An Echocardiographic Evaluation of Left Ventricular Function in Patients with Thalassemia Major

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Conflict of Interest: None declared

This article has been peer reviewed.

Article Submitted on:

Article Accepted on:

Funding Sources: None declared

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Cite this article: Hyder SN, Kazmi U, Malik A. An echocardiographic evaluation of left ventricular function in patients with thalassemia major. J Pak Med Stud 2013; 3 (1):10-15

ABSTRACT

BACKGROUND: Cardiac disease caused by transfusional iron overload remains the principal cause of death in patients with β-thalassemia major, despite improvements in iron chelation therapy during the past 25 years. For this reason, regular evaluation of cardiac function is recommended for all patients with thalassemia major and is now an integral part of their management. Cardiac monitoring should, therefore, ideally identify patients at highest risk for cardiac decompensation before heart failure develops. Sequential and reproducible quantification of ventricular function in principle can identify early changes in the left ventricular ejection fraction from baseline for each patient and could be used as a rationale for identifying patients at high risk.

METHODS: The study was conducted in the Department of Pediatric Cardiology, The Children's Hospital and Institute of Child Health Lahore, Pakistan from 1st April 2006 to 30th October 2010. The study comprised of 50 consecutive confirmed cases of β thalassemia major and 30 controls with normal hemoglobin and electrophoresis pattern. β thalassemia major patients were diagnosed on the basis of hemoglobin electrophoresis. 2-D, M-mode and Doppler echocardiography was performed in all study cases and in control participants. Statistical comparison of study cases and controls was conducted by using unpaired *t*-test.

RESULTS: The age of the patients ranged from 1 year to 25 years with mean age of 9.65 years. There were 34 (68%) males and 16 (32%) females. None of the study cases was on regular chelation while 31 (62%) patients were on irregular chelation therapy with single dose of intravenous desferrioxamine only at the time of blood transfusion. Nineteen (38%) patients had LV dysfunction, of which isolated systolic dysfunction was in 2 (4%), isolated diastolic dysfunction was in 15 (30%) and global dysfunction was in 2 (4%) patients. Left ventricular dimensions, stroke volume and E/A ratio were considerably affected in the study group.

CONCLUSION: A significant percentage of thalassemia patients have left ventricular dysfunction. This is mainly due to chronic anemia, iron overload and poor compliance with chelation therapy. Regular assessment of cardiac function may help to improve the quality of life of these patients and may reduce the morbidity and mortality to a great extent.

Key Words: Beta thalassemia major, Echocardiography, Left ventricular dysfunction

INTRODUCTION

Beta (ß)-thalassemia major is the most common hemolytic anemia in children and adolescents, particularly in countries where consanguinity is highly prevalent [1]. Thalassemia patients have extra vascular hemolysis and ineffective erythropoiesis resulting in severe anemia. Thus, they require regular blood transfusions, which results in iron overload. Patients receive between 0.3 and 0.5 mg/kg/d of iron through transfusion [2]. Thalassemia patients absorb more iron than normal individuals do. Iron overload results in iron deposition in a variety of parenchymal

tissues including the heart, liver, gonads, and pancreas. In heart, the excess free iron leads to impaired function of the mitochondrial respiratory chain, which is clinically manifested by the reduction of cardiac contractility, progressive systolic dysfunction, and development of heart failure [3]. Additionally, increased intracellular ferrous iron inhibits the ryanodine sensitive calcium channels of the sarcoplasmic reticulum, which modulates calcium release, resulting in further reduction of cardiac function, conduction problems, and arrhythmia development [4]. These chronically-transfused patients, if not assiduously chelated, are at high risk for cardiac dysfunction. Cardiac disease is the major cause of death in these patients and even in the best centers, a third of patients die by the age of 35 years [2]. In many patients, despite adequate chelation, cardiac pathology is still present due to a combination of factors such as iron deposition, fibrosis, hypertrophy and structural effects of chronic anemia [3]. In fact, cardiac disease is responsible for 70% of deaths in thalassemia major patients [5]. Congestive heart failure remains the primary cause of death in patients suffering from β-thalassemia major [6]. Early detection of cardiac involvement would allow prompt initiation of aggressive chelation therapy when condition can still be reversed [7]. Echocardiography is a non-invasive technique that evaluates cardiac anatomy and function with images and recordings produced by sound energy. It has an established role in the assessment of left ventricular structure and performance [8]. Chronic anemia is a common clinical condition that is responsible for an increase in cardiac output [9]. This results from decreased systemic vascular resistance due to decreased blood viscosity and vasodilatation [9].

The enhanced left ventricular performance observed in anemia has been attributed to changes in pre-load and after-load. Chronic anemia also causes cardiac dilatation and hypertrophy [10]. Clinical evaluation of cardiac function predominantly involves assessment of the performance of the left ventricle. We studied 30 β-thalassemia major patients in order to determine the effects of chronic anemia and transfusional iron overload on the left ventricular function by Doppler echocardiography. We believe that early detection of cardiac function impairment can assist in preventing further cardiac damage by modifying disease progression and treatment.

METHODS AND MATERIALS

It was an observational cross-sectional study from 1st April 2006 to 30th September 2007, conducted at the Department of Pediatric Cardiology, The Children's Hospital and the Institute of Child Health Lahore, Pakistan. The study protocol was approved by the institutional ethics committee and written informed consent was obtained from all the patients and their parents. Non-probability purposive sampling technique was used. The study comprised of 50 cases of β-thalassemia major and 30 controls with normal hemoglobin and electrophoresis pattern. Diagnosis of β-thalassemia major was based on hemoglobin electrophoresis findings. Patients with any congenital or acquired heart disease, concurrent infective disorder and patients with history of any type of cardiac surgery were excluded from the study. The control group consisted of 30 healthy children comparable in age and sex, free from any cardiovascular disorder and not taking any cardiac drugs. Detailed clinical examination and investigations including hemoglobin, chest X-ray, electrocardiogram and serum ferritin levels were obtained in all the patients who were enrolled for study. Echocardiography (2-D, M-mode, Doppler) was performed in the thalassemia as well as in the control group. General Electronics vivid-7 echocardiogram machine was used. Two dimensional, M-mode and Doppler echocardiographic assessment was performed using mechanical and phased array sector scanner with 5 MHz and 3.0 MHz transducers. The examination was conducted with the patient lying in supine position. The parasternal long axis and short axis and apical four chamber views were obtained in all study cases and control groups.

Echocardiographic Measurements:

The left ventricular end systolic and end diastolic dimensions, left ventricular posterior wall thickness and septal thickness, and fractional shortening (FS%) were measured by M-mode according to the recommendations of the American Society of Echocardiography (ASE). The left ventricular ejection fraction percentage (EF%) and stroke volume were calculated by using Simpson's method. To record left ventricular inflow velocities the apical four chamber view was used and the pulsed-wave Doppler sample volume was placed at the level of the leaflets tips of the mitral valve, where the

Table 1: Echocardiographic Movements

	Age Groups			
Factors	3-8 years	9-12 years	13-18 years	Adult
E-waves (cm/sec)	92±14	86±15	88±14	67±14
A-waves (cm/sec)	42±11	41±09	39±08	48±16
E/A ratio	2.4±0.7	2.2±0.6	2.3±0.6	1.5±0.6
Deceleration time (msec)	145±18	157±19	172±22	195±35
Isovloumetric relaxation time (msec)	62±10	67±10	74±13	83±16

Data are expressed as mean±SD. Statistical comparison of thalassemia patients and controls was conducted by using unpaired t-test. P-value ≤ 0.05 was considered statistically significant.

highest peak velocity was recorded. Peak flow velocities of the left ventricle inflow in early diastole (E) and late diastole with atrial contraction (A) were measured from the baseline to the maximum flow velocity. An E/A velocity ratio, deceleration time (DT) and isovolumetric relaxation time (IVRT) were calculated from each cardiac cycle. Systolic function was considered abnormal if the EF was less than 55% and the FS was below 27%. Left ventricular diastolic function was defined by the pattern of transmitral inflow on spectral Doppler interrogation consisting of E/A ratio, E-wave deceleration time and isovolumetric relaxation time. Diastolic function was classified according to the published ASE guidelines into normal, abnormal relaxation pattern (mild), the intermediate or pseudonormal pattern (moderate) and restrictive physiology (severe) pattern. Diastolic dysfunction was diagnosed as abnormal relaxation pattern (mild) when the E/A ratio was less than normal, deceleration time and the isovolumetric relaxation time were more than expected normal for that particular age group and pseudonormal when E/A ratio was in normal range, but on valsalva maneuver E/A dropped to less than normal or there was associated significant systolic dysfunction. Restrictive left ventricular function was labeled when E/A ratio was more than normal, deceleration time of E-wave and isovolumetric relaxation time were less than expected normal. Following were the cut-off values of mitral inflow velocities, deceleration time and isovolumetric relaxation time used for diastolic dysfunction categorization according to different age groups [9] (measurement taken from ASE z-scoring).

RESULTS

In the study cases, the median age was 8.54 years ranging from 1 year to 25 years. There were 34 (68%) males and 16 (32%) females in the study cases. None of the study cases was on regular five nights per week chelation therapy with subcutaneous or oral desferrioxamine. Thirty one (62%) cases were on irregular chelation with single dose of intravenous desferrioxamine only at the time of blood transfusion. Blood transfusion was started at a mean age of 1.6±1.1 years. Transfusion frequency was at a mean of 21.8±9.7 days. Nineteen (38%) patient with thalassemia major had left ventricular dysfunction, out of which 2 (10%) patients had isolated systolic dysfunction, 15 (79%) had isolated diastolic dysfunction and 2 (11%) had global ventricular dysfunction.

Six (12%) patients had splenectomy. Mean pre-transfusion hemoglobin was 6.4±1.83 g/dl in the study cases. Serum ferritin level more than 5000 ηg/ml was present in 18 (36%) cases while the mean serum ferritin level for the whole study group was 4718±1925 ηg/ml. On chest X-ray, cardiomegaly was detected in 24 (48%) cases, while electrocardiograms of all the patients revealed regular sinus rhythm. Echocardiographic measurements (M-mode, 2-D, and Doppler) in patients with β-thalassemia major and controls are shown in Table 2. Abnormalities in LV function were seen in nineteen patients.

DISCUSSION

In this study, we found that interventricular septal thickness, LV posterior wall thickness, LV dimensions both in systole and diastole, fractional shortening, ejection fraction, stroke volume, E-wave, A-wave and E/A ratio were significantly higher in the study cases as compared to controls while the difference between deceleration time and isovolumetric relaxation time was not statistically significant. On echocardiography, β-thalassemia patients had cardiac enlargement with high stroke volume.

Our findings are generally consistent with previously reported findings in literature. For example, Bosi G *et al*, Chotivittayatarakorn *et al*, Kremastinos DT *et al* and Aessopos *et al* reported that the left ventricular diameter in thalassemic patients were significantly higher

Table 2: Echocardiographic measurements in patients with β-thalassemia major and control subjects (mean±SD)

Echocardiog-raphy 2-D/M mode/Dopp-ler	B-thalass-emia major (N=50) Mean±SD	Contro (N=30) mean±SD	P-Value
IVSd (mm)	8.86±2.19	7.05±1.72	<0.05
LVIDd (mm)	36.8±3.52	31.4±3.67	<0.05
LVIDs (mm)	23.6±3.67	19.2±2.75	<0.05
LVPWd (mm)	8.7±2.37	6.45±1.62	<0.05
FS%	36.4±3.92	32.2±2.68	<0.05
EF%	68.5±7.23	64.3±6.45	<0.05
SV	35.8±8.73	24.5±7.33	<0.05
E-Wave (cm/sec)	101.2±19.5	84.3±21.2	<0.05
A-wave (cm/sec)	41.4±9.5	33.7±10.3	<0.05
E/A ratio	2.42±0.52	1.91±0.61	<0.05
DT (msec)	155±26	149±24	<0.05
IVRT (msec)	62±13	59±14	<0.05

than in controls [11. 12]. The failure to detect impaired ventricular systolic function is not surprising since the hemodynamic effects associated with anemia helped to maintain normal ejection fraction and myocardial fiber shortening. Similarly, Atiq M *et al* reported that 23% of their study patients had LV systolic while 29% had diastolic dysfunction [13]. LV systolic dysfunction in 23% of patients is a higher percentage than our finding but their study comprised of those thalassemia patients who clinically had some symptoms and were actually referred for cardiac evaluation. Aldouri MA *et al* demonstrated that the interventricular septal thickness and left ventricular posterior wall thickness of the thalassemic cases was significantly increased compared to the control group (p<0.001) which is in concordance with present study [8]. Bosi G *et al* and Spiritio P *et al* reported that peak flow velocity in early diastole was increased in patients compared with controls and the ratio between the early and late (atrial) peaks of flow velocity were also increased [11, 14]. On the other hand, Kremastinos *et al* demonstrated an altered diastolic function by an increase of both early and late peak transmitral flow velocity without change of the E/A ratio, although 8% of their study patients had restrictive LV abnormalities [15]. In our study, we found an increase in both early and late peak transmitral flow velocities. An increase in E/A ratio along with shortened deceleration time (DT) and isovolumetric relaxation time (IVRT) was found in 9 (18%) of patients, reflecting a high percentage of restrictive physiology in our setup. However, Favilli S *et al* found that there was no difference between patients with thalassemia major and controls for Doppler diastolic indexes obtained from analysis of transmitral flow, which is not consistent with our finding [16]. Taksande A *et al* described that although there is an increase in LV dimensions and LV mass but LV diastolic function is not altered in asymptomatic patients [17]. In contrast, we found 30% of our asymptomatic patients had diastolic dysfunction. Vaccari M *et al* also concluded an increased E/A ratio in thalassemia major patients which is comparable with our study [18].

The pathophysiology of cardiomyopathy in ß-thalassemia major is complex and multifactorial. It may be related to heart failure secondary to anemia, iron overload cardiomyopathy, acute infectious myocarditis, acute pericarditis, conduction abnormalities or right heart failure due to pulmonary hemosiderosis, alone or in combination [19]. Despite advances in treatment, cardiac dysfunction remains the leading cause of death [4]. All patients in our study had elevated serum ferritin. Iron overload in ß-thalassemia major is the outcome of excessive absorption and transfusional hemosiderosis. The plasma turnover is 10-15 times of the normal value and is caused by the wasteful, ineffective erythropoiesis of an enormously expanded bone marrow. The resulting outpouring of catabolic iron exceeds the iron-binding capacity of transferrin and appears as non-transferrin plasma iron (NTPI).

NTPI is highly toxic due its ability to promote free radical formation through the Haber-Weiss reaction, resulting in perioxidative damage to membrane lipids and proteins [3]. The process of liberating of lysosomal enzymes, damages the cytoplasm of myocytes, resulting in cell death. Another organelle implicated in iron toxicity is the sarcolemmal membrane leading to the loss of Na,K-ATPase activity. This impairs the Na/Ca exchange mechanism, partially causing the functional abnormalities noted in the iron-overloaded heart [20]. Finally, iron overload causes injury to the mitochondria, leading to a decrease in the mitochondrial respiratory complex activity [21], which may be responsible for cardiac disease in some patients.

The relationship of total body iron overload to iron deposition within the myocytes and the development of myocardial dysfunction remains perplexing, because some patients with advanced hemosiderosis of other organs have little myo-

cardial deposition [11]. In one study, conduction abnormalities correlated poorly with conduction tissue infiltration seen at autopsy in patients who died of arrhythmias [22]. Moreover, iron may cause reactive fibrosis or hypertrophy within the myocardium to account for the variable responses observed [12]. Vogel *et al* hypothesized that iron deposition is predominantly in the interventricular septum in the early stages [23]. Iron deposition is mainly within the ventricles and can be patchy [13]. Pathophysiologically, iron overload manifests as left ventricular diastolic dysfunction. However, as the disease progresses, systolic function also becomes impaired [24]. Aggressive chelation therapy may improve prognosis and should not be delayed until the development of overt heart failure [15]. Modell *et al* reported a marked improvement in survival and reduction in deaths due to cardiac iron overload in β-thalassemia major by early identification of myocardial siderosis by cardiac magnetic resonance imaging and appropriate intensification of iron chelation treatment [24]. Therefore, early recognition of cardiac abnormalities is essential in these patients, but not easy as global ventricular function and exercise capacity may remain normal until late in the disease process [16].

Co-operation of the treating physician with the cardiologist is necessary to establish the best treatment protocols. Echocardiography is an investigation that is widely available, relatively inexpensive, and easy to perform [21]. This is a simple, non-invasive way of recording early cardiac alterations in thalassemia major patients and enables long-term monitoring of cardiac function in the assessment of the effectiveness of the chelation therapy [22].

CONCLUSION

To conclude, we found the results that are consistent with previous studies for LV dimensions and systolic dysfunction but we found a higher percentage of diastolic dysfunction in our study. We believe that this higher percentage is most likely due to poor compliance with chelation therapy and non-availability of proper cardiac monitoring. Monitoring cardiac function can be a useful index to the overall prognosis of a patient. The demonstration of impaired myocardial function might not only serve to alert the clinicians to start cardiac treatment, but it would also alert them to warn the individual patient that a much stricter adherence to chelation protocol or the initiation of a more intensive chelation program is required to prevent an inexorable progression to severe cardiac failure. Assessment of cardiac function by echocardiography on regular basis is a useful tool for this purpose.

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