Early Diagnosis of Cardiac Involvement in β-Thalassemia Major

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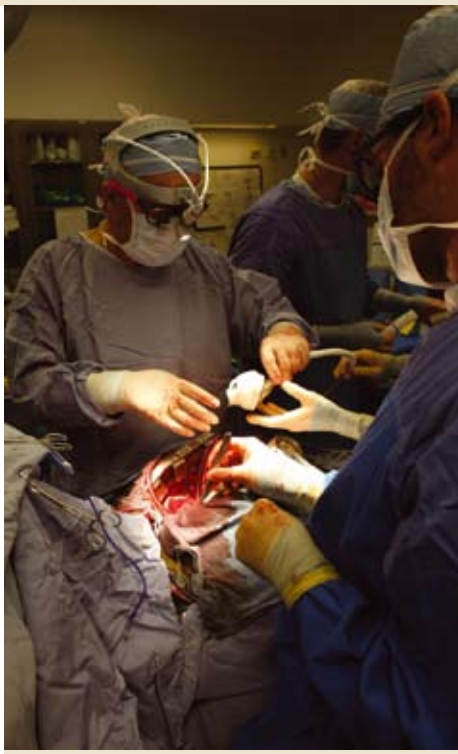

Abstract

Background. Cardiac involvement is the major cause of morbidity and death in (β)-thalassemia Major. We aimed to compare echocardiography findings in early diagnosis of cardiac involvement.

Methods: 46 Beta (β)-thalassemia Major patients aged less than 10-year and 46 beta thalassemia patients aged over 10-year were studied. Echocardiography and Doppler tissue imaging (DTI) were done.

Results: The mean of RV pre-ejection period to ejection time (PEP/ET), LV PEP/ET, mitral and tricuspid peak E:A velocities ratio (E/A), RV myocardial performance index (MPI) and LV MPI in group A and B did not show any significant differences. The mean of tricuspid deceleration time (DT), mitral DT and from DTI the tricuspid and mitral annular velocities in group A and B demonstrated significant differences.

Conclusions: This study showed abnormal diastolic dysfunction in asymptomatic children with Beta (β)-thalassemia Major that could be a useful biomarker to predict later and severe manifestations of cardiac disease.

Key words: Beta (β)-thalassemia Major; Systolic and diastolic dysfunction; Echocardiography.

Introduction

Cardiac complications are still the most common cause of death in Beta (β)-thalassemia Major. Although severe anemia leads to predominant cardiac symptoms, however, iron overload causes severe and permanent cardiac damage including recurrent pericarditis, recurrent forms of cardiac block, ectopic ventricular beats, ventricular tachycardia, ventricular fibrillation, cardiomegaly, left ventricular dysfunction and resistant heart failure [1-3]. Thalassemic patients carrying typical systolic function and iron overload, abnormal left ventricular relaxation time represented as prolonged isovolumic relaxation time (IRT) which is the first symptom of diastolic dysfunction [4,5]. Doppler tissue imaging (DTI) is utilized for evaluation of right ventricular function in children with congenital heart disease. [6, 7]. MPI is a useful index to prove left ventricular dysfunction. MPI is simply measured by Doppler echocardiography without normalizing by heart rate and blood pressure. That is non-invasive and demonstrates systolic and diastolic ventricular functions [5, 8, 9,and10]. There are few studies on echocardiographic parameters and ventricular functions in young thalassemic patients. We, therefore, conducted the present study to eval-

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uate the indices in early diagnosis of cardiac complications in Beta (β)-thalassemia Major.

Materials and Methods:

A case-control study was designed on patients with Beta (β)-thalassemia Major categorized into two groups of 5-10 year and an elder one. The study was approved by institutional ethical committee. Written consent form was obtained from the patients. Data on demographics, life style, family and medical and occupational history were collected using a detailed standard questionnaire. They underwent a detailed interview, physical examination, and laboratory analysis to exclude hypertension, cardiac structural disorders, heart failure, Hb < 10, and cardiac drug usage. Ninety two consecutive patients were selected, 46 patients aged 5-10 year old (group A) and 46 patients aged over 10 years old (group B). All patients underwent blood transfusion and echocardiography. The participants were age and sex-matched. Controls were healthy without any cardiac or other problems. Two-dimensional, M-Mode and Doppler echocardiography were done and mean of every parameter calculated. In each subject, the DTI of the right and left ventricular diastolic velocities was obtained and tricuspid and mitral annular velocities were measured. Echocardiography was done by 3.5/5 and 2.5/3.5 MHZ transducer in supine position without breathe holding. Quantitative variables were defined by mean ± SD. Statistical analysis was performed using SPSS ver.15. A 2-tailed P value of < 0.05 was considered statistically significant.

Results:

The mean of age in group A was 7.3±1.9 year and in group B 16.3±2.9 showing significant statistical difference (P < 0.01). Group A and group B were age-gender matched. The right heart echocardiography findings of both the groups are presented in Table 1. The mean of IRT in both the groups wasn't statistically significant (P > 0.05) reflecting IRT abnormality. Although, the mean of DT and tricuspid annular velocity by DTI in group A and B demonstrated significant difference statistically (P < 0.05), the mean of PEP/ET, E/A and MPI weren't (P > 0.05).

Table 1: Right heart echocardiography findings in under and over 10-year-old patients With β-thalassemia Major

Echo finding	Under 10-year	Over 10-year	P value
IRT ms	126.82 ± 19.12	125.96 ± 23.09	P > 0.05
DT ms	103.82 ± 17.93	111.77 ± 27.27	P < 0.02
PEP/ ET	0.449 ± 0.439	0.369 ± 0.053	P > 0.05
E/A	1.32 ± 0.39	1.31 ± 0.32	P > 0.05
MPI	0.637 ± 0.154	0.605 ± 0.13	P > 0.05
A/E (by DTI)	0. 619 ± 0.125	0.638 ± 0.21	P < 0.05

The left heart echocardiography findings in both the groups are presented in Table 2. The left isovolumic contraction time (ICT) in group A was 21±20 and in group B was 30±15 milliseconds. The mean of DT and mitral annular velocity by DTI in group A and B demonstrated significant difference statistically (P < 0.05). The mean of PEP/ET, E/A and MPI in group A and B weren't statistically different (P > 0.05). Moreover, Interventricular septal dimension in diastole (IVSDD), Left ventricular posterior wall dimension in diastole (PWDD), Left ventricular dimension in diastole (LVDD) and Left ventricular dimension in systole (LVDS) were statistically different in group A and B (P < 0.0001). Age could account for, but statistically significant difference of these parameters may be related to age and not to disease itself. Ejection fraction (EF) and shortening fraction (SF) in group A and B weren't statistically different (P > 0.05). These two parameters aren't good criteria to differentiate cardiac involvement in patients with Beta (β)-thalassemia Major under and over 10 years old.

Table 2: Left heart echocardiography findings in under and over 10-year-old patients with Beta-thalassemia Major

Echo findings	Under-10 year	Over-10 year	P value
IRT(ms)	114.80 ±21.23	108.67 ± 23.29	P > 0.05
DT (ms)	102.27±15.95	114.52 ±19.20	P < 0.0001
PEP/ ET	0.440 ±0.295	0.382 ± 0.061	P > 0.05
E/A	1.73±0.48	1.82±0.45	P > 0.05
MPI	0.527 ±0.149	0.528 ± 0.127	P > 0.05
A/E (by DTI)	0.729 ±0.123	0.619 ± 0.125	P < 0.0001
IVSDD (mm)	5.23±1.18	6.90±1.40	P < 0.0001
PWDD (mm)	3.43±0.67	4.43±1.1	P < 0.0001
LVDD (mm)	42.49±3.39	47.64±4.84	P < 0.0001
LVDS (mm)	29.07±2.98	32.62±4.09	P < 0.0001
EF (%)	60.07±6.85	59.12±6.57	P > 0.05
FS (%)	31.95±4.82	31.51±4.77	P > 0.05
SV (ml)	52.27±15.32	82.18±30.59	P < 0.0001

Discussion:

Beta (β)-thalassemia Major, the most common monogenic disorders in the world, is an inherited hemoglobinopathy characterized by severe chronic hemolytic anemia. The leading cause of mortality and morbidity in Beta thalassemia major, as a lethal hemolytic anemia, is cardiomyopathy attributed to regular blood transfusion and iron overload. Heart failure remains the leading cause of mortality, accounting for roughly two thirds of deaths in Beta (β)-thalassemia Major. Currently echocardiography is a valuable tool in evaluation of cardiac function and diagnosis of early cardiac involvement [1]. Another study was done in older ages that showed the mean right and left MPI in two groups had no significant difference statistically. It seems the difference in MPI is because of its occurrence in low age with an increase in both groups without statistical difference. In Ocal study, patients whom were treated with doxorubicin, MPI revealed a significant increase comparing with control group, due to an increase IRT and decrease ET without change in ICT [5]. Mounting MPI reveals systolic and diastolic ventricular dysfunction in Beta (β)-thalassemia Major; it means that an increased MPI represents a decrease in cardiac function [4, 5, and 6]. Another study also revealed that ICT is a significant parameter in evaluation of systolic function and IRT was a significant parameter in evaluation of diastolic function [11]. These parameters are related to active contracture stage and primary relaxation stage in ventricle. It seems that MPI is a significant parameter in diagnosis of cardiac dysfunction especially in children [12, 13]. MPI is a simple and repeatable and not related to heart rate and ventricular snap and volume index. The mean of IRT in group A and B did not show any significant difference. Increased IRT showed diastolic dysfunction reported in many studies in patients with Beta (β)-thalassemia Major, representing impairment in ventricular relaxation due to iron deposition. That, in turn, leads to gradual restrictive cardiomyopathy [14, 15]. Since IRT increased in lower age and this increase also occurs in upper age, so no meaningful increase between the two groups is suspected. Chafours et al. revealed that an increase in PEP/ET ratio in left ventricle occurred in 2/3 of patients and that was an obvious marker for changing diastolic ventricular function [16]. Hahalis et al. reported abnormal changes in β-thalassemic Major diastolic function; however filling pressure in left ventricle is

correlated with preload pressure. The study showed normal left ventricular function in asymptomatic β-thalassemic patients. But there is a change in right ventricular function similar to increase IRT and decrease DT in tricuspid valve that indicates the second marker has diagnostic value and the first marker shows early involvement of right ventricle [17]. The echocardiography finding is a significant marker in an increased right ventricular pressure, whereas the patients had lower age without any symptoms of heart failure. Another study on the patients with CHD and increased right ventricular pressure used echocardiographic findings with high value like angiography.

In conclusion, patients with Beta (β)-thalassemia Major even in low ages revealed diastolic dysfunction and less often systolic dysfunction. This trouble progresses in older age. Our study showed that in both under l0 year and over l0 year groups, MPI increased in the right and left ventricle however, DTI raised only in over l0-year-old patients. PEP/ET showed no significant difference in both the groups in left ventricle, however in right ventricle, the condition was not the same. This is due to an increased PEP/ET in right ventricule in both the groups; being an early finding of diastolic involvement, especially in right ventricle. Reduced DT occured with an increase of age and revealed cardiac involvement with a raise in age that is one of the earliest predictive outcomes of cardiac involvement. So we suggest serial echocardiograpy in asymptomatic major thalassemia in preschool age in order to provide early diagnosis of cardiac involvement.

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Conflict of interest: None declared

Refferences:

1. A Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and disease complications in thalassemia major. Ann N YAcad Sci. 1998; 850:227-231.
2. Olivieri NF, Weatherall DJ. Pediatric Hematology edited by Johnlilleyman Secindeaition.1999 :307-32.
3. Tiniakos DT G, Theodirakis GN, Katrisis DU, Toutvuzas PK. Myocarditis in B-Thalassemia major. Circulation. 1995; 9: 66-71.
4. Dimitrios TR. Association of heart failure in homozygous B thalassemia with major histocompatibility complex. Circulation. 1999; 100: 2074-8.
5. Ocal B, Oguz O, Karademir S, et al. Myocardial performance index combining systolic and diastolic myocardial performance in Doxorubicin, treated patients and its correlation to conventional Echo/Doppler indicies. Pediatric cardiology. 2002; 23: 522-527.
6. Watanabe M, Ono S, Tomomasa T, et al. Measurement of tricuspid annular diastolic velocities by doppler tissue imaging to asses right ventricular function in patients with CHD. Pediatric Cardiol. 2003; 24: 463-467.
7. Noori NM, Mehralizadeh S, Khaje A. Assessment of right ventricular function in children with congenital heart disease. Saudi Med J. 2008; 29: 1170-1174.
8. Tei C. New non-invasive Index for combined systolic and diastolic ventricular function. J Cardiol. 1995, 26: 133-37.
9. Ucar Ucar T, Ileri T, Atalay S, et al. Early detection of myocardial dysfunction in children with beta-thalassaemia major. Int J Cardiovasc Imaging. 2009; 25: 379–386.
10. Tei C, Nishimura RA, Seward JB, Tajik AJ. Non invasive Doppler, derived MPI correlation with simultaneous measurements of cardiac catheterization measurement. J Am Soc Echo. 1997, 10: 169-178.
11. Ong ML, Hatle LK, Lai VM, Bosco J. Noninvasive cardiac assessment in beta-thalassemia major. Int J Clin Pract. 2002; 56: 345-348.
12. [12] Lavine JS. Left ventricular diastolic function in idiopathic cardiomyopathy: Doppler, homodynamic correlations. Echocardiography. 1991; 8: 151-61.
13. Vaccari M, Crepaz R, Fortini M, et al. Left ventricular remodeling, systolic function, and diastolic function in young adults with beta -thalassemia intermediate. Chest. 2002 ; 121: 506-512.
14. Ghazuddine WS, Kazma HK, Nuwagyhid IA. Doppler characterization of ventricular diastolic function in β-thalassemia major. Evidence for an early stage of impaired relaxation. European journal of echocardiography. 2002; 3: 47-51.
15. Iarussi D,Diosalov G,Pergola V. Pulsed Doppler tissue imaging and myocardial function in thalassemia major. Heart Vessels. 2003; 18:1-6.
16. Chafour-AS. Echocardiographic evaluation of left ventricular function in children with congestive cardiomyopathy. AM-J-Cardiol.1979; 44: 1332-8.
17. Hahalis G, Manolis AS, Gerasimidou I, et al. Right ventricular diastolic function in beta-thalassemia majosr, echocardiography and clinical correlates. Am Heart J. 2001; 141: 428-434.