Value of speckle tracking echocardiography for detection of clinically silent left ventricular dysfunction in patients with β-thalassemia

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\textbf{ABSTRACT}

\textbf{Objective:} β-Thalassemia is an inherited hemoglobin disorder resulting in chronic hemolytic anemia requiring chronic transfusion therapy. Cardiac involvement is the main cause of death in patients with thalassemia major. The narrow border is between overt myocardial dysfunction and clinically silent left ventricular (LV) dysfunction in patients with thalassemia. Therefore, we need novel parameters in different imaging techniques to discover cardiac involvement in an early and subtle stage. We explore to find a novel, straightforward and informative parameter in echocardiography as a noninvasive, economical and really routine in clinical practice.

\textbf{Methods:} In this prospective study, 55 patients, who are known cases of β-thalassemia major, receiving long-term blood transfusions and undergoing iron chelation therapy were enrolled. Ferritin level, cardiac magnetic resonance (CMR) T2 * value, full conventional echocardiography and speckle tracking, LV regional circumferential and longitudinal strain values (%) and time-to-peak strain (ms) of 17 segments cardiac model in eyeball tomogram were measured.

\textbf{Results:} There was a significant reduction in global longitudinal strain (GLS) (−20.9% ± 1.9 vs. −22.2 ± 1.03) and also basal segments longitudinal strain compared to normal subjects group (−17.4% ± 2.7 vs. −19.6% ± 1.2). There was no significant difference in circumferential strain value between thalassemia patients and normal control group. Interestingly, there was no significant correlation between GLS and CMR T2 * values showing no association between cardiac iron load and longitudinal strain.

\textbf{Conclusion:} Speckle tracking echocardiography could be used as a feasible method for evaluating subclinical myocardial dysfunction in patients with thalassemia major. Echocardiography, using GLS, could predict clinically silent myocardial dysfunction independent of CMR (T2 * value) and extension of iron deposition. Our study also puts forward other causes such as chronic tissue hypoxia resulting from chronic anemia as a root cause and initiating factor for subsequent injury by the iron deposition. Speckle tracking can recognize the cardiac involvement in early stages.

\textbf{Keywords:} Thalassemia; speckle tracking echocardiography; longitudinal strain; circumferential strain; cardiac MR T2 *

\textbf{Introduction}

β-Thalassemia is considered as one of the most common inherited hemoglobin disorder caused by the declined synthesis of β-globin chains, resulting in ineffective erythropoiesis, subsequent chronic hemolytic anemia and iron overload [1]. The phenotypic spectrum varies considerably as we face both asymptomatic thalassemia carrier and the clinically severe thalassemia major [1]. β-Thalassemia major represents with severe anemia through the first year of life and depends onlife-long transfusion therapy [2]. In spite of advances in therapeutic management of thalassemia, iron-mediated cardiomyopathy is the leading cause of death and morbidity [3]. Besides iron overload, chronic anemia, the presence of hemoglobin F with increased oxygen affinity and production of free oxygen radicals induced by toxic free iron, all are contributors of cardiomyopathy in these patients [1,4,5]. It is postulated that the development of dilated cardiomyopathy in β-thalassemia is multifactorial including immunoinflammatory and inherited components [6]. Many thalassemia patients may develop no symptom until becoming decompensated. But with development of overt heart failure, only 50% of patients will survive [7]. Global ventricular function and exercise capacity may remain within normal value until late stage of disease process [7]. Nowadays, cardiovascular magnetic resonance imaging, specifically T2* imaging, is used for precise assessment of myocardial and hepatic iron load and for therapeutic guidance [6]. However, echocardiographic strain analysis could define subclinical cardiac involvement in many cardiac disease [8]. Longitudinal left ventricular (LV) strain, predominantly originating from the...
subendocardial region, is the most sensitive component of LV strain in the presence of myocardial disease. However, circumferential strain (CS) represents the mid myocardial and epicardial regions better [9]. As chronic hypoxia from chronic anemia in thalassemia major patients may affect subendocardial tissue and LV myocardial longitudinal strain and iron deposition in the subepicardial level may have influences on CS, the aim of this study was to define whether these two mentioned parameter could identify early cardiac dysfunction in comparison with cardiac MR T2* value.

Study population

From September 2013 to March 2015, 55 patients known as being affected by thalassemia major, receiving long-term blood transfusions and undergoing iron chelation therapy, were prospectively enrolled. In all patients, ferritin levels were measured and cardiac magnetic resonance (CMR) imaging was done for the assessment of myocardial iron load by means of T2* value. All included patients had acceptable echocardiographic image quality and were in normal sinus rhythm. We also evaluated 18 normal subjects with perfectly acceptable echocardiographic images as the control group.

The exclusion criteria were hypertension (newly diagnosed or treated), diabetes mellitus, symptoms of heart failure, LV dysfunction defined as ejection fraction <50%, more than mild valvulopathy, presence of atrial fibrillation or flutter, history of ischemic heart disease or prior cardiomyopathy and pulmonary arterial hypertension <50%, more than mild valvulopathy, presence of atrial fibrillation or flutter, history of ischemic heart disease or prior cardiomyopathy and pulmonary arterial hypertension more than 30 mmHg.

Conventional echocardiography

All patients underwent standard echocardiographic examinations in the supine left lateral decubitus position using a Phillips IE 33 ultrasound system.

Left ventricular end-systolic and diastolic volumes and LV ejection fraction were quantified offline using a semiautomatic measurement tool.

Peak mitral E velocity was obtained by placing the sample volume of Doppler tissue imaging at the level of tip of mitral valve leaflets. By placing the sample volume of Doppler tissue imaging at the septal mitral annulus peak early (E) diastolic myocardial velocity was obtained and E/E’ ratio was measured as an index of myocardial filling pressure.

Right ventricular (RV) end-diastolic diameter at mid-ventricular level was measured in four-chamber view. TAPSE was assessed by placing M-mode cursor line at lateral TV annulus in four-chamber view. And peak RV systolic myocardial velocity (S’) was obtained by placing the sample volume of Doppler tissue imaging at lateral TV annulus. Two-dimensional grayscale loops, from parasternal short-axis views (basal, mid and apical level) and apical views (four, two and three chambers) were carefully acquired, for three consecutive cycles, at about 50–80 frame/s. Images were digitally recorded for subsequent offline analysis.

Speckle tracking for longitudinal strain analysis

Offline analysis was performed by using CMQ lab software available on the Phillips ultrasound system. Based on echocardiographic speckle tracking algorithm, apical four-chamber, two-chamber and three-chamber views were analyzed in each subject. Aortic valve closure time was automatically identified in the three-chamber view and visually controlled and edited if necessary. In each cardiac apical view, three points at the endocardial border were placed including two annular points at the base and one point at the apex. Subsequently, the endocardial border was traced automatically, edited if needed, and approved for calculation. After that, the system represented regional longitudinal strain value (%) and time-to-peak (TTP) strain (ms) of 17 segments cardiac model in eyeball tomogram. It also measured ventricular volumes, ejection fraction, global longitudinal strain (GLS) and standard deviation of TTP strain.

To assess LV CS, the endocardial border was traced automatically in end diastole in each short-axis view, with entire myocardium inside the region of interest for optimal tracking. Mid- and basal-short-axis views were divided in 6 segments while apical short-axis view was divided to one sample Kolmogorov–Smirnov test, parameters could be expressed as mean ± SD. Continuous variables were compared between the two groups using Student’s t-tests. Relationships between two distinct parameters were assessed using Person’s method. P values <0.05 were considered statistically significant.

Statistical analysis

As our parameters have normal distribution according to one sample Kolmogorov–Smirnov test, parameters could be expressed as mean ± SD. Continuous variables were compared between the two groups using Student’s t-tests. Relationships between two distinct parameters were assessed using Person’s method. P values <0.05 were considered statistically significant.
There were no significant differences in age and gender distribution between the groups ($P = 0.4$ and $P = 0.7$, respectively). Body surface area of patients group was significantly lower than that of control subjects ($P = 0.00$). The blood hemoglobin level of the control group was significantly higher than that of the patients group ($P = 0.00$) (Table 1). In the subgroup of patients evaluated by means of CMR imaging, the mean T2* value was $23.5 \pm 9.8$ ms, with 16 patients showing myocardial iron overload (T2* $< 20$ ms).

**Conventional echocardiographic parameters**

The mean values of conventional echocardiographic parameters are briefly summarized in Table 2. LVEDV and LVESV were considerably higher in thalassemia patients. Although LVEF is within normal value in both groups, but LVEF is higher in the control group. While both septal E' and E/E' value are in normal range in both groups, there were significant differences between two groups, as septal E' is higher and E/E' ratio is lower in the control group. There were no significant differences in RV size and its systolic function regarding to Sm and TAPSE between the groups.

**LV mechanics parameters**

The mean value of LV mechanics parameters presented in Table 3. GLS was significantly higher in the patients group while no significant difference in CS was observed between the groups and regarding to segmental longitudinal analysis, basal segments longitudinal strain was significantly higher in the control group. Standard deviation of time-to-peak strain (SD-TTP) was significantly higher in the patients group.

**Correlation between different parameters in patients group**

There is no correlation between LV cardiac mechanics parameters (GLS, CS, Basal, middle and apical segments longitudinal strain) and Hgb, ferritin and injection intervals. There was also no correlation between strain value and control group.

**Table 2. Echocardiographic data.**

| Variables      | Thalassemia (mean ± SD) | Healthy subjects (mean ± SD) | $P$ value |
|----------------|-------------------------|-----------------------------|-----------|
| LVEDV (ml)     | 100.3 ± 23.6            | 87.3 ± 12.4                 | 0.038     |
| LVESV (ml)     | 43.8 ± 11               | 34 ± 5.2                    | 0.002     |
| LVEDV/LSA      | 66.3 ± 13.6             | 49.5 ± 6.2                  | 0.00      |
| LVEF (%)       | 56.4 ± 4.8              | 60.1 ± 2.9                  | 0.005     |
| E/E'           | 9.9 ± 2.3               | 7.2 ± 1.3                   | 0.00      |
| Apical segments (%) | 23.8 ± 4               | 22.6 ± 2.7                  | 0.24      |

**Table 3. LV mechanics data.**

| Variables      | Thalassemia (mean ± SD) | Healthy subjects (mean ± SD) | $P$ value |
|----------------|-------------------------|-----------------------------|-----------|
| GCS (%)        | −24.8 ± 2.5             | −23.7 ± 2.5                 | 0.11      |
| GLS (%)        | −20.9 ± 1.9             | −22.2 ± 1.03                | 0.007     |
| Basal segments LS (%) | −17.4 ± 2.7           | −19.6 ± 1.2                 | 0.002     |
| Mid segments LS (%) | −23.1 ± 2.6            | −23.1 ± 2.5                 | 0.99      |
| Apical segments LS (%) | −23.7 ± 2.7           | −23.5 ± 2.4                 | 0.85      |
| SD-TTP LS (ms) | 14.4 ± 6.7              | 9.2 ± 5                     | 0.004     |

**Discussion**

High cardiac output state from chronic anemia in thalassemia may cause LV enlargement [10] as shown in our study in comparison with healthy individuals. Loading conditions, such as changes in preload, could have different effects on early and annular tissue velocities. E velocity is more load dependent and influenced by both myocardial relaxation and LA pressure but E' velocity declines as diastolic dysfunction worsens [11]. In our study E' velocity remains within normal limits but with significant decline in comparison with normal control group and it is compatible with the results of previous studies representing that there will be no global LV diastolic dysfunction till late stage of disease [12,13].

In our study Doppler measurements of transmitral and annular velocities revealed higher E/E' ratio in thalassemia than the control group. This finding is concordant with previous studies that showed higher E velocity in thalassemia is due to chronic anemia and higher preload state [12–14]. As in our study, poor correlation was also demonstrated between iron overload (cardiac T2* CMR) and classic parameters of diastolic function [13].

As patients with pulmonary hypertension were excluded from our study, there were no significant differences in RV size and related systolic function parameters, including TAPSE and RV-Sm, between patients and control group.

In our study, there was a significant reduction in GLS along with reduced basal segments longitudinal strain. But it revealed no further association between cardiac iron load and longitudinal strain. It can be described as although iron overload still has a central role in development of LV dysfunction in thalassemia, the pathophysiology of ventricular dysfunction is multifactorial and besides iron overload, chronic tissue hypoxia as a result of chronic anemia, various degree of individual's susceptibility to iron toxicity, myocarditis, viral infection as a result of repetitive exposure to different viral burden during transfusions, high level of auto
antibodies in circulation, immunodeficient state of thalassemia patients and vascular endothelial function resulted in LV afterload mismatch [6,15–20]. Patients with thalassemia also have higher value of SD-TTP in comparison with our control group which means that these immunogenetic factors mentioned before, may cause some degree of asynchronous cardiac systolic function. It should be also mentioned that there was smaller number of thalassemia patients with cardiac iron overload (cardiac T2* < 20 ms) in our study (16 patients) than those with normal cardiac iron (cardiac T2* > 20 ms). In contrary to our study, Ines Monte et al. showed no significant differences in longitudinal strain value between thalassemia and healthy individuals. They may be because that they used only two chamber and four chamber strain values, their sample volume was significantly lower than ours (27 patients vs. 55 patients, respectively), and their patients population had higher LVEF than ours (61 ± 6% vs. 56.4 ± 4.8%, respectively). In a study done by Maurizio Cusmà Piccione et al. on thalassemia patients, the global LV longitudinal strain was significantly impaired in the patients compared with the controls, although radial and CS values were similar between the two groups [21]. Their results were compatible with ours.

Longitudinal strain is affected by deformation of the subendocardial fibers, CS is represented of deformation of the mid- or subepicardial fibers, and radial strain results from the transmural deformation. Among these myocardial fibers, subendocardial fibers are the most sensitive to myocardial injury, such that in the case of myocardial damage, longitudinal will be affected the earlier than circumferential and radial strains [22]. As iron deposition occurs predominantly on subepicardial layer [13,15], it is expected that with iron deposition, CS will decrease. But there was no significant difference in CS value between normal subjects and thalassemia in our studies. It is postulated that with early decline in longitudinal strain, compensatory increase in circumferential deformation will take place to preserve stroke volume, so even with Iron deposition, in comparison with normal individuals, there could be no significant differences in CS value although there exist a decremental change from baseline value before iron deposition.

Finally, it should be kept in mind that echocardiographic findings are cumulative and reflect chronic iron overload. They might fail to demonstrate acute changes in function in times when there is severe cardiac iron overload or on the other hand acute therapeu tic changes.

### Conclusion

We did not find a correlation between cardiac MR T2* and GLS assessed by echocardiography. Moreover, our study reveals longitudinal strain but not CS reduces in clinically silent thalassemia patients at initial stages. We highly recommend routine use of GLS in echocardiographic evaluation of thalassemia population; furthermore, we suggest intensive correction of anemia and strict treatment of viral infections along with close follow up in clinically silent thalassemia patients with reduced GLS and normal cardiac MR T2*.

### Disclosure statement

No potential conflict of interest was reported by the authors.

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### Table 4. Pearson correlation between LV mechanics parameters and other variables in thalassemia.

| Parameters       | Hgb            | Ferritin       | Injection Intervals | E/E        | E          | RV-Sm     | TAPSE     | Cardiac T2* |
|------------------|----------------|----------------|---------------------|------------|------------|-----------|-----------|-------------|
| GLS              | -0.02          | -0.034         | -0.2                | 0.02       | -0.08      | -0.19     | 0.07      | -0.011      |
| CS               | -0.11          | -0.23          | -0.19               | -0.002     | -0.05      | -0.02     | 0.03      | -0.11       |
| Basal LS         | -0.01          | 0.001          | 0.023               | -0.04      | -0.19      | 0.2       | -0.1      | -0.02       |
| Mid LS           | 0.06           | 0.01           | -0.09               | -0.18      | 0.014      | -0.04     | -0.019    | -0.1        |
| Apical LS        | 0.06           | 0.02           | -0.11               | 0.07       | -0.06      | -0.368    | 0.087     | -0.01       |
| Cardiac T2*      | 0.08           | 0.002          | 0.07                | 0.2        |            |           |           |             |
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