Original Article

Comparison of Right and Left Side Heart Functions in Patients with Thalassemia Major, Patients with Thalassemia Intermedia, and Control Group

Noormohammad Noori, MD[1], Mehdi Mohamadi, PhD[1], Kambiz Keshavarz, MD[2], Seyed Mostafa Alavi, MD[3], Maziar Mahjoubifard , MD[1*], Yalda Mirmesdagh, MD[3]

[1]*Children and Adolescent Health Research Center, Aliebne Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran.*
[2]*Imam Sajad Hospital, Yasuj University of Medical Sciences, Yasuj, Iran.*
[3]*Rajaei Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, Tehran, Iran.*

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Abstract

Background: *Heart disease is the main cause of mortality and morbidity in patients with beta thalassemia, rendering its early diagnosis vital. We studied and compared echocardiographic findings in patients with beta thalassemia major, patients with beta thalassemia intermedia, and a control group.*

Methods: *Eighty asymptomatic patients with thalassemia major and 22 asymptomatic cases with thalassemia intermedia (8-25 years old) were selected from those referred to Ali Asghar Hospital (Zahedan-Iran) between June 2008 and June 2009. Additionally, 80 healthy individuals within the same age and sex groups were used as controls. All the individuals underwent echocardiography, the data of which were analyzed with the Student t-test.*

Results: *The mean value of the pre-ejection period/ejection time ratio of the left ventricle during systole, the diameter of the posterior wall of the left ventricle during diastole, the left and right isovolumic relaxation times, and the right myocardial performance index in the patients with beta thalassemia major and intermedia increased significantly compared to those of the controls, but the other parameters were similar between the two patient groups. The mean values of the left and right pre-ejection periods, left ventricular end systolic dimension, and left isovolumic contraction time in the patients with thalassemia intermedia increased significantly compared to those of the controls. In the left side, myocardial performance index, left ventricular mass index, isovolumic contraction time, and deceleration time exhibited significant changes between the patients with thalassemia major and those with thalassemia intermedia, whereas all the echocardiographic parameters of the right side were similar between these two groups.*

Conclusion: *The results showed that the systolic and diastolic functions of the right and left sides of the heart would be impaired in patients with thalassemia major and thalassemia intermedia. Consequently, serial echocardiography is suggested in asymptomatic patients with beta thalassemia for an early diagnosis of heart dysfunction and proper treatment.*

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[*]**Corresponding Author:** ***Maziar Mahjoubifard,*** *Assistant Professor of Anesthesiology , Children and Adolescent Health Research Center, Aliebne Abitaleb Hospital, Zahedan University of Medical Sciences, Zahedan, Iran. Tel: +98 912 7308089. Fax: +98 541 3414103. E-mail: m_mahgoobifard@yahoo.com.*

Introduction

Thalassemia is the most common heterogeneous disease of the human being. It is a disease of high prevalence in Mediterranean, Indian, North Chinese, and Pacific populations. Every year, 100,000 neonates are born with hemoglobinopathies around the world. Recently, the quantity and quality of the life of these patients have been significantly improved by regular transfusion and iron chelating therapy.[1]

Heart disease is the main cause of mortality and morbidity in thalassemic patients. The two ends of the broad spectrum of the thalassemia range from asymptomatic carriers to patients with transfusion-related thalassemia major. A high cardiac output following chronic tissue hypoxia and increased pulmonary and systemic vascular resistance are the main factors which lead to heart disease in thalassemia intermedia. Pulmonary hypertension is an important manifestation of heart involvement and is specially presented by right-sided failure in patients with non-blood transfusion-related thalassemia intermedia. The cause of increased pulmonary vascular resistance in patients with beta thalassemia is multifactorial,[2] and the main causes of early death among these patients are systolic and diastolic dysfunction following hemosiderosis. Increased iron re-absorption via the gastrointestinal system is the main cause of hemosiderosis rather than iron overload following blood transfusion.[3]

Research shows that end systolic volume (ESV) and end diastolic volume (EDV) tend to rise significantly in asymptomatic patients with thalassemia intermedia compared to controls.[4] One study showed that iron overload had a major role in the progression of heart dysfunction in patients with beta thalassemia major, while a high cardiac output was the main causative factor in patients with thalassemia intermedia.[5] Aessopos et al.[6] reported bilateral ventricular dilatation and dysfunction in association with pulmonary hypertension as the major culprits for heart dysfunction in patients with sickle beta thalassemia. They also reported that heart disease was the major cause of death in patients with thalassemia and recommended echocardiography and cardiac magnetic resonance imaging (MRI) as useful tools in the early evaluation of cardiac involvement in those patients.[7] Danish et al.[8] suggested tissue Doppler imaging as a safe, simple, and repeatable method for patients with beta thalassemia major, not least in countries with a high incidence of thalassemia, compared to the MRI-T2 method.

Our study compared echocardiographic variables in patients with thalassemia major, patients with thalassemia intermedia, and a control group.

Methods

This study is a case-control research and complies with the current ethical considerations. Informed consent was obtained from each patient included in the study, and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's Human Research Committee. Beta thalassemia major patients and cases with thalassemia intermedia were selected from patients who referred to Ali-Asghar Hospital in Zahedan University of Medical Sciences between June 2008 and June 2009.

There are 1900 registered thalassemic patients in the south east of Iran. Of these patients,750 patients have registered records in the Center for Special Diseases of Ali-Asghar Hospital, Zahedan, Iran. In terms of age, 383 of these patients are older than 8 years. Among those 750 patients, there are only 30 cases with thalassemia intermedia, precluding a study on a larger number of patients with thalassemia intermedia.

After history taking, physical examination, chest radiography, and electrocardiography (ECG), patients with mitral valve dysfunction, hypertension, structural diseases of the heart, heart failure, metabolic diseases, endocrine or renal disorders, pulmonary hypertension, cardiac drug consumption (except for chellators), hemoglobin before transfusion less than 9 g/dl, history of irregular transfusion before two years of age, and duration of chelating therapy less than5 years were excluded from the study. Therefore, 8 patients with thalassemia intermedia were omitted: 2 patients with pulmonary hypertension; 4 patients less than8 years old; and 2 patients over 25 years of age. Finally, 80 patients with thalassemia major and 22 patients with thalassemia intermedia (hemoglobin > 9g/dl in both groups) were recruited into the study. The age of the patients was between 8 and 25 years old.

After the registration of the patients' age, sex, and blood pressure, the whole study population underwent two-dimensional and Doppler echocardiography by one cardiologist, using the Challenge 7000 Instrument with 2.5, 3.5, and 5-MHz transducers (made in Italy). This device was equipped with ECG monitoring. In addition, 80 healthy individuals, between 8 and 25 years of age, who referred for routine examination or follow-up, were chosen and matched for sex with the case groups as controls.

The means of all necessary echocardiographic parameters, namely posterior wall dimension in systole (PWDS) and posterior wall dimension in diastole (PWDD) of the left side, acceleration time (AT), deceleration time (DT), myocardial performance index (MPI), peak E (early mitral valve flow velocity)/peak A (late mitral valve flow velocity) velocity (E/A ratio), isovolumic relaxation time (IRT), isovolumic contraction time (ICT) of both sides, ejection fraction (EF), fractional shortening (FS), interventricular septal dimension in diastole (IVSDD), interventricular septal dimension in systole (IVSDS), left ventricular end-diastolic dimension (LVDD), and left ventricular end-systolic dimension (LVSD) of the left side, were measured in each of the three cardiac

cycles. Additionally, posterior wall dimension in systole of the left ventricle (LVPWS), posterior wall dimension in diastole of the left ventricle (LVPWD), interventricular septal dimension in systole (IVSS), EF, and FS were measured via M-mode echocardiography. Also, the velocity of the blood flow through the heart valves was measured with pulsed Doppler, and the pre-ejection time, ejection time (ET), peak A velocity (A), peak E velocity (E), E/A ratio, and pre-ejection period/ejection time ratio (PEP/ET) of both sides were measured with pulsed Doppler echocardiography.[9]

The sample volume was positioned at the tips of the tricuspid and mitral valve leaflets in the apical four-chamber view to enable the measurement of (a), which is the time of interval between the end and the start of trans-mitral and trans-tricuspid flow. The sample volume was thereafter relocated to the left ventricular outflow tract just below the aortic valve (apical five-chamber view) so as to measure (b), which is the left ventricular ejection time. The right ventricular outflow velocity pattern was also recorded from the parasternal short-axis view with the Doppler sample volume positioned just distal to the pulmonary valve for the measurement of (b).

MPI or the Tie Index was calculated as: a-b/b = IRT + ICT/ET.[9]

The left ventricular mass index (LVMI) was also calculated by the following formula:

$LVMI = 0.8\ (1.04)\ (LVIDD + PWTD + IVSTD)^3 - (LVIDD)^3 + 0.6$.[10]

All the parameters in the above formula were measured in the M-mode view and in diastole and were utilized for left ventricular mass evaluation.

Finally, the a statistical method for making simultaneous comparisons between two or more means (ANOVA) was employed for the normally distributed variables and the Kruskal-Wallis test was used for the non-normally distributed variables. Multiple comparisons between the groups were performed with the Tukey test. A p value < 0.05 was considered statistically significant.

Results

Eighty patients with beta thalassemia major and 22 patients with thalassemia intermedia, between 8 and 25 years old, as well as 80 healthy individuals within the same age range were recruited in this study. There was no significant difference in terms of the mean age between the three groups (p value = 0.875); however, the other demographic parameters (Table 1) were significantly different between the studied groups. The most remarkable of these factors was systolic blood pressure, which exhibited a significant difference between all the groups (p value < 0.001).

Based on Table 2 and Table 3, depicting the echocardiographic parameters of the left heart, the mean interventricular septum diameter in diastole and the mean posterior ventricular wall diameter in diastole were significantly increased in both of the patient groups compared to those in the controls (p value = 0.018 and p value = 0.018,

Table 1. Demographic parameters in the patients with thalassemia major, patients with thalassemia intermedia, and controls

Parameters	Groups	Mean	Standard Deviation	P value	Tukey test	P value
Age (y)	Major	16.26	2.98	0.875	vs. Intermedia	0.956
	Intermedia	16.50	5.82		vs. Control	0.937
	Control	16.07	2.98		vs. Major	0.865
Height (cm)	Major	146.71	9.48	< 0.001	vs. Intermedia	0.011
	Intermedia	137.87	17.86		vs. Control	0.010
	Control	152.60	13.52		vs. Major	< 0.001
Weight (kg)	Major	36.60	6.96	0.012	vs. Intermedia	0.922
	Intermedia	35.65	11.36		vs. Control	< 0.001
	Control	54.01	5.84		vs. Major	< 0.001
Hemoglobin (g/dl)	Major	10.23	1.08	< 0.001	vs. ntermedia	0.952
	Intermedia	10.16	0.88		vs. Control	< 0.001
	Control	14.63	0.84		vs. Major	< 0.001
Systolic BP (mm Hg)	Major	90.31	7.80	< 0.001	vs. Intermedia	0.223
	Intermedia	96.95	10.08		vs. Control	< 0.001
	Control	100.58	23.16		vs. Major	< 0.001
Diastolic BP (mm Hg)	Major	64.31	5.72	< 0.001	vs. Intermedia	0.001
	Intermedia	70.90	7.50		vs. Control	< 0.884
	Control	70.18	6.57		vs. Major	< 0.001

BP, Blood pressure

respectively). In both of the thalassemia groups, the mean left IRT was significantly higher than that of the healthy controls (p value < 0.001).

In the left side, MPI, left ventricular myocardial index (LVMI), ICT, and DT were statistically different between the patients with major thalassemia and those with thalassemia intermedia (p value < 0.001 for all the parameters), while the other parameters of the left side were similar between the two patient groups (Tables 2 and 3).

In the thalassemia major group, the mean DT was significantly less than that of the other groups (p value < 0.001). Comparisons of the other parameters between the study groups are presented in Tables 2 and 3.

Based on the echocardiographic parameters of the right heart (Table 4), the mean MPI and IRT were significantly different between the patient groups and the control group (p value < 0.001, p value < 0.001, respectively). These parameters were higher in the patients with thalassemia intermedia than in the other groups. The mean PEP/ET ratio and the right ventricular PEP increased significantly in the patients with thalassemia major compared to the controls (p value < 0.001). The mean ET and AT did not show significant differences between the study groups. Overall, no significant differences could be detected between the two patient groups on the basis of the right echocardiographic parameters.

Discussion

The major causes of morbidity and mortality in beta thalassemic patients are cardiomyopathy and finally heart failure. Dilated cardiomyopathy leads to ventricular dilatation and impaired contraction. Restrictive cardiomyopathy interferes with left ventricular filling, which finally gives rise to pulmonary hypertension and right heart failure. Myocardial iron deposition and immuno-inflammatory processes are known as important causes of cardiac involvement in such patients.[11]

In this study, the mean age and mean sex were not significantly different between the three study groups,

Table 2. Echocardiographic parameters of the left heart in the patients with thalassemia major, patients with thalassemia intermedia, and controls

Parameters	Groups	Mean	Standard deviation	P value	Tukey test	P value
	Major	0.60	0.13		vs. Intermedia	< 0.001
MPI	Intermedia	0.64	0.12	0.001	vs. Control	< 0.001
	Control	0.52	0.08		vs. Major	< 0.001
	Major	86.65	29.98		vs. Intermedia	0.002
LVMI (g/m^2)	Intermedia	110.05	40.86	0.001	vs. Control	0.065
	Control	76.53	22.06		vs. Major	< 0.001
	Major	98.69	10.87		vs. Intermedia	0.072
PEP (ms)	Intermedia	936.31	9.40	0.001	vs. Control	0.443
	Control	90.35	9.46		vs. Major	< 0.001
	Major	256.95	26.27		vs. Intermedia	0.533
ET (ms)	Intermedia	250.80	25.45	0.113	vs. Control	0.367
	Control	262.07	20.70		vs. Major	0.125
	Major	0.38	0.06		vs. Intermedia	0.576
PEP/ET	Intermedia	0.36	0.03	0.001	vs. Control	< 0.001
	Control	0.34	0.04		vs. Major	0.064
	Major	6.94	1.44		vs. Intermedia	0.328
IVSD (mm)	Intermedia	7.39	1.76	0.018	vs. Control	0.046
	Control	6.44	1.02		vs. Major	0.009
	Major	4.43	1.10		vs. Intermedia	0.700
LVPWD (mm)	Intermedia	4.61	1.40	0.018	vs. Control	0.010
	Control	3.99	0.49		vs. Major	0.018
	Major	10.20	1.82		vs. Intermedia	0.242
IVSS (mm)	Intermedia	10.87	2.52	0.033	vs. Control	0.383
	Control	9.84	1.32		vs. Major	0.037
	Major	4.46	1.22		vs. Intermedia	0.539
LVPWS (mm)	Intermedia	4.72	1.50	0.274	vs. Control	0.103
	Control	4.13	0.48		vs. Major	0.045
	Major	47.64	4.84		vs. Intermedia	0.704
LVEDD (mm)	Intermedia	48.72	6.93	0.790	vs. Control	0.730
	Control	48.31	5.98		vs. Major	0.951
	Major	32.62	4.09		vs. Intermedia	0.827
LVESD (mm)	Intermedia	31.78	5.36	0.426	vs. Control	0.940
	Control	32.93	7.42		vs. Major	0.699

MPI, Myocardial performance index; LVMI, Left ventricular mass index; PEP, Pre-ejection period; ET, Ejection time; PEP/ET, Pre-ejection period/ ejection time ratio; IVSD, Interventricular septal dimension in diastole; LVPWD, Left ventricular posterior wall dimension in diastole; IVSS, Interventricular septal dimension in systole; LVPWS, Left ventricular posterior wall dimension in systole; LVEDD, Left ventricular end – diastolic dimension; LVESD, Left ventricular end- systolic dimension

Table 3. Echocardiographic parameters of the left heart in the patients with thalassemia major, patients with thalassemia intermedia, and controls

Parameters	Groups	Mean	Standard Deviation	P value	Tukey test	P value
EF (%)	Major	59.12	6.57	0.001	vs. Intermedia	0.277
	Intermedia	61.59	7.12		vs. Control	0.001
	Control	65.46	6.63		vs. Major	0.044
FS (%)	Major	31.51	4.77	0.001	vs. Intermedia	0.161
	Intermedia	33.68	5.26		vs. Control	< 0.001
	Control	36.17	4.94		vs. Major	0.091
Diameter Ao (mm)	Major	23.42	3.08	0.543	vs. Intermedia	0.221
	Intermedia	24.26	4.08		vs. Control	0.996
	Control	23.63	2.95		vs. Major	0.200
Diameter LA (mm)	Major	27.93	3.69	0.203	vs. Intermedia	0.512
	Intermedia	29.45	3.81		vs. Control	0.906
	Control	27.89	3.81		vs. Major	0.680
LA/Ao	Major	1.20	0.18	0.454	vs. Intermedia	0.913
	Intermedia	1.22	0.17		vs. Control	0.662
	Control	1.18	0.17		vs. Major	0.593
ICT (ms)	Major	30.04	15.46	0.001	vs. Intermedia	< 0.001
	Intermedia	43.68	18.78		vs. Control	0.635
	Control	28.00	11.10		vs. Major	< 0.001
IRT (ms)	Major	108.67	23.29	0.001	vs. Intermedia	0.950
	Intermedia	110.09	16.49		vs. Control	< 0.001
	Control	96.32	15.26		vs. Major	0.010
AT (ms)	Major	72.75	25.31	0.583	vs. Intermedia	0.089
	Intermedia	61.86	16.33		vs. Control	0.284
	Control	78.17	20.18		vs. Major	0.504
DT (ms)	Major	114.11	19.13	0.001	vs. Intermedia	0.024
	Intermedia	126.09	18.78		vs. Control	< 0.001
	Control	125.37	18.59		vs. Major	0.986
E/A	Major	2.04	2.08	0.415	vs. Intermedia	0.094
	Intermedia	1.59	0.23		vs. Control	0.345
	Control	1.92	0.50		vs. Major	0.008

EF, Ejection fraction; FS, Fractional shortening; Ao, Aorta; LA, Left atrium; LA/Ao, Left atrium/aorta ratio; ICT, Isovolumic contraction time; IRT, Isovolumic relaxation time; AT, Acceleration time; DT, Deceleration time; E /A ratio, peak E (early mitral valve flow velocity)/peak A (late mitral valve flow velocity) ratio

Table 4. Echocardiographic parameters of the right heart in the patients with thalassemia major, patients with thalassemia intermedia, and controls

Parameters	Groups	Mean	Standard Deviation	P value	Tukey test	P value
MPI	Major	0.52	0.12	0.001	vs. Intermedia	0.333
	Intermedia	0.62	0.13		vs. Control	< 0.001
	Control	0.40	0.06		vs. Major	< 0.001
PEP (ms)	Major	96.08	10.15	0.013	vs. Intermedia	0.196
	Intermedia	92.10	11.62		vs. Control	0.013
	Control	91.78	8.18		vs. Major	0.989
ET (ms)	Major	259.86	27.03	0.374	vs. Intermedia	0.407
	Intermedia	251.90	29.81		vs. Control	0.991
	Control	260.37	23.17		vs. Major	0.362
PEP/ET	Major	0.36	0.05	0.015	vs. Intermedia	0.953
	Intermedia	0.36	0.06		vs. Control	0.013
	Control	0.34	0.03		vs. Major	0.255
ICT (ms)	Major	32.70	17.11	0.234	vs. Intermedia	0.333
	Intermedia	38.44	20.89		vs. Control	0.360
	Control	36.33	15.12		vs. Major	0.861
IRT (ms)	Major	125.96	23.09	0.001	vs. Intermedia	0.496
	Intermedia	131.13	20.92		vs. Control	< 0.001
	Control	107.02	12.97		vs. Major	< 0.001
AT (ms)	Major	73.20	25.21	0.636	vs. Intermedia	0.510
	Intermedia	67.68	23.04		vs. Control	0.185
	Control	67.43	13.84		vs. Major	0.999
DT (ms)	Major	111.71	27.10	0.001	vs. Intermedia	0.051
	Intermedia	125.86	26.04		vs. Control	0.001
	Control	134.55	22.19		vs. Major	0.319
E/A	Major	1.23	0.32	0.001	vs. Intermedia	0.441
	Intermedia	1.33	0.37		vs. Control	< 0.001
	Control	1.51	0.33		vs. Major	0.063

MPI, Myocardial performance index; PEP, Pre-ejection period; ET, Ejection time; PEP/ET, Pre-ejection period/ejection time ratio; ICT, Isovolumic contraction time; IRT, Isovolumic relaxation time; AT, Acceleration time; DT, Deceleration time; E /A ratio, peak E (early mitral valve flow velocity)/peak A (late mitral valve flow velocity) ratio

whereas the mean weight and mean height were different significantly, which is similar to the results of the Bosi et al.,[12] Aessopos et al.,[13] and Karimi et al. studies.[14]

The mean hemoglobin and mean hematocrit were significantly different between the patient groups and the control group; however, these parameters were similar between the two thalassemic groups. Other investigations have shown similar results.[4, 12, 13]

Decreases in systolic and diastolic blood pressures were significant in our two patient groups compared to the control group; these results chime in with the findings of the Bosi et al.,[12] and Vaccari studies,[15] which reported that stroke volume, cardiac output, left ventricular end systolic dimension and left ventricular end diastolic dimension volumes, and left ventricular mass would increase in thalassemic patients with no symptoms of cardiac involvement. All such findings have also been reported by a large number of investigators.

Stakos et al.[16] reported that systolic and diastolic blood pressures were not different in thalassemic patients with no iron deposition in the cardiac tissue (measured via MRI) compared to healthy individuals. They also revealed iron overload in the heart tissue as the main cause of the drop in blood pressure in patients with thalassemia. There is also some evidence supporting increased left ventricular mass and aortic wall thickening in asymptomatic patients, caused by iron overload and iron deposition in the cardiac tissue.

Patients with beta thalassemia major even in younger ages reveal diastolic and less often systolic dysfunction. These problems progress in older ages. Our study demonstrated that in the patients under 10 years old and also in those over than 10 years of age, MPI increased in the right and left ventricles. Nevertheless, tissue Doppler imaging also had an increase in the patients over 10 years old. Left PEP/ET showed no significant difference between both thalassemic groups, whereas the condition was not the same in the right side. Early diastolic involvement, especially in the right side, causes increased PEP/ET. During life, in asymptomatic thalassemic patients with cardiac involvement, DT gradually reduces. As a result, decreased DT is known as an important predictive parameter in the early diagnosis of cardiac involvement.[9, 17, 18]

Ocal et al.[19] reported that the mean left MPI significantly increased in the patients with thalassemia treated with Doxorubicin compared to a control group. They also demonstrated that increased IRT and decreased ET without any change in ICT were the main causes of increasing MPI. In the present study, the mean ICT showed significant differences between the two patient groups. Increase in MPI is drawn upon as a sign of the coincidence of systolic and diastolic dysfunction. An increase in IRT (an index for diastolic function) is a marker of relaxation impairment due to iron deposition, which gradually leads to restrictive cardiomyopathy. Restrictive cardiomyopathy is known as the earliest sign of left ventricular diastolic dysfunction.[15, 20, 21]

As the Hahalis and colleagues study[22] showed, right ventricular filling disorder in patients with thalassemia major is caused by increased IRT, even though in the left side, increased preload is known as the main cause of filling disorder. Decreased DT in the tricuspid valve has been used as a good predictor of cardiac dysfunction. These data are similar to our findings.

In the current study, LVMI, an effective factor in ventricular compliance, increased significantly and it was deemed the cause of diastolic dysfunction in the patients with thalassemia. An increase in LVMI has been also reported by Bosi et al.,[12] Kucuk et al.,[23] and Noori.[24] An increase in the ventricular mass was also shown in the Aldouris study.[25]

An increase in the PEP/ET ratio in the patients with thalassemia major and those with thalassemia intermedia compared to the ratio in the controls demonstrated early changes in the ventricular diastolic function. This was similar to the results of Hahalis et al.,[15] Bosi et al.,[12] and Vaccari et al.,[22] who described similar reductions in the EF and FS in patients with thalassemia compared to the controls.

Decreased DT is the best predictive value in patients with thalassemia and it is also the most important factor in the prognosis of such patients.[26] Based on our research, the E/A ratio showed a decrease in the thalassemic patients compared to the controls. Iarassi[21] also described similar results. Interventricular septal dimension during systole and diastole as well as LVPWS increased significantly in our thalassemic patients compared to our controls. These results are different from those in the Karimi study,[14] but similar to the ones in the Stakos et al. study.[16]

The study of Ismaeel et al.[27] showed that the evaluation of the right ventricular performance would be beneficial in future studies in order to localize the pathology in intermedia thalassemic patients with cardiomyopathy. Amoozegar[28] reported that pulsed Doppler and pulsed tissue Doppler imaging were more sensitive than M-mode and two-dimensional echocardiography in beta thalassemic and intermedia patients, and Bilge et al.[29] argued that tissue Doppler imaging assessment by echocardiography was more useful in the early detection of left ventricular dysfunction than conventional echocardiography.

Conclusion

Our study revealed that despite a disruption in the left and right diastolic functions in the patients with thalassemia major and intermedia, only some of the echocardiographic parameters of the left side changed significantly, whereas all the echocardiographic parameters of the right side remained without significant differences. A good knowledge of these differences would help us better evaluate patients with thalassemia major and intermedia with a view to an early detection of cardiac involvement and early commencement

of treatment before the progression of the disease. Serial echocardiography is, therefore, recommended for an early detection of cardiac dysfunction even in asymptomatic patients with thalassemia major and intermedia.

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