**The pro-BNP Serum Level and Echocardiographic Tissue Doppler Abnormalities in Patients with Beta Thalassemia Major**

Taysir S. Garadah¹, Najat Mahdi¹, Salah Kassab², Isa Al Shoroqi¹, 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 Family and Community Medicine, College of Medicine and Medical Sciences, Arabian Gulf University, Kingdom of Bahrain.

Corresponding author email: garadaht@hotmail.com

**Abstract:**

**Background:** Doppler echocardiographic studies of the left ventricle (LV) function in patients with β-Thalassemia Major (β-TM) had shown different patterns of systolic and diastolic dysfunctions associated with abnormal serum brain natriuretic peptide (BNP).

**Aim:** This cross-sectional study was designed to study the LV systolic and diastolic functions and correlate that with serum level of N-terminal pro brain natriuretic hormone (NT-pro BNP) in patients with β-TM using Pulsed Doppler (PD) and Tissue Doppler (TD) echocardiography.

**Methods:** The study was conducted on patients with β-TM (n = 38, age 15.7 ± 8.9 years) and compared with an age-matched controls (n = 38, age 15.9 ± 8.9 years). In all participants, PD and TD echocardiography were performed and blood samples were withdrawn for measuring the serum level of NT-pro BNP, ferritin, and alanine transaminase.

**Results:** Patients with β-TM compared with controls, have thicker LV septal wall index (0.65 ± 0.26 vs. 0.44 ± 0.21 cm, P < 0.001), posterior wall index (0.65 ± 0.23 vs. 0.43 ± 0.21 cm, P < 0.01), and larger LVEDD index (4.35 ± 0.69 vs. 3.88 ± 0.153 mm, P < 0.001). In addition, β-TM patients have higher transmitral E wave velocity (E) (70.818 ± 10.139 vs. 57.532 ± 10.139, p = 0.027) and E/A ratio (1.54 ± 0.17 vs. 1.23 ± 0.19, P < 0.01) and shorter deceleration time (DT) (160.13 ± 13.3 vs. 170.50 ± 19.20 m sec, P < 0.01). Furthermore, 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 (19.6 ± 2.81 vs. 13.868 ± 1.41, P < 0.05). The tissue Doppler systolic wave (Sm) velocity and the early diastolic wave (Em) were significantly lower in β-TM group compared to controls (Sm: 4.82 ± 1.2 vs. 6.22 ± 2.1 mm/sec, P < 0.05; Em: 3.51 ± 2.7 vs. 4.12 ± 2.5 mm/sec P < 0.05, respectively). The tricuspid valve velocity was significantly higher in β-TM patients compared with controls (2.993 ± 0.569 vs. 1.93 ± 0.471 m/sec, respectively, P < 0.01). The mean serum NT pro-BNP in β-TM was significantly higher compared with controls (37.6 ± 14.73 vs. 5.5 ± 5.4 pg/ml, P < 0.05). The left ventricle ejection fraction (EF%) and fractional shortening (FS%) were not significantly different between both groups.

**Conclusion:** We conclude that patients with β-TM had a significantly higher serum level of NT-pro BNP that is positively correlated with the E/Em ratio on tissue Doppler. Furthermore, we confirm our previous findings that patients with β-TM exhibit LV diastolic pattern on echocardiogram suggestive of restrictive type with well preserved left ventricle systolic function.

**Keywords:** NT-pro BNP, beta-thalassemia major, pulsed echo Doppler, tissue Doppler echocardiography, Bahrain

---

Clinical Medicine Insights: Cardiology 2010:4 135–141
doi: 10.4137/CMC.S6452

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
Patients with beta-thalassemia major (β-TM) are maintained on continuous blood transfusion regimens to keep hemoglobin levels close to normal and allow adequate tissue oxygenation. Hemolysis of red blood cell and repeated blood transfusion in β-TM is associated with iron overload. Iron deposition adversely affect both the structure and function of the heart and other vital organs. Treatment with iron chelating therapy in patients with β-TM showed improvement of morbidity and increased survival and is considered the standard of care of this blood disorder.

Brain natriuretic peptide (BNP) is a 32-amino acid polypeptide secreted primarily by the left ventricle (LV) in response to increased stretching or wall tension of the heart muscle cells. At the time of BNP release, the inactive NT-pro BNP is cleaved from the precursor peptide pro BNP and is co-secreted in quantities directly proportional to its biologically active counterpart (BNP). Both BNP and NT-pro-BNP have been shown earlier to be sensitive biomarkers for the detection of asymptomatic LV dysfunction and that they had important diagnostic and prognostic implications in patients with LV dysfunction. The prognostic predictive value of NT-pro BNP in patients with thalassemia major as a model disease with isolated diastolic dysfunction has been assessed where there were a direct relationship between the diastolic indices on echo Doppler and the serum level of the NT-pro BNP.

LV diastolic filling patterns have been classified into normal, restrictive and abnormal relaxation patterns on the basis of early filling E wave and late filling A wave on the pattern of LV diastolic filling. 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, shortened deceleration Time (DT) with high E/A ratio. The tissue Doppler echocardiography (TD) can detect regional myocardial diastolic dysfunction even in early phases of cardiac injury. 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 velocity (Em) does correlates positively with the LV end-diastolic pressure (LVEDP). Furthermore, it was shown that TD velocities of the early diastolic wave (Em) and systolic wave (Sm) were both reduced in stiff hypertensive myocardium.

The aim of this study is to examine the relationship between the serum level of NT-pro BNP and LV diastolic function using different echocardiographic indices of tissue Doppler echocardiogram in patients with β-TM in the absence of overt heart failure.

Material and Methods
This study included 38 patients with transfusion-dependent β-TM and 32 healthy individuals who were used as a control group. A constitutional ethical approval was obtained for the study. The study was conducted over six month period from September 2009 to March 2010. Patients’ selection was consecutive from those who are on regular follow-up in the Pediatric Hematology clinic at Salamaniya Medical Complex (SMC) in Bahrain.

Inclusion and exclusion criteria
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. Each patient had been receiving blood transfusions every three weeks to maintain hemoglobin levels above 9 g/dl since infancy. All patients had also been receiving oral deferasirox as a chelating therapy (20 mg/kg/day) regularly for at least six months. In the control group, individuals were healthy with no renal or hepatic diseases, no cardiac valve diseases, normal LV function on echo and negative blood tests for thalassemia. The control group was selected from the pool of age-matched healthy individuals who were referred for evaluation of a systolic murmur and turned out to have normal echo.

The blood sampling in the β-TM group and the echo test were carried out at the end of the week prior to the blood transfusion. Patients were excluded if they have an end-stage renal disease with creatinine clearance <30% of normal, severe liver disease, diabetes mellitus, hypoparathyroidism, advanced heart failure, hypertrophic cardiomyopathy or if the patient is taking active cardiac medications.

Clinical and biochemical variables
Each patient in the study had a clinical and hematological data file including duration of disease,
using Teichholz formula: $V = \frac{7.0}{(2.4 + D)} \times D^3$. The LV diastolic filling indices including early filling $E$-wave velocity ($Em$), late filling $A$-wave velocity, and the $E/Em$ ratio were measured with tissue Doppler. The correlation coefficient ($r$) of the slope was then calculated. The mean of tissue Doppler indices taken at septal mitral annulus ring of the LV were corrected for heart rate.

Doppler echocardiography
Each patient in the study had the echo examination by 2.5–5 MHz transducer, using HP E33 echo machine. The echocardiography tests were performed by an echo technologist who was blinded about 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 two readings. All measurements were conducted according to the recommendations of the American Society of Echocardiography (ASE). Each patient enrolled in the study had echocardiographic measurements including M-mode, 2D echo, color flow, LV systolic and diastolic transmitral indices and tissue Doppler evaluation of the septal mitral annulus. The $M$-mode echo parameters including the LV septal wall thickness, posterior LV wall thickness, annulus, and mitral annulus, early filling $E$-wave velocity ($Em$), late filling $A$-wave velocity, $E/Em$ ratio. The correlation coefficient ($r$) of the slope was then calculated. The mean of tissue Doppler indices taken at septal mitral annulus ring of the LV were corrected for heart rate.

Results
The demographic data of $\beta$-TM patients and the healthy controls are summarized in Table 1. The $\beta$-TM patients had a significantly lower body surface area compared with control patients ($1.02 \pm 0.2$ vs. $1.15 \pm 0.2$, $P < 0.05$). There was no significant difference in the mean age between the $\beta$-TM group (15.92 ± 8.92 years, range; 7–25) and the control group (15.79 ± 8.94 years, range; 6–24) with comparable gender distribution between the two groups.

Table 2 shows the hemodynamic and biochemical variables in both groups. The systolic and diastolic pressure values were comparable in both groups. The heart rate was lower in the $\beta$-TM compared with control group (68.16 ± 7.40 vs. 72.92 ± 6.08 bpm respectively, $P < 0.05$). The mean serum NT pro-BNP serum level and echocardiographic tissue doppler abnormalities

| Table 1. Demographic characteristics of control (n = 32) and thalassemia patients (n = 38) in the study. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                 | Control group   | $\beta$-TM group | $P$ value       |
| Age (Years)                    | 15.79 ± 8.94    | 15.92 ± 8.92    | 0.92            |
| Male                           | 22 (57%)        | 23 (60%)        | 0.75            |
| Weight (kg)                    | 41.26 ± 8.60    | 31.00 ± 7.87    | 0.034           |
| Height (cm)                    | 135.66 ± 8.80   | 134.87 ± 9.74   | 0.001           |
| BSA                            | 1.15 ± 0.20     | 1.02 ± 0.20     | 0.001           |

**Notes:** Data are presented as mean ± SD. $P$ value < 0.05 is considered statistically significant.

**Abbreviation:** BSA, body surface area.

Statistical analysis
All data were entered and analyzed using the Statistical Package of Social Sciences (SPSS) version 17.0. Data are presented as mean ± SD. Unpaired student $t$-test was used to analyze the differences between the variables in the control and the $\beta$-TM groups. The $M$-mode dimensions of the LV were adjusted and indexed for Body Surface Area (BSA) of each patient. Linear regression analysis was used to assess the correlation between the serum NT-pro BNP and $E/Em$ ratio. The correlation coefficient ($r$) of the slope was then calculated. The mean of tissue Doppler indices taken at septal mitral annulus ring of the LV were corrected for heart rate.
pro-BNP in β-TM was significantly higher compared with controls (37.62 ± 14.73 pg/ml versus 5.53 ± 5.41 pg/ml respectively, \( P < 0.001 \)). The serum ferritin level was significantly higher in the β-TM group compared with the control group (5124 ± 1931 pg/ml vs. 164 ± 48 pg/ml, \( P < 0.001 \)). There were no significant differences in serum levels of creatinine, alanine transaminase and hemoglobin between the two groups.

### Echocardiographic findings

Table 3 summarizes the indexed pulsed 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 inter-ventricular 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 in β-TM group compared with the control (172.85 ± 65.30 vs. 87.65 ± 14.76 respectively, \( P < 0.001 \)).

Compared with the control group, patients with β-TM had slightly higher LVEF% and FS, but these differences did not achieve the statistical significance.

Table 4 shows the pulsed and tissue Doppler indices of the LV in both groups. The pulsed Doppler velocities of LV in diastolic showed significantly higher E wave, and E/A ratio in β-TM group compared to control while significantly shorter interval of DT time and higher velocity of E wave. 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 (\( P < 0.05 \)), while the early diastolic velocity (Em) and the systolic wave velocity (Sm) were significantly lower in β-TM group (\( P < 0.05 \)).

### Table 2. Hemodynamic and biochemical parameters in beta thalassemia (β-TM) patients on deferasirox (20 mg/kg/day) and the control group.

| Parameter                      | Control group (n = 32) | β-TM group (n = 38) | \( P \) value |
|-------------------------------|------------------------|---------------------|-------------|
| Systolic pressure (mmHg)      | 128.16 ± 12.49         | 123.34 ± 13.27      | 0.108       |
| Diastolic pressure (mmHg)     | 74.71 ± 7.61           | 71.26 ± 7.21        | 0.102       |
| Heart rate (bpm)              | 72.92 ± 6.08           | 68.16 ± 7.40        | 0.04        |
| Serum pro-BNP (pg/ml)         | 5.53 ± 5.41            | 37.62 ± 14.73       | 0.001       |
| Serum ferritin (μg/L)         | 164 ± 48               | 5124 ± 1931         | 0.001       |
| Serum creatinine (μmol/l)     | 80.80 ± 10.12          | 75.23 ± 11.13       | 0.076       |
| Serum alanine transaminase (U/L) | 39 ± 10.72            | 40.45 ± 14.83       | 0.085       |
| Hemoglobin (gm/dl)            | 10.23 ± 0.51           | 9.5 ± 0.42          | 0.065       |

**Notes:** Data are presented as mean ± SD. \( P < 0.05 \) is considered statistically significant.

### Table 3. Indexed M-Mode and 2D echocardiography findings in beta thalassemia (β-TM) patients and the control group.

| Parameter     | Control group (n = 32) | β-TM group (n = 38) | \( P \) value |
|---------------|------------------------|---------------------|-------------|
| IVS (cm/m²)   | 0.44 ± 0.22            | 0.65 ± 0.26         | <0.001      |
| PW (cm/m²)    | 0.43 ± 0.21            | 0.65 ± 0.24         | <0.001      |
| LVEDD (mm/m²) | 3.89 ± 0.15            | 4.35 ± 0.70         | <0.001      |
| LVESD (mm/m²) | 2.72 ± 0.17            | 2.85 ± 0.47         | <0.01       |
| LV mass (gm/m²)| 87.65 ± 14.76          | 172.85 ± 65.30      | <0.001      |
| LVEF (%)      | 59.00 ± 3.33           | 63.47 ± 6.76        | 0.089       |
| FS (%)        | 32.37 ± 4.36           | 34.41 ± 3.36        | 0.107       |

**Notes:** Data are presented as mean ± SM per body surface area (m²). \( P < 0.05 \) is considered statistically significant.

**Abbreviations:** IVS, inter ventricular septal thickness; PW, posterior wall thickness; LVEDD, left ventricle end diastolic diameter; LVESD, left ventricle end systolic diameter; FS, fractional shortening; LVEF, left ventricular ejection fraction.
The LV fractional shortening and LVEF% at mid-cavity sector were with not significantly different between the two groups.

There was a significant positive correlation between the pro BNP and the E/Em ratio (r = 0.31, P < 0.001).

The tricuspid valve velocity was significantly higher in β-TM group (P < 0.01). In patients with β-TM group, the color flow and continuous wave velocity of the LV and RV showed mild mitral regurgitation in nine patients and three patients had mild aortic regurgitation with none in the control group.

Discussion

In this study, patients with β-TM were evaluated with pulse and tissue Doppler echocardiogram for systolic and diastolic functions of the left ventricle (LV) compared with age and sex-matched individuals with no β-TM (controls). Compared with controls, the diastolic indices of LV in β-TM patients showed higher early diastolic filling of LV and E/A ratio suggesting restrictive diastolic pattern and stiff myocardial wall. These findings are in keeping with one study by Yaprak et al. who demonstrated that β-TM patients had significantly higher E wave, E/A ratio, and lower A wave velocity, suggesting a restrictive pattern but with no correlation with hemoglobin level. Similar observations were reported by Spirit et al. who demonstrated a restrictive pattern in patients with β-TM with no heart failure. This was also in agreement with a previous report that high E/A ratio is the most common finding in patients with β-TM.

In one study, the magnitude of E wave velocity is governed by the initial left ventricular pressure and shown to be directly related to it, the decreased DT of E wave was mostly related to the increased amplitude of the E wave and may be due to the impaired relaxation of LV with a constrictive pattern. The exact mechanism of these findings is not known but may be due to iron overload and increased stiffness of LV wall.

The tissue Doppler ratio of E/Em was significantly higher in β-TM patients compared with controls. Likewise, the early diastolic velocity (Em) and the systolic velocity wave (Sm) of the basal segments of LV lateral wall showed increased E/Em ratio, suggesting a restrictive diastolic pattern and possibly high LV stiffness. These findings are in agreement with those previously reported in hypertensive patients.

The LVEF% and fractional shortening in mid cavity sector were normal indicating that β-TM patients are having a preserved systolic function. In the current study, the serum ferritin was more than 30 times higher in the β-TM group compared with controls. These findings confirm our previously published studies that iron overload appear to mediate the impaired diastolic function leading to stiffness of the myocardial wall but with well preserved LV systolic function. However, increased serum ferritin concentration may not be associated with a concordant...
and comparable increase in myocardial iron content. Future studies which examine the cardiac iron content by using more sensitive measures such as MRI will be required.

In this study, the serum level of pro-BNP in patients with $\beta$-TM in the absence of overt heart failure was not exceeding the normal level in our laboratory of 125 pg/ml, but was significantly higher than the control group with a positive correlation with E/Em ratio indicating a stiff myocardium with restrictive diastolic abnormality. It seems in this population, as observed previously, that myocardial disease go through a stage of impaired relaxation before development of systolic dysfunction.\textsuperscript{8,9} This finding is in agreement with one report where patients with $\beta$-TM with no heart failure had higher NT-pro-BNP and E/Em ratio compared with controls with positive correlation between both variables.\textsuperscript{25} In one study on $\beta$-TM patients, it was found that NT pro-BNP serum level was significantly increased in patients with documented left ventricular diastolic dysfunction on echocardiogram.\textsuperscript{26}

In the $\beta$-TM group, the increase ratio of E/Em ratio compared with the control group is highly suggestive of stiff myocardial wall and increased left ventricular end diastolic pressure LVEDP.\textsuperscript{27}

**Conclusion**

We conclude that patients with $\beta$-TM had a significantly higher serum level of NT-pro BNP that is positively correlated with the E/Em ratio on tissue Doppler. Furthermore, we confirm our previous findings that patients with $\beta$-TM exhibit on echocardiogram a LV diastolic pattern suggestive of restrictive type with well preserved left ventricle systolic function.

**Disclosure**

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 and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

**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. Longitudinal study of cardiac function in thalassemia major. *Ann N Y Acad Sci*. 1980;344:397–404.
4. Atish D, Bhalla MA, Morrison LK, et al. A prospective study in search of an optimal B-natriuretic peptide level to screen patients for cardiac dysfunction. *Am Heart J*. 2004;104(3):518–23.
5. Maisel A, Kirshnaswamy P, Nowak R, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347(3):161–7.
6. Bhalla MA, Chiang A, Ephsteyn VA, et al. prognostic role of B-type natriuretic level in patients with type 2 diabetes mellitus. *J Am Coll Cardiol*. 2004;44(5):1047–52.
7. Daar S, Parthure AV. Combined therapy with desferrioxamine and deferiprone in beta thalassemia major patients with transfusional iron overload. *Am J Hematol*. 2006;85(5):315–9.
8. Gharzuddine WS, Kazma HK, Nuwayhid IA, et al. Doppler characterization of left ventricular diastolic function in beta-thalassemia major. Evidence for an early stage of impaired relaxation. *European Journal of Echocardiography*. 2002;3:47–51.
9. Nishimura 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;88:146–55.
10. Choong CY, Herman HC, Weymen AE, Fifer MA. Preload dependent Doppler derived indexes of left ventricular diastolic function in human. *J Am Coll Cardiol*. 1987;10:800–8.
11. Aessopos A, Delfteroes S, Tisroni M, et al. Predictive echo–Doppler indexes of left ventricular impairment in $\beta$-thalassemic patients. *Am J Hematol*. 2007;86:429–34.
12. Nagueh S, Middleton K, Koplen H. 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. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressure: A comparative simultaneous Doppler catherization study. *Circulation*. 2000;102:1788–94.
14. Kobayashi K, Tamano K, Takahashi T, Honda T, Uetake 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;414(4):175–82.
15. Wang G, Yap GW, Wang YY, et al. Tissue Doppler imaging provides incremental prognostic value in patients with systemic hypertension and left ventricle hypertrophy. *NEJM*. 2005;259(8):183–91.
16. 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.
17. Devereux RB, Alonso DR, Lutas EM. Echocardiographic assessment of Left ventricle hypertrophy: comparison to necropsy findings. *Am J Cardiol*. 1986;57:450–8.
18. Yaprak I, Aksit S, Ozturk C, Bakiler AR, Dorak C, Turker M. Left ventricle diastolic abnormalities in children with beta-thalassemia major: Doppler echocardiographic study. *Turk J Pediatr*. 1988;40(2):201–9.
19. Spirit P, Lapi G, Melevendi C, Veccio C. Restrictive diastolic abnormalities identified by Doppler echocardiography in patients with thalassemia major. *Circulation*. 1990;82(1):188–94.
20. Oki T, Tabata T, Yamada H, et al. Left ventricle diastolic properties of hypertensive patients measured by pulsed tissue Doppler imaging. *J Am Coll Cardiol*. 1993;11:1106–12.
21. Kremastinos DT, Tsapras DP, Tsetsos GA. Left ventricular diastolic Doppler characteristics in $\beta$-thalassemia major. *Circulation*. 1993;11:127–35.
22. Yu CM, Sanderson JE, Marwick TH, Oh JK. Tissue Doppler imaging as a new prognosticator for cardiovascular disease. *J Am Coll Cardiol*. 2007;49(19):1903–14.
23. Kremastinos D, Tsapras D, Kostopoulou A, Hamodraka E, Chaidaroglou A, Kapasali E. NT-pro BNP levels and diastolic dysfunction in B-Thalassemia Major patients. *European Journal of Heart Failure*. 2007;9:531–6.
24. Garadah T, Kassab S, Mahdi N, Abu-Taleb A, Jamsheer A. Pulsed and Tissue Doppler Echocardiographic Changes in Patients with Thalassemia Major. *Clinical Medicine: Blood Disorders*. 2010;3:1–8.

25. Kremastinos D, Hamodraka E, Parissis J, Tsiapras D, Dima K, Maisel A. Predictive value of B-type natriuretic peptides in detecting latent left ventricular diastolic dysfunction in beta thalassemia major. *Am Heart J*. 2010;159(1):68–74.

26. 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.

27. 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.

---

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](http://www.la-press.com)