Cardiac Iron Overload Detection Using Longitudinal Strain in Asymptomatic Children with Beta Thalassemia Major

IKRAM CHAMTOURI (✉ ikram_chamtouri@hotmail.fr)

Hopital Universitaire Fattouma Bourguiba a Monastir <https://orcid.org/0000-0001-9745-5041>

Rouaida khalifa

Hopital Universitaire Fattouma Bourguiba a Monastir

habib besbes

Hopital Universitaire Fattouma Bourguiba a Monastir

walid jomaa

Hopital Universitaire Fattouma Bourguiba a Monastir

wajih abdallah

Hopital Universitaire Fattouma Bourguiba a Monastir

khaledoun ben hamda

Hopital Universitaire Fattouma Bourguiba a Monastir

Chokri Chouchene

Hopital Universitaire Fattouma Bourguiba a Monastir

faouzi maatouk

Hopital Universitaire Fattouma Bourguiba a Monastir

Research Article

Keywords: speckle tracking, detection, infant, Cooley's anemia.

Posted Date: February 17th, 2022

DOI: <https://doi.org/10.21203/rs.3.rs-1295016/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at The International Journal of Cardiovascular Imaging on March 19th, 2022. See the published version at <https://doi.org/10.1007/s10554-022-02597-w>.

Abstract

Background.

Cardiomyopathy mediated by iron disposition in cardiomyocytes is a dreadful cause of morbidity and mortality in patients with beta thalassemia major (BTM). Conventional transthoracic echocardiography (TTE) parameters are preserved at late stages of cardiomyopathy induced by iron overload. Therefore, cardiac imaging modalities based on myocardial deformation such as strain imaging are used for early detection of cardiac iron overload.

Aim.

To demonstrate the contribution of longitudinal strain (LS) in early detection of cardiac iron overload in children with BTM.

Methods.

Sixty children (30 children with BTM and 30 healthy controls) were enrolled in this study. Conventional TTE study was performed in both patient and control groups. LV regional longitudinal strain (RLS) were determined and compared between the two study groups.

Results.

Mean age was 10.4 ± 5 years in BTM group compared to 10.2 ± 5 years in control group ($p=0.876$). Compared to control group, there was no significant difference in conventional TTE parameters except for indexed left atrium (LA) area and volume. LA was significantly larger in BTM children ($27.59 \pm 13.1 \text{ ml/m}^2$ vs. $18.23 \pm 4.33 \text{ ml/m}^2$, $p=0.001$). RLS was lower in anterior, septal and inferior walls in basal and middle segments of LV in BTM group while there was no significant difference in RLS in apical segment between the two groups (-27.30 ± 5.1 vs. -28.83 ± 4.33 , $p=0.22$).

Conclusion.

In asymptomatic BMT children with normal conventional TTE parameters, LS could be used for the detection of subclinical myocardial dysfunction.

Introduction

Beta thalassemia major (BTM) is the most severe form of inherited hemolytic anemia. It is caused by the absence of beta chain hemoglobin production, essential to normal hemoglobin synthesis. Thalassemia patient has ineffective erythropoiesis leading to hemolysis and severe anemia [1, 2]. Treatment consists mainly in repeated blood transfusions which generate iron overload in almost all organs. Myocardial iron deposition could lead to systolic and/or diastolic left ventricle (LV) dysfunction, pulmonary hypertension (PHT) and arrhythmia [3]. Morbidity and mortality were reported in 50–70% of cases with myocardial

involvement [4–6]. Therefore, regular chelation therapy and early diagnosis of myocardial involvement remain important measures to improve prognosis. Conventional transthoracic echocardiography (TTE) parameters are often insufficient to detect subclinical LV dysfunction. Strain imaging, a modality of myocardial deformation determination could be used for early assessment of myocardial dysfunction as it was widely described in ischemic and valvular heart disease as well as in heart failure [7–11]. The purpose of this study was to evaluate LV iron overload by conventional TTE parameters and regional longitudinal strain (RLS) in BTM children in comparison with a healthy control group.

Methods

Study population. This is an observational, multicenter, prospective study performed during the period between January and June 2019. We included all consecutive children with BTM, aged ≤ 18 years, and having a regular follow-up in pediatrics departments in two distinct major Tunisian tertiary care facilities. All patients had no cardiac or respiratory symptoms upon inclusion. BTM diagnosis relied on measuring red blood cell indices that revealed microcytic hypochromic anemia and hemoglobin electrophoresis that revealed the absence or a significant decrease in hemoglobin A rate and increased fetal hemoglobin rate associated with the clinical severity of anemia [12]. Exclusion criteria were congenital or acquired heart disease, other hemoglobin disorders and idiopathic hemochromatosis. All BTM patients received repeated blood transfusions starting at the age of 6 months on an average of 10-16 transfusions per year per patient. Chelation therapy including either deferoxamine or deferiprone, was prescribed according to serum ferritin level. A recent serum ferritin level was performed in all BTM patients. We constituted a control group made of 30 healthy children with no cardiac history. Healthy children in the control group were selected according to criteria comparable to BTM group: mean age, gender repartition, height and weight. Written consent of all children's parents was obtained for inclusion in this study. Physical examination and 12 leads electrocardiogram (ECG) were performed for all patients.

Echocardiography. Both BTM and control groups underwent standard TTE using a Vivid E9 echocardiography system (General Electric Medical System). TTE was performed in all participants by the same operator to limit inter-operator variations. Conventional TTE parameters including LV end systolic and end diastolic diameters (LVESD and LVEDD), LV end systolic and end diastolic volumes (LVESV and LVEDV), interventricular septum (IVS) and posterior wall thickness of LV were measured. The description of LV dilatation and thickness severity was referred to z-score. LV ejection fraction (LVEF) was measured using Simpson method. LV diastolic function was estimated by peak mitral E and A waves in pulse Doppler, e' wave in tissue Doppler imaging, E/e' ratio, difference in duration of pulmonary venous and mitral A waves (Ap-Am), ratio of peak E wave to flow propagation velocity (V_p) (E/V_p), deceleration time (DT), isovolumic relaxation time (IVRT), indexed left atrium (LA) area and volume. Right ventricle (RV) function was evaluated by using peak of right ventricular systolic myocardial velocity (S wave) measured in base, tricuspid annular plane systolic excursion (TAPSE), and indexed right atrium (RA) area and volume. Systolic pulmonary artery pressure (SPAP) was measured. Offline speckle tracking analyses using Echopac software version 112 and based on apical two, three and four chambers views were performed in all study participants. Automated functional imaging (AFI) was used for strain analysis. Six

segments were required on each view for the analysis. RLS values of 17 myocardial segments were calculated after tracking endocardial borders. Bull's eye plot was obtained (figure1 and figure 2).

Statistical Analysis. Categorical variables are presented as absolute values and proportions. Continuous variables are presented as means $\pm$ standard deviations (SD). The independent t-test and Chi-square test were used for comparison of continuous and categorical variables between groups, respectively. Pearson correlation coefficient was used to study relationship between two quantitative variables and Tau-b of Kendall was used in relationship study between two qualitative variables. A p value <0.05 was set for statistical significance. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) version 21 (IBM, Armonk, NY, USA).

Results

Study population . A total of 60 children were enrolled in this study (Table I). In the BTM group (20 boys and 10 girls) mean age was 10.4 ± 5 years. Twenty children derived from a consanguineous marriage in BTM group. BTM diagnosis was made at the age of 5.4 ± 3.1 months. Chelation therapy was started at the age of 1.7 ± 1.6 years. Nine (30%) patients had splenectomy. All included patients were in functional Class I according to the New York Heart Association (NYHA) classification. Mean age in the control group was 10.2 ± 5 years and 20 patients were boys. Weight, height and heart rate were comparable between the two groups. Compared to control group, systolic blood pressure (SBP) was higher in BTM group (109.3 ± 15.9 mmHg vs. 97.5 ± 2.54 mmHg, $p < 0.01$) with no significant difference in diastolic blood pressure (DBP). Mean ferritin serum level was 2944.6 ± 2333.8 $\mu\text{g/L}$ in BTM group and 8 patients had ferritin level < 1000 $\mu\text{g/L}$. ECG showed sinus rhythm in all study subjects and an incomplete right bundle branch block in 10% of BMT group.

Conventional echocardiographic parameters. As mentioned in Table II, no significant difference was detected between the two study groups regarding conventional TTE parameters including LVESD, LVEDD, LVESV, LVEDV and LV wall thickness. LV was numerically enlarged in BTM group compared to control group by using indexed LVEDV (69.8 ± 18.6 ml/m² vs. 61.4 ± 18.3 ml/m², $p = 0.08$). LVEF measured by Simpson method was preserved in the two groups. There were no LV wall motion abnormalities in the two groups. LV diastolic function parameters including E, A and e' waves as well as E/A, E/e', E/Vp ratios, Ap-Am, DT and IVRT were comparable between the two groups. LA was significantly enlarged in BTM group compared to control group by using the indexed LA volume (27.5 ± 13.1 ml/m² vs. 18.2 ± 4.3 ml/m², $p = 0.001$). RV systolic function parameters including TAPSE and S' were comparable between the two groups. Compared to control group, SPAP was numerically higher in BTM group (27.1 ± 8.1 mmHg vs. 24.3 ± 3.5 mmHg, $p = 0.09$). Indexed RA volume was significantly higher in BTM patients (23.1 ± 6.6 vs. 18.3 ± 4.7 , $p = 0.003$).

Speckle tracking study. Myocardial deformation analysis using speckle tracking showed lower values of RLS in different myocardial walls in BTM patients compared to control group (table III). In the basal location, compared to control group, RLS was significantly reduced in the anterior wall (-18.2 ± 10.2

vs. -27.1 ± 5.02 , $p < 0.001$), in the septal wall (-19.43 ± 4.37 vs. -24.6 ± 5.64 , $p < 0.001$) and in the inferior wall (-19.13 ± 8.89 vs. -25 ± 5.11 , $p = 0.003$) in BMT group while lateral RLS was similar between the two groups. The same results of RLS were found in the mid-cavity segments with a significant reduction of strain in the anterior wall (-21.9 ± 10.6 vs. -29.1 ± 4.2 , $p = 0.001$), in the antero-septal wall (-23.6 ± 3.6 vs. -26.9 ± 4.2 , $p = 0.002$) and in the inferior wall (-22.1 ± 6.1 vs. -26.7 ± 3.9 , $p = 0.01$) in BMT group compared to control group while lateral RLS was similar between the two groups. RLS was similar between the two groups in the apical segments. The apex was spared from strain reduction (-27.3 ± 5 vs. -28.8 ± 4.3 , $p = 0.22$).

Correlation study. There was no correlation between serum ferritin level and LVEF, indexed LA area and volume, E/e', TAPSE, S' wave, SPAP and LS (Table IV).

Discussion

According to previous studies, cardiac involvement caused by myocardial iron deposition remains one of the chief causes of morbidity and mortality in BTM [4, 5]. The progressive asymptomatic cardiac iron overload leads to misdiagnosed cardiac dysfunction at the early stage in BTM patients. According to the current study results, LV strain study could contribute to early detection of iron myocardial involvement in asymptomatic BTM patients. Referring to these results, normal conventional TTE parameters are insufficient to conclude to iron myocardial deposition and subclinical myocardial dysfunction. Although important for tissue homeostasis, elevated intracellular iron concentration is responsible for oxidative stress, leading to wreckage of mitochondrial, lysosomal and sarcoplasmic membranes of the cardiomyocyte with subsequent fibrosis [13]. Oxidative stress induced by accumulated iron seems to be tolerated for a long time before leading to cardiac dysfunction [14, 15]. Iron overload induced cardiomyopathy ranges from subclinical alterations of myocardial function to overt ventricular dilatation or hypertrophy, LV systolic and/or diastolic dysfunction, RV dysfunction, PHT and rhythm or conduction disturbances [16–19]. Thus, several cardiac imaging modalities such as tissue Doppler imaging, radionuclide angiography, speckle tracking echocardiography and magnetic resonance imaging were used to anticipate and to early screen myocardial involvement in subclinical cases with preserved LV function parameters in standard TTE [20–22]. Our data have illustrated these findings, because we observed an impairment of LV longitudinal strain in asymptomatic BTM children with preserved standard systolic LV parameters suggesting that even a low myocardial iron deposition could be responsible for subclinical cardiac dysfunction. The heart seems to tolerate iron accumulation for a long time before the onset of systolic heart dysfunction. Such findings could be explained by the link between myofiber geometry deformation and preeminent iron deposition site. Longitudinal strain is mainly driven by deformation of the subendocardial fibers that are the most vulnerable to iron deposition and the earliest to be affected [23]. Lattanzi *et al.* [24] and Vogel *et al.* [25] showed that regional motion abnormalities determined by speckle tracking are caused by regional cardiac iron overload in BTM patients. These findings could be explained by the patchy iron deposition in different cardiac walls and the predominant iron deposition in cardiomyocytes rather than the interstitium [26]. The current study demonstrated a reduced RLS located in the basal and middle anterior and septal segments suggestive of regional LV

dysfunction while other studies showed reduced RLS in lateral wall [19, 27]. RLS in apical segments was conserved in our BTM group as already shown in other conditions such as cardiac amyloidosis [28]. This result could be explained by the higher wall stress in the basal septal region making it susceptible to iron deposition. In our study, diastolic function was preserved in BTM patients while previous studies showed that diastolic dysfunction precedes systolic dysfunction in BTM patients [29, 30]. Diastolic parameters in BTM patients with normal LV systolic function are similar to those observed in conditions with increased preload, probably caused by chronic anemia. Nevertheless, severe myocardial iron overload leads to a restrictive filling pattern of LV [31, 32]. An increase in volume and structural remodeling of both right and left atria, even in the absence of LV and RV dysfunction is possibly due to volume overload caused by chronic anemia [33]. RV iron overload is tolerated for a long time before RV dysfunction and PHT occur. PHT may be explained by severe lung iron overload resulting in increased pulmonary arteriolar resistance and elevated vascular endothelial growth factor serum level in BTM patients [34–36]. Our results are in line with these findings by demonstrating an increase in SPAS and indexed RA volume in BTM group. Besides, no correlation was observed between serum ferritin level and GLS which may hint that a normal ferritin level does not exclude cardiac overload. Other studies [37, 38] showed that a high ferritin level ($>2500 \mu\text{g/L}$) was associated to high prevalence of cardiac overload which is in opposition with our results that showed no GLS alteration in BTM patients with high ferritin level. This phenomenon could be explained by inflammation, infection or liver diseases in BTM patients responsible for ferritin level increase and it could result in the low specificity of serum ferritin level observed in BTM patients.

Study limitations. The low number of enrolled patients, the absence of radial and circumferential strain studies and the absence of LV strain study according to chelation treatment type represent the main limitations of our study. Moreover, we recognize that other factors beyond cardiac iron overload could affect the reduction of GLS in BTM patients. Indeed, despite an excellent sensitivity of longitudinal strain for early detection of myocardial dysfunction, its low specificity remains a major concern in this context.

Conclusion

According to our study, GLS and RLS could predict clinically silent myocardial dysfunction, regional deposition and extension of iron overload. Speckle tracking can identify cardiac involvement at early stages. We think that routine use of RLS and GLS could be a part of cardiac work-up in asymptomatic BTM patients to choose the appropriate strategy for preventing advanced heart dysfunction.

Abbreviations

BTM: Beta thalassemia major

DT: deceleration time.

ECG: electrocardiogram

ED: end diastolic

EDIVS: end diastolic inter-ventricular septum

GLS: global longitudinal strain

IVRT: isovolumic relaxation time

LA: left atrium

LV: left ventricle

LVEDD: LV end diastolic diameter

LVEF: LV ejection fraction

LVESD: LV end systolic diameter.

LVEDV: LV end diastolic volume

LVESV: LV end systolic volume

PHT: pulmonary hypertension

RA: right atrium

RLS: regional longitudinal strain

S': peak of right ventricular systolic myocardial velocity

SPAP: systolic pulmonary artery pressure

TAPSE: tricuspid annular plane systolic excursion

TTE: transthoracic echocardiography

Declarations

Ethics approval and consent to participate

All patients included in the present study gave informed and written consent for inclusion and follow-up in the present study. The study does not entail other ethical issues. In the case of the present study, the local ethics committee ruled that no formal ethics approval was required.

Consent for publication

Not applicable

Availability of data and materials

All data used in the present study are stored and managed by IkramChamtouri, MD. (First author)

Competing interests

Nothing to declare.

Funding

No funding of any kind was received for the present study.

Authors' contributions

IC, RK, HB and were actively involved in data collection and processing. IC, RK, WA and WJ were involved in manuscript preparation. KBH, CH and FM were involved in manuscript reviewing. All authors have read and approved the manuscript.

Acknowledgment

The authors have no financial or nonfinancial conflict of interest to declare.

References

1. Rund D, Rachmilewitz E. β -Thalassemia. *N Engl J Med*. 2005;353: 1135–1146.
2. Aessopos A, Berdoukas V, Tsironi M. The heart in transfusion dependent homozygous thalassaemia today – prediction, prevention and management. *Eur J Haematol*. 2008; 80: 93–106.
3. Meloni A, Puliyl M, Pepe A, Berdoukas V, Coates TD, Wood JC. Cardiac iron overload in sickle-cell disease. *Am J Hematol*. 2014; 89: 678–683.
4. Peng CT, Chang JS, Wu KH, Tsai CH, Lin HS. Mechanisms of and obstacles to iron cardiomyopathy in thalassemia. *Front Biosci*. 2008;13: 5975–5987.
5. C Borgna-Pignatti, M D Cappellini, P De Stefano, G C Del Vecchio, G L Forni, M R Gamberini. et al. Survival and complications in thalassemia. *Ann N Y Acad Sci*. 2005;1054: 40–47.
6. M G Zurlo, P De Stefano, C Borgna-Pignatti, A Di Palma, A Piga, C Melevendi. et al. Survival and causes of death in thalassaemia major. *Lancet* 1989; 2: 27-30.
7. Moustafa S, Elrabat K, Swailem F, Galal A.
The correlation between speckle tracking echocardiography and coronary artery disease in patients with suspected stable angina pectoris. *Indian Heart J*. 2018;70:379-386.
8. Marta Cvijic, Jens-Uwe Voigt. Application of strain echocardiography in valvular heart diseases. *Anatol J Cardiol*. 2020; 23: 244–253
9. Jin-Oh Choi¹, Dae-Hee Shin, Sung Won Cho, Young Bin Song, Jun Hyung Kim, Yoon Goo Kim. et al. Effect of preload on left ventricular longitudinal strain by 2D speckle tracking. *Echocardiography*. 2008; 25: 873–879.

10. Edvardsen T, Helle-Valle T, Smiseth OA. Systolic dysfunction in heart failure with normal ejection fraction: speckle-tracking echocardiography. *Prog Cardiovasc Dis*. 2006; 49: 207–214.
11. Mentz RJ, Khouiri MG. Longitudinal strain in heart failure with preserved ejection fraction: is there a role for prognostication? *Circulation*. 2015; 132:368–370.
12. Cao A, Galanello. Beta-thalassemia. *R.Genet Med*. 2010; 12:61-76
13. Cohen AR, Galanello R, Pennell DJ, Cunningham MJ, Vichinsky E. Thalassemia. *Hematology Am SocHematolEduc Program*. 2004:14–34
14. Ali Bay, Osman Başpınar, Göksel Leblebisatan, Ali Seçkin Yalçın, and Ahmet İrdem. Detection of Left Ventricular Regional Function in Asymptomatic Children with beta-Thalassemia Major by Longitudinal Strain and Strain Rate Imaging. *Turk J Haematol*. 2013; 30: 283–289.
15. Hershko C. Pathogenesis and management of iron toxicity in thalassemia. *Ann N Y AcadSci* 2010; 1202: 1-9.
16. Spirito P, Lupi G, Melevendi C, Vecchio C. Restrictive diastolic abnormalities identified by Doppler echocardiography in patients with thalassemia major. *Circulation* 1990; 82: 88–94.
17. Kremastinos DT, Tsiapras DP, Tsetsos GA, Rentoukas EI, Vretou HP, Toutouzas PK. Left ventricular diastolic Doppler characteristics in beta-thalassemia major. *Circulation* 1993; 88:1127–1135.
18. Kremastinos DT, Farmakis D, Aessopos A, Hahalis G, Hamodraka E, Tsiapras D. et al. Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. *Circ Heart Fail* 2010; 3:451–458
19. Kremastinos DT, Farmakis D. Iron overload cardiomyopathy in clinical *Circulation* 2011; 124: 2253–2263.
20. Abdelmuktader AM, Azer HY. Usefulness of pulsed wave tissue doppler imaging in assessment of left ventricular functions in children with beta-thalassemia major. *Indian J Pediatr*. 2013; 80: 721-5.
21. De Chiara B, Crivellaro W, Sara R, Ruffini L, Parolini M, Fesslovà V. et al. Early detection of cardiac dysfunction in thalassemic patients by radionuclide angiography and heart rate variability analysis. *Eur J Haematol*. 2005; 74: 517-22
22. Marsella M, Borgna-Pignatti C, Meloni A, Caldarelli V, Dell'Amico MC, Spasiano A. et al. Cardiac iron and cardiac disease in males and females with transfusion-dependent thalassemia major: a T2* magnetic resonance imaging study. *Haematologica* 96:515–520.
23. Sengupta PP, Narula J. Reclassifying heart failure: predominantly subendocardial, subepicardial, and transmural. *Heart Fail Clin* 2008; 4: 379e382.
24. Lattanzi F, Bellotti P, Picano E, Chiarella F, Mazzarisi A, Melevendi C. et al. Quantitative ultrasonic analysis of myocardium in patients with thalassemia major and iron overload. *Circulation*. 1993; 87: 748–754.
25. Vogel M, Anderson LJ, Holden S, Deanfield JE, Pennell DJ, Walker JM. Tissue Doppler echocardiography in patients with thalassaemia detects early myocardial dysfunction related to myocardial iron overload. *Eur Heart J*. 2003;24:113–119

26. Fitchett DH, Coltart DJ, Littler WA, Leyland MJ, Trueman T, Gozzard DI. Et al. Cardiac involvement in secondary haemochromatosis: a catheter biopsy study and analysis of myocardium. *Cardiovasc Res.* 1980;14:719–724
27. Hamdy AM. Use of strain and tissue velocity imaging for early detection of regional myocardial dysfunction in patients with beta thalassemia. *Eur J Echocardiogr* 2007; 8: 102-109.
28. Di Nunzio D, Recupero A, de Gregorio C, Zito C, Carerj S, Di Bella G. Echocardiographic Findings in Cardiac Amyloidosis: Inside Two-Dimensional, Doppler, and Strain Imaging. *CurrCardiol Rep.* 2019; 21:7.
29. Mancuso L, Vitrano A, Mancuso A, Sacco M, Ledda A, Maggio A. Left Ventricular Diastolic Dysfunction in beta-Thalassemia Major with Heart Failure. *Hemoglobin.* 2018 ;42:68-71
30. Parale GP, Pawar SS, Tapare VS. Assessment of LV diastolic function in patients with beta-thalassemia major with special reference to E/Eann ratio. *J PediatrHematolOncol.* 2009; 31: 69–73.
31. Efthimiadis GK, Hassapopoulou HP, Tsikaderis DD, Karvounis HI, Giannakoulas GA, Parharidis GE. et al. Survival in thalassaemia major patients. *Circ J.* 2006; 70:1037-42.
32. Efthimiadis GK, Giannakoulas G, Hassapopoulou HP, Karvounis HI, Parcharidis GE. Prognostic value of Doppler-demonstrated left versus biventricular restrictive filling pattern in thalassemia major. *Echocardiography.* 2008; 25:553.
33. Cheung YF, So EK, Hwang GY, Chan GC, Ha SY. Left and Right Atrial Function and Remodeling in Beta-Thalassaemia Major. *PediatrCardiol.* 2019;40:1001-1008
34. Koren A, Garty I, Antonelli D, Katzuni E. Right ventricular cardiac dysfunction in beta-thalassemia major. *Am J Dis Child.* 1987; 141:93–96.
35. Zakynthinos E, Vassilakopoulos T, Kaltsas P, Malagari E, Daniil Z, Roussos C. et al. Pulmonary hypertension, interstitial lung fibrosis, and lung iron deposition in thalassaemia major. *Thorax.* 2001;56:737-9.
36. Alkholy UM, Mohamed SA, Elhady M, Attar SE, Abdalmonem N, Zaki A. Vascular endothelial growth factor and pulmonary hypertension in children with beta thalassemia major. *J Pediatr (Rio J).* 2019 ;95:593-599
37. Isa OnerYuksel, ErkanKoklu, ErdalKurtoglu, SakirArslan, GokselCagirci, VolkanKarakus. et al. The association between serum ferritin level, tissue doppler echocardiography, cardiac T2* MRI, and heart rate recovery in patients with beta thalassemia major. *ActaCardiol Sin.* 2016;32:231–238
38. Koohi F, Kazemi T, Miri-Moghaddam E. Cardiac complications and iron overload in beta thalassemia major patients-a systematic review and meta-analysis *Ann Hematol.* 2019;98:1323-1331

Tables

Table I: demographic characteristics of population study

	BMT group	Control group	P
	N=30	N=30	
Age (years)	10.4 ± 5	10.2 ± 5	0.876
Male sex	20	20	
Diagnostic age (months)	5.4 ± 3.17	-	-
Age of chelation onset (years)	1.7 ± 1.6 132.14 ± 23.7	-	-
Height(cm)	31.95 ± 13.9	127.7 ± 33.8	0.564
weight (Kg)	90.33 ± 12.45	40.5 ± 35.6	0.226
Heart rate	109.33 ± 15.91	88.83 ± 11.04	0.620
SBP (mmHg)	63.83 ± 5.03	97.5 ± 2.54	< 0.01
DBP (mm Hg)		62.5 ± 2.54	0.200

DBP: diastolic blood pressure. SBP: systolic blood pressure

Table II: conventional echocardiography parameters of 2 groups

	BTM group N=30	Control group N=30	p
LV systolic parameters			
EDIVS thickness (mm)	7.37 ± 1.84	6.6 ± 2.23	0.153
ED Posterior wall thickness(mm)	7.07 ± 1.98	6.93 ± 2.37	0.814
LVEDD (mm)	39.73 ± 7.80	38.97 ± 6.05	0.646
LVEDV (ml)	74.80 ± 29.07	68.63 ± 25.8	0.389
Indexed LVEDV (ml/m ²)	69.82 ± 18.61	61.44 ± 18.38	0.08
LVESD (mm)	23.66 ± 4.58	24.17 ± 4.91	0.685
LVESV(ml)	22.43 ± 8.40	21.46 ± 9.63	0.682
Indexed LVESV(ml/m ²)	21.10 ± 6.51	19.47 ± 8.55	0.41
LVEF by Simpson (%)	68.67 ± 5.99	67.80 ± 7.99	0.636
LV Diastolic parameters			
E(m/s)	1.14 ± 0.24	1.06 ± 0.17	0.16
A (m/s)	0.65 ± 0.18	0.40 ± 0.14	0.86
E/A	1.80 ± 0.61	1.80 ± 0.61	0.95
septal E/e'	7.33 ± 1.93	6.83 ± 1.02	0.22
latéral E/e'	7.34 ± 6.83	6.79 ± 1.49	0.8
E/Vp	1.44 ± 0.65	1.49 ± 0.42	0.73
DT (ms)	125.5 ± 43.3	115.3 ± 25.27	0.27
IVRT (ms)	82.55 ± 85.43	85.43 ± 14.87	0.55
Ap-Am	27.67 ± 29.12	16.90 ± 23.82	0.12
LA area (cm ²)	11.72 ± 4.92	10.07 ± 2.65	0.11
Indexed LA area (cm ² /m ²)	11.16 ± 3.36	9.24 ± 2.13	0.01
LA volume (ml)	29.78 ± 19.1	20.47 ± 7.6	0.02
Indexed LA volume (ml/m ²)	27.59 ± 13.1	18.23 ± 4.33	0.001
Right heart parameters			
	10.38 ± 2.87	9.83 ± 2.61	0.44

RA area (cm ²)	10.18 ± 2.93	9.08 ± 2.27	0.11
Indexed RA area (cm ² /m ²)	24.00 ± 9.07	20.53 ± 7.75	0.12
RA volume (ml)	23.16 ± 6.69	18.39 ± 4.75	0.003
Indexed RA volume (ml/m ²)	23.97 ± 5.22	24.33 ± 5.00	0.78
TAPSE (mm)	14.97 ± 2.93	16.03 ± 3.01	0.17
S'(cm/s)	27.1 ± 8.19	24.33 ± 3.5	0.09
SPAP(mmHg)			

A: late trans-mitral diastolic velocity. AP-AM: difference in duration of pulmonary venous and mitral wave. DT: deceleration time of the early trans-mitral diastolic flow. E: early trans-mitral diastolic velocity. e': mitral annular early diastolic myocardial tissue velocity. ED: end diastolic. EDIVS: end diastolic inter-ventricular septum. IVRT: isovolumic relaxation time. LA: left atrium. LV: left ventricle. LVEDD: LV end diastolic diameter. LVEF: LV ejection fraction. LVESD: LV end systolic diameter. LVEDV: LV end diastolic volume. LVESV: LV end systolic volume. RA: right atrium. S': peak of right ventricular systolic myocardial velocity. SPAP: systolic pulmonary artery pressure. TAPSE: tricuspid annular plane systolic excursion. Vp: flow propagation velocity.

Table III: Comparison of regional longitudinal strain values of basal, middle and apical myocardial segments between BTM and control groups.

	BTM group N=30	Control group N=30	P
Basal RLS			
Antero-lateral	-20.63 ± 8.23	-24.93 ± 10.98	0.09
Anterior	-18.20 ± 10.22	-27.1 ± 5.02	<0.001
Antero-septal	-19.43 ± 4.37	-24.6 ± 5.64	<0.001
Infero-septal	-22.73 ± 4.99	-25.6 ± 5.53	0.039
Inferior	-19.13 ± 8.89	-25 ± 5.11	0.003
Infero-lateral	-20.72 ± 7.64	-23.5 ± 8.36	0.289
Basal GLS	-19.98 ± 4.34	-25.4 ± 5.09	<0.001
middle RLS			
Antero-lateral	-23.43 ± 6.28	-26.67 ± 9.18	0.117
Anterior	-21.90 ± 10.69	-29.17 ± 4.27	0.001
Antero-septal	-23.63 ± 3.66	-26.93 ± 4.21	0.002
Infero-septal	-25.37 ± 4.67	-26.9 ± 5.19	0.23
inferior	-22.17 ± 6.15	-26.7 ± 3.92	0.01
infero-lateral	-23.03 ± 6.26	-25.9 ± 8.16	0.13
middle GLS	-23.69 ± 3.65	-27.05 ± 4.17	0.002
Apical RLS			
Anterior	-26.17 ± 6.59	-28.77 ± 5.32	0.09
Septal	-28.07 ± 5.35	-29.43 ± 4.34	0.28
Inferior	-27.50 ± 6.38	-28.60 ± 4.8	0.45
Lateral	-24.50 ± 12.17	-29.03 ± 4.06	0.06
Apical GLS	-23.19 ± 15.25	-27.08 ± 11.11	0.26
Apex	-27.30 ± 5.1	-28.83 ± 4.33	0.22

GLS: global longitudinal strain. RLS: regional longitudinal strain

Table IV: Correlation between serum ferritin level and LVEF, indexed LA area and volume, E/e', TAPSE, S' wave, SPAP and GLS

First parameter	Second parameter	R	P-value
serum ferritin level	LVEF	-0,03	0,88
	Indexed LA area	-0.22	0.25
	Indexed LA volume	-0.08	0.68
	SPAP	-0.2	0.27
	TAPSE	-0.14	0.45
	S' wave	-0.14	0.45
	E/e'	0.75	0.06
	GLS	-0.01	0.92

Note : correlation is significant at the 0.05 level

E: early trans-mitral diastolic velocity. e': mitral annular early diastolic myocardial tissue velocity. GLS: global longitudinal strain. LA: left atrium. LVEF: LV ejection fraction. S': peak of right ventricular systolic myocardial velocity. SPAP: systolic pulmonary artery pressure. TAPSE: tricuspid annular plane systolic excursion.

Figures

Figure 1

Bull's eye plotsshowing RLS values of 17 myocardial segmentsin a healthy child.

Figure 2

Bull's eye plotsshowing RLS values of 17 myocardial segments in a BTM chid.