

Pulsed and Tissue Doppler Echocardiographic Changes in Patients with Thalassemia Major

Taysir S. Garadah¹, Salah Kassab², Najat Mahdi¹, Ahmed Abu-Taleb³ and Anwer Jamsheer¹

¹Cardiac Unit, Salmaniya Medical Complex, Ministry of Health, Kingdom of Bahrain. ²Royal College of Surgeons in Ireland, Medical University of Bahrain, Kingdom of Bahrain. ³Department of Community and Family Medicine, College of Medicine and Medical Sciences, Arabian Gulf University, Kingdom of Bahrain. Email: garadaht@hotmail.com

Abstract

Background: Doppler echocardiographic studies of left ventricle (LV) systolic and diastolic function in patients with β -Thalassemia Major (β -TM) had shown different patterns of systolic and diastolic dysfunction.

Aim: This cross-sectional study was designed to study the LV systolic and diastolic function in patients with β -TM using Pulsed Doppler (PD) and Tissue Doppler (TD) echocardiography.

Methods: All patients were evaluated clinically and by echocardiography, The study included patients with β -TM (n = 38, age 15.7 ± 8.9 years) compared with an age-matched control group (n = 38, age 15.9 ± 8.9 years). The pulse Doppler indices were normalized for age and heart rate.

Results: Compared with control patients, M-Mode showed that patients with β -TM have thicker LV septal wall index (0.659 ± 0.23 vs. 0.446 ± 0.219 cm, $P < 0.001$), posterior wall index (0.659 ± 0.235 vs. 0.437 ± 0.214 cm, $P < 0.01$), and larger LVEDD index is (3.99 ± 0.48 vs. 2.170 ± 0.57 mm, $P = 0.035$). Pulsed Doppler showed high LV trans-mitral E wave velocity (70.818 ± 10.139 vs. 57.532 ± 10.139 , $p = 0.027$) and E/A ratio (1.54 vs. 1.23 , $P < 0.01$). The duration of Deceleration time (DT) and isovolumic relaxation time (IVRT) were significantly shorter in patients with β -TM (150.234 ± 20.023 vs. 167.123 ± 19.143 msec, $P < 0.01$) and (60.647 ± 6.77 vs. 75.474 ± 5.83 msec, $P < 0.001$), respectively. The ratio of transmitral E wave velocity to the tissue Doppler E wave at the basal septal mitral annulus E/Em' was significantly higher in β -TM group (14.024 ± 2.29 vs. 12.132 ± 1.82 , $P < 0.01$). The Tissue Doppler systolic velocity (Sm) and the early diastolic velocity (Em) were significantly lower in β -TM group compared to control (4.31 ± 1.2 cm/s vs. 6.95 ± 2.1 , $P < 0.01$ and 4.31 ± 2.7 cm/s vs. 5.82 ± 2.5 , $P < 0.01$) respectively. The tricuspid valve velocity was significantly higher than controls (2.993 ± 0.569 vs. 1.93 ± 0.471 m/sec, respectively, $P < 0.01$). However, the LVEF% and fractional shortening were normal with no significant difference in both groups.

Conclusion: In this study, patients with β -thalassemia major compared with controls, have significantly thicker LV wall, and larger LV cavity and LV diastolic filling indices suggestive of restrictive pattern with a higher tricuspid valve velocity. These data showed that left ventricle diastolic indices are compromised initially in patients with β -thalassemia major.

Keywords: beta-thalassemia major, pulsed Doppler, tissue Doppler echocardiography, Bahrain

Clinical Medicine Insights: Blood Disorders 2010:3 1–8

This article is available from <http://www.la-press.com>.

© the author(s), publisher and licensee Libertas Academica Ltd.

This is an open access article. Unrestricted non-commercial use is permitted provided the original work is properly cited.



Introduction

Beta-Thalassemia Major (β -TM) is a genetic blood disorder caused by reduced synthesis of β -globin chain. The consequences of chronic anemia include growth retardation, bone marrow expansion, extramedullary hematopoiesis, splenomegaly, greater intestinal iron absorption, hypercoagulability and higher susceptibility to infection.^{1,2} Patients are usually maintained on continuous blood transfusion regimens to keep hemoglobin levels close to normal and allow adequate tissue oxygenation. Because of the hemolysis and repeated blood transfusion, β -TM is associated with iron overload.³ The iron deposition could adversely affect both the structure and function of the heart. Previous studies indicated that patients with β -TM develop ventricular systolic dysfunction leading to congestive heart failure.⁴

LV Diastolic filling pattern has been classified into normal, restrictive and abnormal relaxation pattern on the basis of early filling E wave and late filling A wave on LV trans-mitral diastolic filling.⁵ The filling pattern depends on the degree of predominance of the abnormal active relaxation or altered wall stiffness. The restrictive pattern is characterized by high E wave velocity, decreased A wave and shortened Deceleration Time (DT) with high E/A ratio >1.29 .^{6,7} In one report, the DT of E wave velocity of <180 msec predicted LA pressure >20 mmHg.⁸

The tissue Doppler echocardiography (TD) is a non-invasive technique that can detect regional myocardial diastolic dysfunction even in early phases of cardiac injury.⁹ The tissue velocity at the basal septum of mitral annulus has been evaluated as a marker of myocardial stiffness, and in one report it was suggested that the ratio of early diastolic filling wave (E) to mitral annulus tissue Doppler (TD) velocity (E/Em) correlates positively with the LV end-diastolic pressure (LVEDP), as the E/Em >15 predicts high LVEDP >15 mmHg.¹⁰ In one study, the TD early diastolic velocity Em and the systolic wave Sm were reduced in hypertensive patients.¹¹

The National Student Screening Project in Bahrain indicated that the prevalence of β -TM in high school students is 0.09%, with β -thalassemia trait representing 2.9% of the sample population.¹² Similar findings were observed in a study targeting subjects seeking premarital screening in Bahrain.¹³ The echocardiographic changes in patients with β -TM had not been

previously studied in Bahrain. Evaluation of cardiac function by echo Doppler can assist in staging the disease progression and may help to prevent further cardiac damage by applying intense chelating regimens and combination therapy.¹⁴

Thus, the aim of this study is to use pulsed Doppler echo (PD) and TD in assessing myocardial systolic and diastolic functions in young patients with β -TM in Bahrain.

Subjects and Methods

This study included 38 patients with transfusion-dependent β -TM and 38 patients with no thalassemia were used as a control group. The study was conducted during the interval from January 2009 to June 2009. A constitutional ethical approval was obtained for the study.

Inclusion and Exclusion Criteria

Selection was consecutive from patients who are on regular follow-up in Pediatric Hematology clinic at Salmaniya Medical Complex (SMC) in Bahrain. Patients were included if they had a follow-up for more than 3 years at SMC, with a confirmed diagnosis of β -TM based on electrophoresis. Selected patients have been receiving blood transfusions every three weeks to maintain hemoglobin levels above 9 g/dl since infancy. All patients had also been receiving desferrioxamine as a chelating therapy (25–50 mg/kg body weight by subcutaneous infusion with an infusion pump for 8–12 h) regularly for at least one year. In the control group, patients were healthy with no renal or hepatic disease, no valve disease, normal LV function on echo and negative blood tests for thalassemia. They were selected from the pool of healthy patients who are referred for evaluation of systolic murmur and turned to have normal echo. The time frame for the echo Doppler and the blood test is one week. The control patients' age was counted to match the study patients. The blood samples in the control group and echo test were carried out in the week prior the blood transfusion. Patients were excluded if they have end stage renal disease with creatinine clearance of $<30\%$ of normal, severe liver disease, diabetes mellitus, hypoparathyroidism, advanced heart failure, hypertrophic cardiomyopathy or if the patient is taking active cardiac medications. Each patient in the study had a clinical and haematological data file including



duration of disease, cardiovascular assessment for pulse rate, jugular venous pressure wave, apex beat, blood pressure, heart sounds and presence or absence of murmur, ankle edema and body weight. Data of the blood hemoglobin, serum Ferritin and creatinine concentrations were all recorded.

Doppler echocardiography

Each patient in the study and control group had the echo examination by 2.5–5 MHz transducer, using HP E33 echo machine. The echocardiography test and the values measured were performed by an echo technologist who was blinded for the clinical condition of the patient. Data were reported as an average of at least five cardiac cycles. Another echo technician analyzed the data blindly and the data were taken as an average of the two readings. The acquisition sector were according to the criteria of the American Society of Echocardiography.¹⁵ Each patient enrolled in the study had echocardiographic measurements including M Mode, 2D echo, color flow, systolic and LV diastolic transmitral indices and tissue Doppler evaluation of the septal mitral annulus.

The M mode measurement study of the left ventricle was performed under 2D echo controls. The septal and posterior wall thickness in cm, LV cavity diameter in diastole and systole were measured in long parasternal view with M-Mode beam just distal to the tips of mitral leaflet and at the papillary muscle level in short axis (mid cavity). The left ventricle mass was calculated as previously reported.¹⁶ Pulsed Doppler acquired in the apical view, while patients in the partial left lateral decubitus position during end of expiration, with sample volume situated between the mitral leaflet tips. The peak velocity of early rapid filling (E velocity) and the peak velocity of the atrial filling (A velocity) were recorded and the E/A ratio was calculated. The time of E wave deceleration was measured as the interval between the peak E velocity and the point at which the descending segment crosses the zero line. The isovolumic relaxation time is measured in the apical four chambers as the time in ms from the aortic valve closure and the onset of the mitral flow. The tissue Doppler velocity is taken at the septal mitral annulus in the apical view. The early diastolic velocity (Em), the systolic velocity (Sm), and the ratio of E/Em were all measured. The velocity tracing was read as a mean of five measurements.

The intra-observer variability between the pulsed Doppler measures was assessed in 20 thalassemia patients who were examined twice, with one week apart. The mean differences \pm SD were -0.002 ± 0.035^{-1} m/s for peak E velocity, -0.004 ± 0.061 m/s⁻¹ for A velocity and 0.017 ± 0.164 for the E/A velocity ratio.

The M mode echo parameters including the left ventricle (LV) septal wall thickness, posterior LV wall thickness, mid and basal LV cavity dimension in systole and diastole as well as the LV end diastolic volume. LV fractional shortening (FS) and LV ejection fraction percentage (LVEF %) were measured using Teicholz formula: $V = \{7.0/(2.4 + D)*D^3\}$.

The left ventricle diastolic filling indices included early diastolic wave (E wave), late diastolic wave (A wave), deceleration time of E wave (DT), isovolumic relaxation time (IVRT) and E wave to A wave (E/A) ratio were all measured with the sample volume at the tip of the mitral leaflets in the apical view. The IVRT, DT and all Pulsed Doppler velocities and ratios were corrected for age and heart rate of each patient in the study. The tricuspid valve velocity in systole in cm/s was measured in apical view. The tissue Doppler velocity of the septal mitral annulus, early filling E wave velocity (Em), the calculated E/Em ratio and the systolic wave (Sm) were all were recorded as a mean of five readings and corrected for age and heart rate. The septal mitral annulus ring was chosen to measure the tissue Doppler rather than the lateral because the changes in left ventricular hypertrophy and hypertension are more pronounced and marked in the mitral annulus rather than in the other wall.^{17,18}

Statistical analysis

All data were entered and analyzed using the Statistical Package of Social Sciences (SPSS) version 17.0. Data are presented as mean \pm SD. Unpaired *student t-test* was used to analyze the differences between the variables in the control group and patients with β -TM. The M-mode dimensions of the LV were adjusted and indexed for Body Surface Area (BSA) of each patient in both groups. Linear regression analysis was used to assess the linear relationship between the serum ferritin as the independent variable and ratio of the transmitral early velocity of pulsed Doppler (E) to the tissue Doppler velocity (Em) of septal mitral annulus. Regression lines of (heart rate and age) for each variable in the study



Table 1. Demographic characteristics of thalassemia patients (n = 38, β -TM) and healthy controls (n = 38) in the study. Data are presented as mean \pm SD. P value < 0.05 is considered statistically significant.

Parameter	β -TM	Control	P-value
Age (Years)	15.92 \pm 8.92	15.79 \pm 8.94	0.92
Male	23 (60%)	22(57%)	0.75
Weight (kg)	25.6 \pm 8.30	33.00 \pm 7.25	0.034
Height (cm)	133.4 \pm 9.64	144.3 \pm 9.62	0.001
BSA	1.02 \pm 0.2	1.15 \pm 0.2	0.001
Systolic pressure (mmHg)	128.16 \pm 12.03	123.34 \pm 12.15	0.108
Diastolic pressure (mmHg)	70.71 \pm 8.23	69.61 \pm 7.06	0.101
Heart rate (BPM)	92 \pm 6.99	67.58 \pm 7.26	0.001
Serum Ferritin (μ g/L)	1628.6 \pm 243.8	230 \pm 22	0.001
Serum Creatinine (μ mol/l)	75.23 \pm 11.13	80.8 \pm 10.12	0.076
Hemoglobin (gm/dl)	9.5 \pm 0.4	10.2 \pm 0.5	0.065

Abbreviation: BSA, body surface area.

were analyzed and the slope of each variable was calculated. The pulsed and Tissue Doppler indices were calculated for E/Em ratio normalization using the following equation:

$$\{E/Em \text{ ratio adjusted} = E/Em \text{ observed} + 0.01709 \\ \times (\text{age} - \text{mean age}) + 0.07313 \\ \times (\text{heart rate} - \text{mean heart rate}),$$

where the slope of the age = (0.01709) and the slope of HR = -0.07313 .^{19,20}

Each parameter was adjusted for age and heart rate and the mean value in each group was measured and compared with the control group. All other pulsed Doppler and tissue Doppler for systolic and diastolic functions were corrected or normalized for age and heart rate such as: E wave velocity, A wave velocity, DT, IVRT, Em, E/Em, and Sm. Differences between groups were considered statistically significant at a probability value of <0.05.

Results

The demographic data of β -TM patients and the healthy controls are summarized in Table 1. The β -TM patients had a significant lower body surface area compared with control patients, (1.15 \pm 0.2 vs. 1.01 \pm 0.2, P < 0.05). The mean age for β -TM was 15.7 \pm 8.94 year (range; 7–25), while the mean age of the control group was 15.9 \pm 8.30 year (range; 6–24). The gender distribution between the two groups was comparable. The systolic and diastolic pressures values were comparable in both groups. In β -TM the heart rate was significantly higher of 27% in β -TM (92 \pm 6.99 vs. 67.58 \pm 7.26, P < 0.001) compared with

control group. The serum ferritin was significantly higher in the β -TM group compared with the control group (P < 0.001). No significant differences in serum creatinine and hemoglobin level were found between both groups.

Echo doppler findings

Table 2 summarized the raw (un-indexed) pulsed Doppler data and M-mode values in both control and β -TM groups. The β -TM group showed significantly higher LV wall thickness manifested by significantly thicker posterior wall and interventricular septum (P < 0.001 in both). The LV dimensions at the end of systole (LVESD) and diastole (LVEDD) were significantly larger in β -TM compared with control group. The left ventricle mass was significantly higher (172 \pm 65.3 vs. 87 \pm 14.8, P < 0.001) in β -TM group compared with the control. The Doppler indices of the LV diastolic filling showed significantly higher E wave, and E/A ratio in the β -TM group compared to control while significantly shorter interval of DT time of E wave and IVRT.

Table 3 showed the mean of Tissue Doppler indices taken at septal mitral annulus ring of the LV after being corrected for age and heart rate in each patient in the study.

The ratio of transmitral E wave velocity to TD (Em) of the septal mitral annulus (E/Em) was significantly higher in the β -TM group compared to the control group (P < 0.01), the early diastolic velocity (Em) was significantly lower in β -TM group. Likewise, the systolic wave velocity (Sm) was significantly lower in the β -TM group compared to the control. However,

**Table 2.** Unindexed Echocardiographic findings in thalassemia patients (n = 38) and the control group (n = 38) in the study. Data are presented as mean \pm SD. P value < 0.05 is considered statistically significant.

Parameter	β -TM	Control	P-value
IVS (cm)	0.96 \pm 0.183	0.446 \pm 0.219	<0.001
PW (cm)	0.97 \pm 0.235	0.437 \pm 0.214	<0.001
LVEDD (cm)	5.1 \pm 0.48	2.170 \pm 0.57	<0.035
LVESD (cm)	2.8 \pm 0.54	2.217 \pm 0.45	<0.001
LV mass	172 \pm 65.3	87 \pm 14.8	<0.001
E wave (cm/sec)	77.318 \pm 10.139	62.42 \pm 12.959	0.027
A wave/ (cm/sec)	48.346 \pm 7.776	50.230 \pm 9.851	0.109
E/A ratio	1.604 \pm 0.235	1.233 \pm 0.27	0.021
DT (msec)	170.834 \pm 20.023	187.123 \pm 19.143	<0.01
IVRT (msec)	76.347 \pm 6.770	93.374 \pm 5.83	<0.01

Abbreviations: IVS, interventricular septal thickness; Pw, posterior wall thickness; LVEDD, left ventricle end diastolic diameter; LVESD, left ventricle end systolic diameter wave; mitral E wave peak velocity; A wave, mitral A wave peak velocity; DT, E wave deceleration time; IVRT, isovolumic relaxation time.

no significant differences in fractional shortening at the base and at mid-cavity sector or in LV ejection fraction (EF%) were observed between the two groups. The normalized tricuspid valve velocity for age and heart rate was significantly higher in β -TM group. (P < 0.01).

The E/Em ratio of tissue Doppler had a significant positive correlation with serum ferritin level (r = +0.74, P < 0.001).

Table 4 showed the indexed data of the M-mode values for the LV wall thickness for septum and posterior wall, LV cavity dimension in systole and diastole as well as the calculated LV mass. The LV end diastolic volume was significantly high in β -TM (126.28 \pm 18 ml vs. 76.25 \pm 14 ml < 0.001) compared

with control. Both the un-indexed and the indexed data were significantly higher in the β -TM patients compared with controls. The color flow and continuous flow of the LV and RV in the β -TM group showed mild mitral regurgitation in nine patients and three patients had mild aortic regurgitation.

Discussion

In this study, patients with β -TM were evaluated with pulse and tissue Doppler echocardiogram for systolic and diastolic functions of left ventricle (LV) compared with age- and sex-matched controls. Compared with controls, the diastolic indices of LV in β -TM patients showed higher early diastolic filling of LV and high E/A ratio suggesting restrictive diastolic

Table 3. The age- and heart rate-adjusted diastolic Doppler indices for β -thalassemia (β -TM) patients and healthy controls. Data are presented as mean \pm SD. P value < 0.05 is considered statistically significant.

Parameter	β -TM	Control	P-value
FS (%)	34.421 \pm 0.337	33.368 \pm 0.880	0.107
LVEF (%)	61.464 \pm 1.66	61.47 \pm 1.28	0.103
E wave (cm/sec)	74.29 \pm 10.139	64.08 \pm 12.959	0.027
A wave/ (cm/sec)	48.346 \pm 7.776	50.230 \pm 9.851	0.109
E/A ratio	1.54 \pm 0.235	1.233 \pm 0.27	0.021
DT (msec)	150.834 \pm 9.023	167.123 \pm 4.143	<0.01
IVRT (msec)	66.347 \pm 2.770	79.374 \pm 1.83	<0.01
Em at SMA (cm/s)	4.31 \pm 2.7	5.82 \pm 2.5	<0.05
Sm at SMA (cm/s)	4.82 \pm 1.2	6.95 \pm 2.1	<0.01
E/Em ratio	15.027 \pm 2.291	11.132 \pm 1.82	<0.01
Tricuspid velocity (cm/sec)	2.853 \pm 0.569	1.743 \pm 0.471	<0.01

Abbreviations: FS, fractional shortening; EF, left ventricle ejection fraction; E wave, mitral E wave peak velocity; A wave, mitral A wave peak velocity; DT, E wave deceleration time; IVRT, isovolumic relaxation time; Em, early diastolic tissue Doppler velocity at mitral annulus; Sm, systolic tissue Doppler velocity of the mitral annulus; E/Em, E wave velocity/tissue velocity of septal area at mitral annulus (SMA).



Table 4. Indexed left ventricle wall thickness, cavity dimensions and mass Echocardiographic findings in thalassemia patients (n = 38) and the control group (n = 38) in the study. Data are presented as mean \pm SM per body surface area (m²). P value < 0.05 is considered statistically significant.

Parameter	β -TM	Control	P value
IVS (cm/M ²)	0.66 \pm 0.26	0.44 \pm 0.219	<0.001
PW (cm/M ²)	0.65 \pm 0.235	0.43 \pm 0.214	<0.001
Basal LVEDD (mm/M ²)	3.88 \pm 0.48	2.10 \pm 0.57	<0.001
Mid Cavity LVEDD (mm/M ²)	3.98 \pm 0.54	2.297 \pm 0.46	<0.001
LVESD (mm/M ²)	2.400 \pm 0.54	2.217 \pm 0.45	<0.01
LV MASS (gm/M ²)	168.53 \pm 55.3	85.29 \pm 12.8	<0.001
LVEDV/BSA (cm)	126.28 \pm 18	76.25 \pm 14	<0.001

Abbreviations: IVS, interventricular septal thickness; PW, posterior wall thickness; LVEDD, left ventricle end diastolic diameter; LVESD, left ventricle end systolic diameter, LVEDV, left Ventricle end diastolic Volume.

pattern and thus stiff myocardial wall. These findings are in keeping with another study by Yaprak et al²¹ who demonstrated that β -TM patients (n = 63) had significantly higher E wave, E/A ratio, and lower A wave velocity, suggesting restrictive pattern in 54% in the study population; no correlation was found with hemoglobin level. Similar observations were reported by Spirit P et al²² who demonstrated that transmitral diastolic filling measured by Doppler in patients with β -TM (n = 32, none of them had heart failure) was described of restrictive pattern. This was also in agreement with a previous report that high E/A ratio is the most common finding in patients with β -TM.²³ The left Ventricle (LV) diastolic filling measured by pulsed wave Doppler echocardiography reflect the diastolic filling characteristics of the LV and depends on various factors including LV ventricle relaxation, compliance, systolic function and loading conditions.^{24,25}

In the current study, the tissue Doppler ratio of E/Em was significantly higher in β -TM patients compared with controls, the TD of early diastolic velocity (Em) and the systolic velocity wave (Sm) were significantly reduced, suggesting stiff myocardium and possibly high LVEDP.²⁶ These findings are in agreement with previously reported findings in hypertensive patients.²⁷

The LVEF% and fractional shortening in basal and mid cavity were normal with no difference between patients with β -TM and the control group. The normal LVEF% indicates that β -TM patients are having minimal deleterious effect of iron overload on myocardial systolic function and that was evident by the optimal level of serum ferritin in the study population.

This may also explain the absence of heart failure or significant valve diseases in the current study population. In one report it was shown that the overall cardiovascular prognosis was good if the serum ferritin is below 2500 ng/dl. Serum ferritin levels <1000 ng/dl were associated with normal LVEF% while high levels were associated with low LVEF%.²⁸ In another study, however, right sided heart failure was reported in 16% of β -TM patients with high serum ferritin of >2500 ng/ml.²⁹ Therefore, the iron overload in the current study appears to mediate the impaired diastolic function leading to stiffness of the myocardial wall with mean pre-transfusion hemoglobin concentration of 9.5 gm/dl in the β -TM group, there is an increased dimension of LV cavity and LV volume in diastole. The increase of the volume load in this population may be a reflection of Frank Starling mechanism or due to increased heart rate in β -TM patients. This was observed by others who related the increment of LV volume to factors mediated by chronic anemia rather than iron overload.³⁰

In order to avoid the influence of the heart rate in this study, all the Doppler indices were normalized for the heart rate and the age. The echocardiographic measurements were all conducted during the week preceding the blood transfusion in order to eliminate the high volume effect on the pulse wave velocity.³¹

The decreased DT time of E wave was mostly related to the increased amplitude of the E wave and may be due to the impaired relaxation of LV of constrictive pattern where the E wave is high with shorter DT and IVRT interval. This is probably due to iron overload and increased stiffness of LV wall.³²



In the β -TM group, the increase ratio of E/Em ratio compared with the control group is highly suggestive of stiff myocardial wall and an increased left ventricle end diastolic pressure.^{10,26,27} The significant high velocity of the tricuspid valve in β -TM compared to controls may be due to pulmonary diffusion defect, hypoxia or possibly airway obstruction due to iron overload.^{33,34}

Conclusions

We conclude from this study that patients with β -thalassemia have larger left ventricle dimension, abnormal LV relaxation pattern suggestive of restrictive type and higher LV end-diastolic pressure, while the left ventricle ejection fraction is normal. These data suggest that abnormalities of diastolic indices are initial findings in patients with β -thalassemia major.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

References

1. Fujita S. Congenital hemolytic anemia–hemoglobin abnormality–thalassemia. *Nippon Rinsho*. 1996;54:2454–9.
2. Fosburg MT, Nathan DG. Treatment of Cooley's anemia. *Blood*. 1990; 76:435–44.
3. Ehlers KH, Levin AR, Markenson AL, Marcus JR, Klein AA, Hilgartner MW, et al. Longitudinal study of cardiac function in thalassemia major. *Ann N Y Acad Sci*. 1980;344:397–404.
4. Hahalis G, Manolis AS, Apostolopoulos D, Alexopoulos D, Vagenakis AG, Zoumbos NC. Right ventricular cardiomyopathy in beta-thalassaemia major. *Eur Heart J*. 2002;23:147–56.
5. Al-Arrayed S, Hafadh N, Amin S, Al-Mukhareq H, Sanad H. Student screening for inherited blood disorders in Bahrain. *Eastern Mediterranean Health Journal*. 2003;9(3):344–52.
6. Al-Arrayed SS, Hafadh N, Al-Serafi S. Premarital counselling: an experience from Bahrain. *Eastern Mediterranean health journal*. 1997; 3:415–9.
7. Daar S, Pathare AV. Combined therapy with desferrioxamine and deferoxamine in beta thalassemia major patients with transfusional iron overload. *Ann Hematol*. 2006;85(5):315–9.
8. Gharzuddine WS, Kazma HK, Nuwayhid IA, et al. Doppler characterization of left ventricular diastolic function in beta-thalassaemia major. Evidence for an early stage of impaired relaxation. *European Journal of Echocardiography*. 2002;3:47–51.
9. Nishaimura RA, Schwartz RS, Tajik AJ, Holmes DR. Non invasive measurement of rate of the left ventricular relaxation by Doppler echocardiography: validation with simultaneous cardiac catheterization. *Circulation*. 1993;88:146–155.
10. Choong CY, Herrman HC, Weyman AE, Fifer MA. Preload dependent Doppler derived indexes of left ventricle diastolic function in human. *J Am Coll Cardiol*. 1987;10:800.
11. Aessopos A, Deftereos S, Tsironi M, et al. Predictive echo-Doppler indices of left ventricular impairment in B-thalassemic patients. *Ann Hematol*. 2007;86:429–34.
12. Nagueh S, Middleton K, Koplen H, et al. Doppler tissue imaging: A noninvasive technique for evaluation of left ventricular relaxation and estimation of filling pressures. *J Am Coll Cardiol*. 1997;30:1527–33.
13. Ommen SR, Nishimura Ra, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressure: A comparative simultaneous Doppler catheterization study. *Circulation* 2000;102:1788–94.
14. Kobayashi K, Tamano K, Takahshi T, Honda T, Ueetake S, Ohru M. Myocardial systolic function of the left ventricle along the long axis in patients with essential hypertension: a study by pulsed tissue Doppler imaging. *NEJM*. 2003;41(4):175–82.
15. Sahn DJ, De Maria A, Kisslo J, Weyman A. The committee on M mode standardization of the American Society of Echocardiography: results of survey of echocardiographic measurements. *Circulation*. 1978;58: 1072–82.
16. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of Left ventricle hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57:450–8.
17. Oki T, Tabata T, Yamada H, et al. Left ventricle diastolic properties of hypertensive patients measured by pulsed tissue Doppler imaging. *Journal of the American Society of Echocardiography*. 1998;11:1106–12.
18. Haqvi TZ, Neyman G, Broyde A, Mustafa J, Siegel RJ. Comparison of myocardial tissue Doppler with transmitral flow Doppler in left ventricle hypertrophy. *Journal of the American Society of Echocardiography*. 2001;14:1143–60.
19. Schillaci G, Pasqualini L, verdecchia P, et al. Prognostic significance of left ventricular diastolic dysfunction in essential hypertension. *J Am Coll Cardiol*. 2002;19:39(12):2005–11.
20. Kirkwood BR. Essentials of medical statistics, first edition, Blackwell Scientific publications, 1988. p. 65–72.
21. Yaprak I, Aksit S, Ozturk C, Bakiler AR, Dorak C, Turker M. Left ventricle diastolic abnormalities in children with beta-thalassemia major: a Doppler echocardiographic study. *Turk J pediatr*. 1988;40(2):201–9.
22. Spirit P, Lupi G, Melevendi C, Veccio C. Restrictive diastolic abnormalities identified by Doppler echocardiography in patients with thalassemia major. *Circulation*. 1990;82(1):88–94.
23. Kremastinos DT, Tsiapras DP, Tsetsos GA, et al. Left ventricular diastolic Doppler characteristics in β -thalassemia major. *Circulation*. 1993; 1127–35.
24. Thomas JD, Weyman AE. Echocardiography Doppler evaluation of left ventricle diastolic function. Physics and physiology. *Circulation*. 1991; 84:977–90.
25. Appleton CP, Hatle LK, Popp RL. Relation of trans-mitral flow velocity patterns to left ventricular diastolic function: New insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol*. 1998;12:426–40.
26. Yu CM, Sanderson JE, Marwick TH, Oh JK. Tissue Doppler imaging a new prognosticator for cardiovascular disease. *J Am Coll Cardiol*. 2007;49(19): 1903–14.
27. Wang G, Yip GW, Wang AY, et al. Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricle hypertrophy. *NEJM*. 2005;2391:183–91.
28. Bosi G, Crepaz R, Gamberini MR, et al. Left ventricle remodelling and systolic and diastolic function in young adult with beta thalassemia major: a Doppler echocardiographic assessment and correlation with hematological data. *Heart*. 2003;89(7):762–6.
29. Iarussi D, Di Salvo G, Pergola V, et al. Pulsed Doppler tissue imaging and myocardial function in thalassemia major. *Heart Vessels*. 2003; 18:1–6.
30. Duke M, Abeimann WH. The haemodynamic response to chronic anemia. *Circulation*. 1969;34:503–15.
31. Bulck FA, Mott MG, Martin RP. Left ventricle diastolic function in children measured by Doppler echocardiography normal values and relation with growth. *Br Heart J*. 1995;73:334–9.



32. Stewart RA, Joshi J, Alexander N, Nihoyannopoulos P, Oakley CM. Adjustment for the influence of age and heart rate on Doppler measurement of left ventricle filling. *Br Heart J*. 1992;68:608–12.
33. Cooper DM, Mansell AL, Weiner MA, et al. Low lung capacity and hypoxemia in children with thalassemia major. *Ann Rev Respir Dis*. 1980;121:639–46.
34. Grant GP, Mansell AL, Graziano JH, Mellins RB. The effect of Transfusion on lung capacity, diffusion capacity and arterial oxygen saturation in patients with thalassemia major. *Pediatr Res*. 1986;20:20–3.

Publish with Libertas Academica and every scientist working in your field can read your article

“I would like to say that this is the most author-friendly editing process I have experienced in over 150 publications. Thank you most sincerely.”

“The communication between your staff and me has been terrific. Whenever progress is made with the manuscript, I receive notice. Quite honestly, I’ve never had such complete communication with a journal.”

“LA is different, and hopefully represents a kind of scientific publication machinery that removes the hurdles from free flow of scientific thought.”

Your paper will be:

- Available to your entire community free of charge
- Fairly and quickly peer reviewed
- Yours! You retain copyright

<http://www.la-press.com>