Cardiac iron overload detection using longitudinal strain in asymptomatic children with beta thalassemia major

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Abstract
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. To demonstrate the contribution of longitudinal strain (LS) in early detection of cardiac iron overload in children with BTM. 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. 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 ± 13.1 ml/m² vs. 18.23 ± 4.33 ml/m², 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). In asymptomatic BMT children with normal conventional TTE parameters, LS could be used for the detection of subclinical myocardial dysfunction.

Keywords   Speckle tracking · Detection · Infant · Cooley’s anemia

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  
LVSV  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

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 deferasiprone, 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), cardiac index, interventricular septum (IVS) and posterior wall thickness of LV were measured. The description of LV dilatation and thickness severity was adjusted to body surface area (BSA) using z-scores. 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 (Vp) (E/Vp), 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 (Figs. 1 and 2).

Statistical analysis

Categorical variables are presented as absolute values and proportions. Continuous variables are presented as means ± 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 1). 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 µg/L in BTM group and 8 patients had ferritin level < 1000 µg/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 2, 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 BMT 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). No significant difference between the two groups in term of indexed cardiac index. 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 BMT group compared to control group (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 BMT group (27.1 ± 8.1 mmHg vs. 24.3 ± 3.5 mmHg, p = 0.09). Indexed RA volume was significantly higher in BMT 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 BMT patients compared to control group (Table 3). 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 4).

**Discussion**

According to previous studies, cardiac involvement caused by myocardial iron deposition remains one of the chief causes of morbidity and mortality in BMT [4, 5]. The progressive asymptomatic cardiac iron overload leads to mis-diagnosed cardiac dysfunction at the early stage in BMT patients. According to the current study results, LV strain study could contribute to early detection of iron myocardial involvement in asymptomatic BMT 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.

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**Table 1** Demographic characteristics of population study

|                  | BMT group N=30 | Control group N=30 | P       |
|------------------|----------------|-------------------|---------|
| 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)      | 10.4 ± 5       | 62.5 ± 2.54       | 0.200   |

*DBP* diastolic blood pressure, *SBP* systolic blood pressure.
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

| Table 2 | Conventional echocardiography parameters of 2 groups |
|------------------|------------------|------------------|
|                     | BTM group N=30   | Control group N=30 |
| 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/m²) | 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/m²) | 21.10 ± 6.51    | 19.47 ± 8.55     | 0.41  |
| LVESV by simpson (%) | 68.67 ± 5.99    | 67.80 ± 7.99     | 0.636 |
| Indexed cardiac index (l/min/m²) | 4.27±1.18    | 3.71±1.14       | 0.07  |
| 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 (cm²) | 11.72 ± 4.92   | 10.07 ± 2.65     | 0.11  |
| Indexed LA area (cm²/m²) | 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/m²) | 27.59 ± 13.1  | 18.23 ± 4.33     | 0.001 |
| Right heart parameters |              |                  |
| RA area (cm²) | 10.38 ± 2.87   | 9.83 ± 2.61      | 0.44  |
| Indexed RA area (cm²/m²) | 10.18 ± 2.93   | 9.08 ± 2.27      | 0.11  |
| RA volume (ml) | 24.00 ± 9.07   | 20.53 ± 7.75     | 0.12  |
| Indexed RA volume (ml/m²) | 23.16 ± 6.69   | 18.39 ± 4.75     | 0.003 |
| TAPSE (mm) | 23.97 ± 5.22   | 24.33 ± 5.00     | 0.78  |
| S' (cm/s) | 14.97 ± 2.93   | 16.03 ± 3.01     | 0.17  |
| SPAP (mmHg) | 27.1 ± 8.19     | 23.43 ± 3.5      | 0.09  |

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, LVESV LV end systolic volume, LVEDV LV end diastolic volume, LVEF by simpson, 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 3 Comparison of regional longitudinal strain values of basal, middle and apical myocardial segments between BTM and control groups

| Parameter          | BTM group N = 30 | Control group N = 30 | P     |
|-------------------|------------------|----------------------|-------|
| Basal RLS         |                  |                      |       |
| Anterolateral      | −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         |                  |                      |       |
| Anterolateral      | −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  |

Table 4 Correlation between serum ferritin level and LVEF, indexed LA area and volume, E/e’, TAPSE, S’ wave, SPAP and GLS in BTM group

| 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    |

$E$ 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

Correlation is significant at the 0.05 level

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. 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 [28, 29]. 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 [30, 31]. 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 [32]. LA could provide useful information in early BTM thalassemia states, regardless of the LVEF and diastolic abnormalities appears after the onset of cardiac failure [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 µg/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. On the one hand, high ferritin level could be explained by inflammation, infection or liver diseases in BTM patients. On the other hand, there is a low specificity of serum ferritin level observed in BTM patients. Several studies revealed that serum ferritin level is not appropriate to predict myocardial iron deposition due to its lack of relationship with cardiac iron [39, 40].

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.

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Declarations

Conflict of interest The authors have not disclosed any competing interests.

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