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Original Research Article

Left ventricular dysfunction by strain echocardiography in thalassemia patients: a pilot study

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ABSTRACT

Background: To evaluate the myocardial function and its correlation with serum ferritin and the number of transfusions in beta-thalassemia major patients by using standard echocardiography and left ventricular strain imaging.
Methods: This was a cross-sectional exploration study comprised of 56 beta-thalassemia patients conducted at a tertiary-care center in India between September 2016 and August 2017. Patients with age less than 18 years, diagnosed with thalassemia major, recipients of >20 units of blood transfusions, and normal Left Ventricular (LV) function by 2D-echocardiography were included in the study. Severity of iron overload was determined by using serum ferritin levels and LV strain imaging parameters were evaluated by using strain values of 17 LV segments.
Results: A total of 56 beta-thalassemia patients were included in the study. Of these, 29(51.8%) patients were boys and 27(48.2%) patients were girls with a mean age of 7.8±1.84 years. Average serum ferritin level was found to be 4089.83 ng/dl. Strain values of the basal lateral wall of the left ventricle were significantly abnormal in patients who received more (>80) transfusions compared with those who received lesser transfusions (p=0.025 and p=0.045), respectively. Patients with serum ferritin >6000 ng/ml had impaired strain (p=0.03).
Conclusions: Conventional echocardiographic parameters and Left Ventricular Ejection Fraction (LVEF) do not provide adequate information about LV dysfunction. Systolic strain index imaging of the LV indicated the presence of early LV systolic dysfunction in patients who received a greater number of blood transfusions and patients with higher serum ferritin levels.

Keywords: Beta-thalassemia, Blood transfusion, Echocardiography, Heart ventricles, Iron overload

INTRODUCTION

Beta thalassemia is considered as one of the most common inherited hemoglobin disorders characterized by impaired synthesis of beta globin chains leading to chronic hemolytic anemia and iron overload.[1] Beta-thalassemia has three main forms based on the severity of disease: minor, intermediate, and major. The phenotypic spectrum varies considerably as we face asymptomatic thalassemia carrier, very mild anemia, and clinically severe thalassemia major.[2] Patients with beta-thalassemia major experience severe anemia through the first year of life and are dependent on periodic life-long transfusion therapy.[3] If regular transfusion program that maintains an iron concentration of 0.3-0.5 mg/kg/dL is initiated, growth and development tend to be normal up to 10-12 years.[4] In transfusion-dependent patients, complications related to iron overload may develop after 1-2 years of

regular transfusions.[5] This iron overload leads to iron deposition in various tissues of the body including the heart, liver, gonads, and pancreas.[6]

Iron-mediated cardiomyopathy is the major cause of death in thalassemia patients.[7] Nearly, 50% of thalassemia major patients die before the age of 35 due to iron-induced heart failure.[8] In the heart, the presence of free iron leads to diminished function of the mitochondrial respiratory chain, which is clinically demonstrated by the reduction of cardiac muscular contractility, continuing systolic dysfunction and development of heart failure.[9]

Moreover, increased intracellular ferrous iron inhibits the ryanodine-sensitive calcium channels of sarcoplasmic reticulum, which regulates calcium release and results in further reduction of cardiac function and arrhythmia development.[10] Many thalassemia patients remain asymptomatic with the normal left ventricular function for a long period of time.[11] Nevertheless, if once overt heart failure is present, only 50% of patients survive.[12] Therefore, early detection of ventricular dysfunction and risk of heart failure before the appearance of symptoms is needed. Early detection can alter the prognosis of thalassemia patients because it reinforces the need to optimize the therapy with chelators, drugs that reduce iron overload in the organism.[4]

The conventional echocardiographic parameters such as Left Ventricular Ejection Fraction (LVEF) or Left Ventricular Fraction Shortening (LVFS) are not sensitive to detect cardiac dysfunction. Some reports indicate Doppler-echocardiogram with tissue Doppler as a favorable technique for this situation.[13] However, data acquired by this method are still inadequate, particularly in relation to left ventricular diastolic function and right ventricular structure and function. Recently, tissue Doppler imaging modalities with tissue velocity imaging and strain imaging have proven to be very useful for the assessment of cardiac dysfunction.[14] Thus, this study was conducted to evaluate the myocardial function and its correlation with serum ferritin and the number of transfusions in beta-thalassemia major patients by using standard echocardiography and left ventricular strain imaging.

METHODS

Study design and patient population

This was a cross-sectional exploration study comprised of 56 beta-thalassemia patients conducted at a tertiary-care center in India between September 2016 and August 2017. Thalassemia patients were selected among cases encountered by the thalassemia cell department of the hospital. Patients with age less than 18 years, diagnosed with thalassemia major, recipients of >20 units of blood transfusions, and normal left ventricular function by 2D-echocardiography were included in the study. Patients with any structural heart disease, rheumatic or congenital heart disease, primary cardiomyopathy, and Left Ventricular Ejection Fraction (LVEF) <50% were excluded from the study. Signed inform consent forms were obtained from the parents/guardians of the patients.

Study intervention

The severity of iron overload was determined by using the serum ferritin level. All patients underwent 2D-echocardiography and color Doppler techniques. The standard 2D-echocardiographic examination was performed by using General Electric Vivid T8 (GE Healthcare, Chicago, Illinois, United States) electrocardiography device. All patients were in normal sinus rhythm at the time of examination.

Left Ventricular Ejection Fraction (LVEF %) was quantified offline by using Simpson's method. Tricuspid Annular Plane Systolic Excursion (TAPSE) electrocardiographic measures was used to assess the right ventricular systolic function. In addition to echocardiographic conventional parameters, Strain Imaging (SI) parameters were also evaluated. For the measurement of left ventricular global longitudinal strain, three apical views of the left ventricle i.e., four- and two-chamber and long-axis were recorded. The average of the values in all the 17 segments was expressed as the Global Longitudinal Strain (GLS). In this study, the considered normal global strain values were between -17% and -15%.

Statistical analysis

Continuous variables were expressed as mean±standard deviation. Categorical variables were expressed as frequencies and percentages. Student t test or Mann-Whitney test was used for the comparison of continuous variables while the chi-square test or Fischer's exact test was used for the comparison of categorical values. A p value of <0.05 was considered to be statistically significant. Analysis were performed using Statistical Package for Social Sciences (SPSS) software (IBM SPSS, version 20.0. Armonk, 2012).

RESULTS

Baseline demographics

A total of 56 beta-thalassemia patients were included in the study. Of these, 29(51.8%) patients were boys and 27(48.2%) patients were girls. The overall mean age of the patients was 7.8±1.84 years.

The average serum ferritin level was found to be 4089.83 mg/dl. The mean number of blood units transfused was 90.21±28.49. At the time of examination, all the patients had low hemoglobin levels of 7.99±0.96 g/dl. The baseline demographics of all the study population are displayed in (Table 1).

Table 1: Baseline demographic details of all the patients.

Characteristics	Patients (n=56)
Girls (mean±sd)	27(7.8±1.84)
Serum ferritin, mean (range, mg/dl)	4089.83 (2115.3-15112)
Blood transfused, (units, ml)	90.21±28.49
Haemoglobin (g/dl)	7.99±0.96
LVEF (%)	58±6

LVEF - left ventricular ejection fraction

Echo parameters

The size of the ventricle and wall thickness was found to be normal in echo analysis. Left ventricular ejection fraction percentage was found to be normal (58±6%) in all the patients. Conventional echocardiography revealed that patients with more transfusions had higher left ventricular mass indices (p=0.021). In strain imaging, patients who had received a greater number (>80) of transfusions had an abnormal global strain and regional strain values. The strain echo parameters values are outlined in (Table 2).

Table 2: Strain echo parameters of all the patients.

Characteristics	Patients (n=56)
TAPSE	-19.55±2.11
GLS APLAX	-19.94±3.75
GLS 2C	-20.10±3.24
GLS 4C	-20.10±3.26
GLS Average	-20.14±2.76

TAPSE - Tricuspid annular plane systolic excursion; GLS APLAX - global longitudinal strain apical long axis; GLS - global longitudinal strain; 2C - two chamber; 4C - four chamber

In particular, strain values of the basal lateral wall of the left ventricle were significantly abnormal in patients who received more than 80 transfusions compared with those who received lesser transfusions (p=0.025), respectively. The relationship between number of blood transfusions and impaired strain is displayed in (Figure 1).

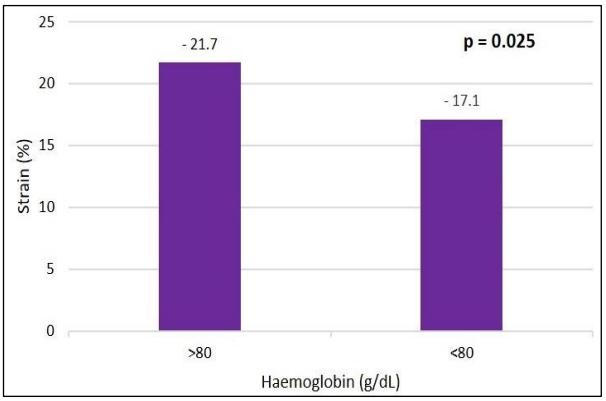

Figure 1: Relationship between number of transfusions and impaired strain.

Patients with serum ferritin >6000 ng/ml had significantly impaired strain (p=0.03). The relationship between serum ferritin with left ventricular strain parameters are shown in (Figure 2).

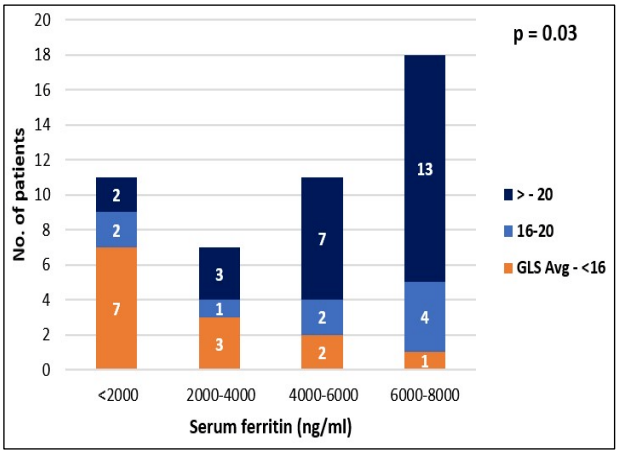

Figure 2: Relationship of serum ferritin with left ventricular strain parameters.

Patients with hemoglobin levels of <8 g/dl, 8-10 g/dl, 10-12 g/dl and >12 g/dl had a strain value of -20.8%, -20.4%, -19% and -18.8%, respectively. However, the severity of anemia had no impact on the strain (p=0.7). The relationship between hemoglobin and strain values are demonstrated in (Figure 3).

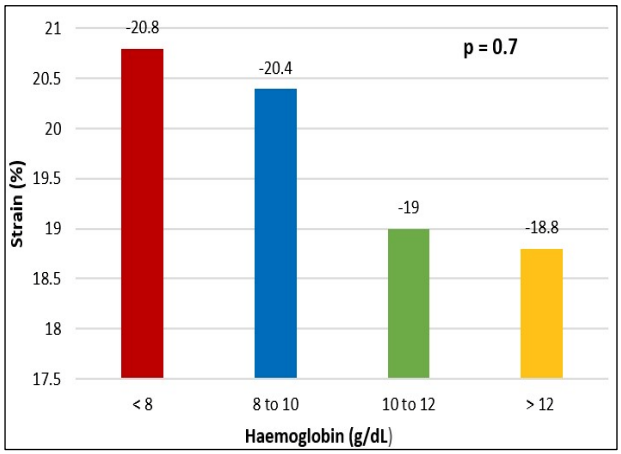

Figure 3: Relationship between haemoglobin and strain.

DISCUSSION

The novel contribution of this study was the demonstration of strain imaging over the conventional echocardiographic parameters and LVEF in the detection of regional myocardial function. Modell, et al, reported a marked improvement in survival and reduction in mortality due to cardiac magnetic resonance imaging and appropriate augmentation of iron chelation therapy.[15] Hence, early recognition of cardiac abnormalities is

essential in these patients, but not as easy as global ventricular function and exercise capacity may remain normal until late in the disease process.[12]

In the majority of the patients with thalassemia major, heart failure is the result of impaired left systolic function with ventricular dilation. In a published series of 52 thalassemia major patients with heart failure, 83% of cases had left-sided heart failure with left ventricular dilation and reduced contractility with a mean ejection fraction of 36±9%.[16] In this study, thalassemia patients had normal LVEF and did not have overt heart failure. However, they had abnormal strain values in the basal lateral wall of the LV indicating the presence of regional systolic dysfunction in the LV walls. These wall motion abnormalities may represent an early sign of cardiac disease. The assessment of cardiac iron status and cardiac dysfunction are based on imaging techniques.

A study by Rodrigues, et al, compared cardiac function in thalassemia major patients with anemic patients and showed that cardiac alterations found in thalassemia group are caused by iron overload and not by anemia.[11] However, the severity of anemia has no impact on the strain in the current study. In this study, patients who received more (>80) transfusions and patients with serum ferritin levels >6000 ng/ml have significantly abnormal impaired strain values. There are only two studies about the use of strain imaging in the early detection of myocardial dysfunction in thalassemia patients.[17,18] Similarly, to this study, these two studies also demonstrated abnormal strain imaging parameters indicating early myocardial involvement in thalassemia patients' even though they did not have overt clinical cardiac dysfunction. Although magnetic resonance with T2* technique remains the gold standard for early diagnosis of cardiac iron overload, strain imaging has emerged as a quantitative technique to accurately measure the myocardial contractility and function.[19] Strain imaging is potentially superficial to tissue Doppler imaging in regional myocardial functional assessment and also helps in detecting the LV dysfunction at its earliest in thalassemia patients compared to conventional echocardiography.[6,20] Hence, strain imaging can help us to monitor patient conditions by early detection of cardiac dysfunction.

This study have few limitations such as small sample size, absent controls, and broad age group. There was no availability of cardiac Magnetic Resonance Imaging (MRI) data to correlate with the findings of strain imaging. During imaging, the results were inconclusive, and the procedure had to be repeated due to the occurrence of heart rate variability. As abnormal strain values were associated with >80 transfusions, strain imaging monitoring was recommended after 60-70 transfusions.

CONCLUSION

Thalassemia patients have early systolic dysfunction in the basal lateral wall of the left ventricle even if they do not have overt heart failure. Systolic strain index imaging of the LV indicated the presence of early LV systolic dysfunction in patients with more blood transfusions and patients with higher serum ferritin levels. Conventional echocardiographic parameters and LVEF do not provide adequate information about LV dysfunction. Strain imaging is helpful in early detection of LV dysfunction in thalassemia patients and may provide additional data for the management of thalassemia patients suspected with iron-mediated cardiomyopathy.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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