



ORIGINAL RESEARCH PAPER

Medicine

AN ECHOCARDIOGRAPHIC EVALUATION OF LEFT VENTRICULAR FUNCTION IN CHILDREN WITH BETA-THALASSEMIA MAJOR

KEY WORDS: Beta-thalassemia major, Echocardiography, Strain imaging, Cardiac failure

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ABSTRACT

Objective: Cardiac failure due to iron overload remains the most common cause of death in patients with beta-thalassemia major. This study aimed to evaluate myocardial function in children with beta-thalassemia major using standard echocardiography technique and strain rate imaging.
Materials and Methods: Conventional echocardiographic analysis, strain imaging of the left ventricle were evaluated in 50 children with beta-thalassemia major (11 girls, 39 boys; 7.99±1.97 years) and 50 healthy children (19 girls, 31 boys; 8.22±2.24 years).
Results: Conventional echocardiographic examinations revealed that beta-thalassemia patients had larger left ventricular end-systolic diameter (<.001), end-diastolic diameter (<.01).LVEF, mitral diastolic flow velocities were not significantly different between the two groups. Strain imaging study of the basal lateral wall of the left ventricle was higher in patients than in controls, at p<.001.
Conclusion: We found that superior systolic strain imaging of the left ventricle indicated the presence of regional systolic function in the left ventricular wall. This study demonstrates the ability of strain imaging to accurately depict regional myocardial function in asymptomatic beta-thalassemia patients with normal systolic and diastolic function. LV dilatation was balanced with increased basal segment Strain measurements

INTRODUCTION

Cardiac failure due to iron overload remains the most common cause of death in patients with beta-thalassemia major, accounting for up to 71% of all deaths from this disease [1,2]. Cardiac complications are related to left ventricle dysfunction leading to gradual cardiac failure and cardiogenic death.

Standard echocardiographic measurements may remain normal until late stages during this disease process.

A number of cardiological parameters of left ventricular (LV) function have therefore been assessed to determine their efficacy in identifying early myocardial iron overload in order to prevent heart failure and avert its poor prognosis through increased chelation therapy. The stored iron in the heart is heterogeneous. Regional myocardial asynchrony characterizes diastolic abnormalities even in the absence of changes in systolic functions reported in thalassemia patients and, thus, LV diastolic function may be more sensitive as an early marker of myocardial iron overload. A number of techniques used in clinical practice have been utilized to assess diastolic function in thalassemia major [3,4,5].

Recent strain imaging may prove useful in early detection of regional myocardial dysfunction before the occurrence of abnormal indices of global ventricular functions. Strain imaging is a new noninvasive echocardiographic method for the analysis of local myocardial stress. This study aimed to evaluate myocardial function in children with beta-thalassemia major by using the standard echocardiography technique and strain imaging and to compare them with healthy controls.

Material and Method
Patient Population

Two distinct groups were studied. The patient group comprised 50 beta-thalassemia major patients (11 girls, 39 boys; , mean 7.99±1.97 years).

Thalassemia major patients were selected from cases in follow-up in the S.M.S Hospital, Jaipur. The diagnosis of thalassemia was based on hemogram, blood smear, hemoglobin electrophoresis, and clinical evaluation. All patients were under chelation therapy with an oral iron chelator (deferasirox, 30 mg/kg/d) or a parenteral iron chelator (deferoxamine, 40 mg/kg 5 days a week).

Serum ferritin levels were noted as ng/mL. Inclusion criteria were diagnosis of beta-thalassemia major, normal renal function, normal left ventricular functions, normal estimated pulmonary pressures by echocardiographic Doppler evaluation, and absence of congenital or acquired structural heart or lung diseases.

All thalassemia patients had asymptomatic heart failure and were in New York Heart Association functional class I. They had been receiving blood transfusions since the age of 6 months to 2 years. Nine (18%) of the patients had been splenectomized. Severity of iron overload was defined by serum ferritin level. Fifty healthy children (19 girls, 31 boys; 8.22±2.74 years) without history of cardiac disease were included in the study as a control group. All children were in normal sinus rhythm and had normal resting 12-lead electrocardiographs.

All studies were performed in accordance with the rules of the local ethics committee. Informed consent was obtained from all participants prior to the study.

ECHOCARDIOGRAPHY

Conventional echocardiography (Phillips ie 33) and strain imaging were performed . Echocardiographic images were obtained in the parasternal long-axis and short-axis, and apical 2-chamber and 4-chamber views were obtained with standard transducer positions. Conventional echocardiographic measurements were done according to the American Society of Echocardiography guidelines From the parasternal long-axis view, the LV end-diastolic and end-systolic diameters, interventricular septal and posterior wall thicknesses were expressed in millimeters. Left ventricular ejection

fraction (EF) was measured using the Teichholz formula. LV filling was evaluated by pulse wave Doppler from the apical 4-chamber view with the sample volume position at the tips of the mitral valve, and velocities in early (E) and late (A) diastole were recorded, in addition to the calculation of the E/A ratio. Furthermore, myocardial velocities of the left ventricle were evaluated by strain imaging.

Scanning was performed longitudinally from the apex to acquire apical 2-chamber and 4-chamber views with a 3-MHz transducer and a frame rate of 100 ± 20 frames/s, depending on the heart rate, to minimize the noise level. Myocardial velocities were measured for the local motion of a tissue by strain imaging. Longitudinal strain and strain rate in the basal septal, basal lateral, mid-septal, and mid-lateral wall were estimated by measuring the spatial velocity gradient over a computational area of 3 mm × 5 mm. Longitudinal strain values were obtained at each site from 3 consecutive beats and average values were calculated.

End-diastole was defined as the R peak in echocardiography, and end-systole was defined as the end of the T wave in echocardiography. Peak positive systolic values were calculated from the extracted curve. Mean values of early diastolic, late diastolic, and systolic myocardial velocities were calculated as cm/s.

STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS 11.0 (SPSS Inc., Chicago, IL, USA). All data were expressed as mean ± standard derivation. Comparison of measurements between 2 groups was analyzed with the unpaired Student t-test. Correlation coefficients between various measurements were determined by the linear regression analysis. A p value of less than 0.05 was considered significantly different.

RESULTS

The 2 groups were similar regarding age, hemoglobin status.

Parameters	Control (n=50)	Case (n=50)	P-value	Significance
Age (Mean + Sd)	8.22 + 2.24	7.99 + 1.97	> .05	NS
Sex (M/F)	31/19	39/11		
Splenectomy		9 (18.00 %)		
Hb	8.17 + 0.53	7.96 + 0.72	> .05	NS

Conventional echocardiographic examinations revealed that beta-thalassemia patients had larger LV end-systolic diameter (p<.001), end-diastolic diameter (p<.01), IVST(P<.01). other parameters like mitral inflow velocities, LVEF were not significantly different between the two groups (Table 2).

Table 2: Conventional and basic systolic and diastolic echocardiographic parameters of the Case and Control group subjects

Parameters	Control (n=50)	Case (n=50)	P-value	Significance
LVEDD	35.91 + 3.06	38.14 + 4.59	< .01	Sig
LVESD	22.87 + 3.40	25.13 + 3.45	< .001	Sig
IVST	6.62 + 0.80	7.20 + 1.12	< .01	Sig
LVPWT	6.31 + 0.88	6.57 + 0.95	> .05	NS
LVEF	65.17 + 3.61	66.34 + 3.82	> .05	NS
E	1.00 + 0.03	1.00 + 0.03	> .05	NS
A	0.55 + 0.03	0.56 + 0.03	> .05	NS
E/A	1.79 + 0.10	1.80 + 0.12	> .05	NS

Strain study included the following measurements: basal lateral and septal segments and mid-lateral and septal segments of the LV walls. The basal lateral walls' Strain measurements were higher in patients compared to controls: p<.001(Table 3).

Table 3: Mean + Sd of Left ventricular Strain (%) of case & control group subjects

Parameters	Control (n=50)	Case (n=50)	P-value	Significance
Basal Lateral Wall	-17.59 + 0.92	-18.43 + 0.98	< .001	HS

Mid Lateral Wall	-19.64 + 1.09	-19.54 + 1.09	> .05	NS
Basal septal Wall	-15.48 + 6.22	-15.21 + 6.15	> .05	NS
Mid septal Wall	-17.04 + 7.10	-17.31 + 5.09	> .05	NS

Pearson's correlation coefficient showed significant correlations between the serum ferritin levels and the following echocardiographic variables: LV end-diastolic diameter (r=0.351, p<.01), LV end-systolic diameter (r=0.430, p<.01), EF (r=-0.394, p<.01),E (r=-0.389, p<.01).

Table 4 Correlation between Serum Ferritin and other parameters

Correlation	r-value	p-value	Significance
SF v/s LVEDD	+ 0.351	< .01	Sig
SF v/s LVESD	+ 0.430	< .01	Sig
SF v/s LVEF	- 0.394	< .01	Sig
SF v/s E	- 0.389	< .01	Sig
SF v/s A	- 0.080	> .05	NS
SF v/s E/A	- 0.136	> .05	NS

DISCUSSION

The most common cause of morbidity and mortality in thalassemia major patients is cardiomyopathy due to iron overload. Heart disease is mainly expressed by a particular cardiomyopathy that progressively leads to heart failure and death [1,2,11]. Iron toxicity has been attributed to the production of free oxygen radicals, as a result of the Fenton and Haber-Weiss reactions, which take place in the presence of free iron, the most toxic form of iron.

Since cardiac function remains normal until late stages in the spectrum of iron cardiomyopathy, other tools are necessary to anticipate and prevent iron cardiomyopathy. Cardiac magnetic resonance imaging, tissue Doppler echocardiography, radionuclide angiography, and stress echocardiography are useful imaging studies for the detection of early cardiac dysfunction. Recently, tissue Doppler echocardiography and radionuclide angiography (with exercise or low-dose dobutamine stimulation) have been shown to detect regional wall motion abnormality, even in early-stage thalassemic patients [11]. This finding may also reflect patchy, nonhomogeneous deposition of iron in cardiac muscle.

Fitchett et al. demonstrated the deposition of iron within the myocytes rather than the interstitium, and this cardiac iron deposition was patchy [12]. Lattanzi et al. and Vogel et al. showed that regional wall motion abnormalities and regional iron overload were seen in patients with beta-thalassemia major [13, 14]. These regional changes can be easily detected with an echocardiographic assessment including TVI and S/SRI analysis.

The novel contribution of our study is the demonstration of the superiority of Strain imaging over the conventional echocardiographic parameters, LVEF, in the detection of regional myocardial function. Our patients had superior systolic Strain values of the LV lateral wall, indicating the presence of regional systolic function in the left ventricular wall.

Regular clinical follow-up is strongly recommended for precocious detection of symptoms and signs of myocardial dysfunction [15]. On the hypothesis that longitudinal ventricular function may give early information about impending ventricular function, we used longitudinal strain measurements[6, 7].

Regional findings suggest the presence of differences in myocardial function between the asymptomatic patients with beta-thalassemia major in the early stage of disease and the healthy controls. These regional changes can be easily detected with an echocardiographic assessment including strain analysis. Previous studies have shown that beta-thalassemia major is frequently associated with progressive LV dysfunction, leading to congestive heart failure. LV diastolic function, measured by traditional measurements such as transmitral flow recordings, is preserved until the final stages of diseases [16,17,18]. Conventional Doppler indices frequently lead to incorrect diagnosis.

In our patients, chronic iron overload resulted in significant increase in serum ferritin. However, EF was not altered significantly in patients compared with controls, suggesting preserved systolic functioning until late stages of the disease. This finding is consistent with those of Parale et al. and Selim et al. [18,19].

Magri et al. suggested TDI and strain imaging as a potential method for detecting early stages of abnormal iron deposition [20]. Olivieri et al. and Bosi et al. demonstrated that serum levels of ferritin below 2500 ng/mL were considered as the safe level [1,21]. Our mean value of serum ferritin was at this level. Fitchett et al. demonstrated iron deposition within the myocytes rather than the interstitium and this cardiac iron deposition was patchy [12]. Lattanzi et al. and Vogel et al. showed that regional wall motion abnormalities and regional iron overload were seen in patients with beta-thalassemia major [13,14]. We found wall motion abnormality located in the basal lateral segment of the LV wall. There is no clear explanation for this observation.

Strain offers a new way of measuring regional tissue deformation noninvasively with both good spatial and temporal resolution. Authors have demonstrated it to be a tool that would appear to offer reproducible and reliable data [8]. Our findings suggest that Strain parameters have the potential to detect early myocardial changes that precede abnormal LV filling.

RESULTS

This study demonstrates the ability of Strain to accurately depict regional myocardial function in asymptomatic beta-thalassemia patients with normal systolic and diastolic function. LV dilatation was balanced with increased basal segment S/SRI measurements. During this period, increased LV dilatation may progress to lower strain values and to LV diastolic and systolic function disorders. Until the critical level of iron overload, peak systolic strain may accurately reflect local systolic function, and we may say that iron overload is not related to a specific area of LV myocardium and that cardiac changes are possibly related to a threshold level of iron overload.

While serum ferritin levels remain above 2500 µg/L, echocardiographic measurements such as basal longitudinal strain parameters might show compensatory increase although LV dilatation starts with normal systolic function. This compensation would probably be inadequate at greater ferritin levels and systolic and diastolic functions would globally decrease eventually. Therefore, clinical manifestations usually occur in adulthood rather than childhood. According to the Frank-Starling law, if heart volume increases, this compensation might be inadequate, and these parameters worsen through adulthood.

Accurate assessments of cardiac dysfunction and cardiac iron status are currently based on imaging techniques. The T2-star magnetic resonance is currently the best noninvasive modality to estimate iron in the heart and other organs [22]. In addition, it can be used for monitoring myocardial iron levels during iron chelation therapy. Unfortunately this examination cannot be performed in our hospital; we could not correlate this technique with the results.

Limitations

One of the limitations of our study is that we could not compare the patients within every ferritin level. In asymptomatic patients, normal systolic and diastolic functions might be related to good LV compensation. Strengthening the chelation treatment in this period may normalize these measurements. Even when LVEF is normal, increased LV mass and volume may be seen. In this study we found compensatory increase in Strain measurements, and these parameters would probably worsen first to be followed by cardiac failure appearing due to decreased LVEF and LVFS.

CONFLICT OF INTEREST STATEMENT

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/ or affiliations relevant to the subject matter or materials included.

REFERENCES

- Olivieri NF, Nathan DG, MacMillan JH, Wayne AS, Liu PP, McGee A, Martin M, Koren G, Cohen AR. Survival in medically treated patients with homozygous beta-thalassemia. *N Eng J Med* 1994;331:574-578.
- Leonardi B, Margossian R, Colan SD, Powell AJ. Relationship of magnetic resonance imaging estimation of myocardial iron to left ventricular systolic and diastolic function in thalassemia. *JACC Cardiovasc Imaging* 2008;1:572-578.
- Chrysohoou C, Greenberg M, Pitsavos C, Panagiotakos DB, Ladis V, Barbetseas J, Brili S, Singh S, Stefanadis C. Diastolic function in young patients with beta-thalassemia major: an echocardiographic study. *Echocardiography* 2006;23:38-44.
- Ayyar E, Alehan D, Hazirolan T, Gümruk F. The efficacy of tissue Doppler imaging in predicting myocardial iron load in patients with beta-thalassemia major: correlation with T2* cardiovascular magnetic resonance. *Int J Cardivasc Imaging* 2010;26:413-421.
- Balci YI, Gurses D. Detection of early cardiac dysfunction in patients with -thalassemia major and thalassemia trait by tissue doppler echocardiography. *Pediatr Hematol Oncol* 2011;28:486-496.
- Nesbitt GC, Mankad S. Strain and strain rate imaging in cardiomyopathy. *Echocardiography* 2009;26:337-344.
- Nesbitt GC, Mankad S, Oh JK. Strain imaging in echocardiography: methods and clinical applications. *Int J Cardiovasc Imaging* 2009;25:9-22.
- Voigt JU, Lindenmeier G, Werner D, Flachskampf FA, Nixdorff U, Hatle L, Sutherland GR, Daniel WG. Strain rate imaging for the assessment of preload-dependent changes in regional left ventricular diastolic longitudinal function. *J Am Soc Echocardiogr* 2002;15:13-19.
- Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation* 1978;58:1072-1083.
- Devereux RB. Detection of left ventricular hypertrophy by M-mode echocardiography. Anatomic validation, standardization, and comparison to other methods. *Hypertension* 1987;9:19-26.
- Cohen AR, Galanello R, Pennell DJ, Cunningham MJ, Vichinsky E. Thalassemia. *Hematology Am Soc Hematol Educ Program* 2004:14-34.
- Fitchett DH, Coltart DJ, Littler WA, Leyland MJ, Trueman T, Gozzard DJ, Peters TJ. Cardiac involvement in secondary haemochromatosis: a catheter biopsy study and analysis of myocardium. *Cardiovasc Res* 1980;14:719-724.
- Lattanzi F, Bellotti P, Picano E, Chiarella F, Mazzarisi A, Melevendi C, Forni G, Landini L, Distante A, Vecchio C. Quantitative ultrasonic analysis of myocardium in patients with thalassemia major and iron overload. *Circulation* 1993;87:748-754.
- Vogel M, Anderson LJ, Holden S, Deanfield JE, Pennell DJ, Walker JM. Tissue Doppler echocardiography in patients with thalassaemia detects early myocardial dysfunction related to myocardial iron overload. *Eur Heart J* 2003;24:1113-1119.
- Marci M, Pitrolo L, Lo Pinto C, Sanfilippo N, Malizia R. Detection of early cardiac dysfunction in patients with Beta thalassemia by tissue Doppler echocardiography. *Echocardiography* 2011;28:175-180.
- Koren A, Garty I, Antonelli D, Katzuni E. Right ventricular cardiac dysfunction in beta-thalassemia major. *Am J Dis Child* 1987;141:93-96.
- Kremastinos DT, Tsiapras DP, Tsetsos GA, Rentoukas EI, Vretou HP, Toutouzas PK. Left ventricular diastolic Doppler characteristics in beta-thalassemia major. *Circulation* 1993;88:1127-113.