dilation and hypertrophy resulting from anemia (6, 17, 20-23).

The various echocardiographic techniques applied on LV systolic function among SCD patients can lead to difference and contradictory conclusions (24, 25). For example, preload-independent end-systolic LV wall stress-velocity measurements showed abnormal LV systolic function in the study of Lamers et al. on SCD children (26), whereas this finding was reported normal in a study by Covitz et al. on 191 children and young adults with SCD based on normal LV fractional shortening as a preload dependent parameter (20).

Regarding results of a study on SCD child through common echocardiographic techniques, the RV function is preserved in these patients (27), conversely a cohort study demonstrated high pulmonary artery systolic pressure among adolescents and adults with SCD (28). However, in some SCD patients, RV failure has been shown in other studies (18, 19). No significant change was observed for RV function with TDE between our healthy subjects and adult SCD patients. Nevertheless, higher RVS, peak velocities of systolic and early diastolic excursions of lateral tricuspid valve annular measurements were found in SCD patients compared to the healthy subjects. Small sample size might affect our results.

According to the findings of Ferit Akgu et al., all SCD patients with or without pulmonary hypertension had no changes in the LV systolic and diastolic functions and only the patients with pulmonary hypertension showed the RV diastolic function (24). The SCD patients may suffer from myocardial micro emboli resulting from an ischemic area and diastolic abnormalities that are progressive with age. Another leading risk factor for developing pulmonary hypertension is hemolysis whose different markers of are associated with hemolysis in these patients (29).

The SCD patients showed higher velocities of systolic and early diastolic excursions of lateral tricuspid valve annular measurements according to TDE assessment than in control group (8), which might be due to the anemia-induced high cardiac output according their claim. They reported also decreased LV velocity compared to control. Because of abnormal LV systolic and diastolic functions, significantly less lateral mitral annular peak systolic velocity and  $E_m$  were observed in SCD patient compared to the control. In contrast with this study, our patients had higher E and E' waves that indicates no LV systolic and diastolic dysfunction. With the passage of time in these patients, the increase can be observed in the tissue Doppler echocardiographically derived myocar-

dial velocities in the RV (peak velocities of systolic and early diastolic excursions of lateral tricuspid valve annulus). The reason for this can be a combination of myocardial ischemia and progressively increasing RV afterload that is frequently associated with the incidence of pulmonary hypertension.

In assessing the RV and LV function, one of the easy factors is the Tei-index that is related to the invasive measurements of the cardiac systolic and diastolic functions. The systolic and diastolic velocities can be measured during the same beat via TDE (16). We found normal Tei-index among the SCD patients and the ejection fraction was in the normal ranges, non-significantly lower than control group.

There were several limitations in the present study, such as probably selection bias, small sample size and short study period (3 months), which could affect the most echocardiographic findings concerning no significant differences between the two groups. Another limitation was ignoring iron overload indexes like ferritin and cardiac iron siderosis by magnetic resonance imaging (MRI) and Hb levels. It is recommended to be done extensive prospective and long-term study to monitor the cardiopulmonary function in SCD patients.

## 5. CONCLUSION

The evaluation of LV systolic and diastolic function via TDE did not indicate significant differences between SCD patients compared to healthy subjects. High E and E' waves in these patients, could be indicated progression towards cardiac disorders and pulmonary hypertension in future.

- **Acknowledgment:** The authors hereby express their thanks and appreciations to Research Deputy of Mazandaran University of Medical Sciences (MUMS) for funding and providing all required facilities.
- **Conflict of interest:** There are no conflicts of interest among the authors.

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