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Left atrial strain in patients with β-thalassemia major: a cross-sectional CMR study

ABSTRACT

Objectives: The aim of this cross-sectional study was to investigate the association of left atrial (LA) strain parameters with demographics, clinical data, cardiovascular magnetic resonance (CMR) findings, and cardiac complications (heart failure and arrhythmias) in a cohort of patients with β-thalassemia major (β-TM).

Materials and Methods: We considered 264 β-TM patients (133 females, 36.79±11.95 years) consecutively enrolled in the Extension-Myocardial Iron Overload in Thalassemia (E-MIOT) project. Moreover, we included 35 sex- and age-matched healthy controls (14 females, mean age 37.36±17.52 years).

Reservoir, conduit, and booster LA functions were analysed by CMR feature tracking using dedicated software.

Results: Compared to the healthy control group, β-TM patients demonstrated lower LA reservoir strain and booster strains, as well as LA reservoir and booster strain rates. However, no differences were found in LA conduit deformation parameters.

In β-TM patients, ageing, sex, and left ventricle (LV) volume indexes were independent determinants of LA strain parameters. The number of segments with late gadolinium enhancement (LGE) significantly correlated with all LA strain parameters, with the exception of the LA conduit rate. Patients with cardiac complications exhibited significantly impaired strain parameters compared to patients without cardiac complications.

Conclusion: In patients with β-TM, LA strain parameters were impaired compared to control subjects, and they exhibited a significant correlation with the number of LV segments with LGE. Furthermore, patients with cardiac complications had impaired left atrial strain parameters.

Clinical relevance statement

In patients with β-thalassemia major, left atrial strain parameters were impaired compared to control subjects and emerged as a sensitive marker of cardiac complications, stronger than cardiac iron levels.

KEYWORDS: Magnetic Resonance Imaging, Left Atrium, Thalassemia

Key Points

- Compared to healthy subjects, β-thalassemia major patients demonstrated significantly lower left atrial reservoir strain and booster strains, as well as left atrial reservoir and booster strain rates.

- In β-thalassemia major, ageing, sex, and left ventricular volume indexes were independent determinants of left atrial strain parameters, while left atrial strain parameters were not correlated with myocardial iron overload.

- An independent association between reduced left atrial strain parameters and a history of cardiac complications was found in β-thalassemia major patients.

ABBREVIATIONS

β-TM beta-thalassemia major

MIO myocardial iron overload

HF heart failure

CMR cardiovascular magnetic resonance

LV left ventricular

LA left atrium

E-MIOT Extension-Myocardial Iron Overload in Thalassemia

RV right ventricular

SR strain rate

LGE late gadolinium enhancement

ANCOVA analysis of covariance

ROC receiver operating characteristic

AUC area under the curve

INTRODUCTION

Beta-thalassemia stands as the most frequent hemoglobinopathy, characterised by impaired production of β chains of haemoglobin [1,2]. Beta-thalassemia major(β-TM) patients require lifelong red blood transfusions that inevitably result in iron overload in various organs, including the heart[1,3]. Myocardial iron overload(MIO) determines cardiac dysfunction and heart failure(HF), which remain the primary cause of morbidity and mortality in β-TM patients[4-6].

An important issue that has changed over the past decades, owing to regular blood transfusions and iron chelation therapy, is the age of onset and the outcome of HF[7]. Nevertheless, despite the early diagnosis of myocardial iron overload facilitated by cardiovascular magnetic resonance(CMR)[8], some patients are still detected in the late stage of the disease with impaired left ventricular(LV) systolic function and irreversible myocardial damage[7,9]. In the progression of thalassemia cardiomyopathy, LV diastolic dysfunction typically precedes systolic dysfunction. Therefore, the early identification of LV diastolic impairment is crucial to ensure timely and appropriate adjustments to therapeutic decisions[7]. It is well known that the left atrium(LA) strain represents a useful non-invasive parameter for evaluating LV diastolic function[10-12]. In addition, the LA mechanism in β-TM patients is impaired not only by LV diastolic dysfunction but also by direct atrial damage due to iron overload and increased oxidative stress[13,14].

Among non-invasive modalities, CMR has been shown to quantify atrial strain with higher accuracy compared to speckle-tracking echocardiography. Indeed, CMR overcomes some intrinsic limitations of ultrasound, such as the requirement for high-quality echocardiography images and intra-observer variability[11,15,16].

Currently, little is known about the importance of factors involved in the physiology of LA strain in β-TM. Therefore, this study aimed to evaluate the relationship of the CMR-derived LA strain with demographics, clinical data, CMR parameters, and cardiac complications.

MATERIALS AND METHODS

Study population

We considered 264 β-TM patients (133 females, 36.79±11.95 years) consecutively enrolled in the Extension-Myocardial Iron Overload in Thalassemia(E-MIOT) project. E-MIOT is an Italian network comprisisng 66 thalassemia centers and 15 validated MR sites[17,18], interconnected through a web-based database collecting demographic, clinical, laboratory, and specific CMR parameters of all patients.

All patients received regular blood transfusions since early childhood to maintain a pre-transfusion haemoglobin level of 9-10g/dl and were chelated.

Thirty-five healthy subjects (14 females, 37.36±17.52years) were included as control group. Inclusion criteria were: normal electrocardiogram, no history of cardiac diseases or symptoms, no cardiovascular risk factors, no history of blood or systemic disorders or known conditions/treatments which could affect iron content, and no absolute contraindications to the CMR.

All subjects gave written informed consent. The study complied with the Declaration of Helsinki and was approved by the institutional ethics committee.

CMR

CMR exams were performed in the reference MR center (Pisa) of the E-MIOT Network using a 1.5T scanner (Signa Excite HD/Signa Artist, GE Healthcare, Milwaukee, WI, USA). A cardiac phased-array receiver surface coil with breath-holding and ECG gating was used.

MIO was assessed by acquiring three parallel short-axis views (basal, medium, and apical) of the LV by a T2* gradient–echo multiecho sequence[19]. Image analysis was conducted using a custom-written, previously validated software (HIPPO MIOT®)[20]. The software provided the T2* value on each of the 16 LV segments, according to the standard AHA/ACC model[21]. Susceptibility artefacts

were compensated by applying an appropriate correction map[20]. The global LV T2* value was calculated as the average of all segmental values.

To assess cardiac chamber size and function, cine images were acquired using a steady-state free procession sequence in two-, three- and four-chamber planes and in the short-axis plane with whole ventricular coverage from base to apex[22]. Thirty cardiac phases were acquired per heartbeat. Offline post-processing was performed by expert (>10years) operators using a commercially available software system (Circle CVI42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). LV and right ventricular(RV) volumes and ejection fractions and LV mass were quantified in a standard way from short-axis cine images. Papillary muscles were included in the left ventricular cavity volume.

CMR-tissue tracking analysis for assessing LA deformation was performed using CVI42 software. LA endocardial borders were manually traced on long-axis cine images when the atrium was at its minimum volume. The software algorithm automatically tracked the myocardial borders throughout the cardiac cycle. The quality of the tracking and contouring was visually evaluated by the operator. If the automatic boundary tracking was not accurate, the contours were manually adjusted, and the algorithm was reapplied. The following global longitudinal strain parameters were measured: LA reservoir (passive LA expansion during LV contraction), LA conduit (passive filling of the LV in early-mid LV diastole), and LA booster (the atrial kick in late diastole) (Figure 1). Consequently, three LA strain rate(SR) parameters were derived: LA reservoir SR (positive SR), LA conduit SR (early negative SR), and LA booster SR (late negative SR). LA strains and strain rates were evaluated from 2-chamber and 4-chamber cine images, and the average values were determined.

The two-plane area-length method was employed to quantify the LA volume in the LV end-systole from 2- and 4-chamber views[23].

To detect replacement/focal myocardial fibrosis, late gadolinium enhancement(LGE) short-axis, vertical, horizontal, and oblique long-axis images were acquired by a T1-weighted gradient-echo inversion-recovery pulse sequence, 8–18min after the intravenous administration of Gadobutrol

(Gadovist®; Bayer Schering Pharma; Berlin, Germany) at the standard dose of 0.2mmol/kg of body weight. LGE image acquisition was not done in patients who refused the contrast medium administration or with renal dysfunction. LGE was considered present if visualised in two different views[24]. The extent of LGE was quantified in the number of segments involved using the standard AHA/ACC model.

Diagnostic criteria

A T2* measurement of 20ms was the "conservative" normal value for the segmental and global LV T2* values[8,20].

Diabetes mellitus was defined as fasting plasma glucose≥126mg/dl or 2-h plasma glucose≥200mg/dl during an oral glucose tolerance test or random plasma glucose≥200mg/dl with classic symptoms of hyperglycaemia[25].

Cardiac complications were defined as a composite event, including HF and arrhythmias, clinically active at the time of the CMR. HF was diagnosed based on symptoms (breathlessness, ankle swelling, and fatigue), signs, and instrumental findings, according to the current guidelines[26]. Arrhythmias were diagnosed if documented by ECG or 24-hour Holter ECG and requiring specific medications. Arrhythmias were classified according to the AHA/ACC guidelines[27].

Statistical Analysis

All data were analysed using SPSS version 27.0 (IBM Corp, Armonk, NY) and MedCalc version 19.8 (MedCalc Software Ltd, Ostend, Belgium) statistical packages.

Continuous variables were described as mean±standard deviation and categorical variables as frequencies and percentages.

The normality of the distribution of the parameters was assessed by using the Kolmogorov-Smirnov test or the Shapiro-Wilk test for a sample size≤50.

The comparison between two groups was performed by independent-samples t-test for continuous values with normal distribution, Wilcoxon's signed rank test for continuous values with non-normal distribution, and $\chi 2$ testing for categorical data.

Correlation analysis was performed using Pearson's or Spearman's tests where appropriate.

Analysis of covariance(ANCOVA) was used to evaluate the impact of potential covariates on group differences in continuous parameters. Covariates were included if a variable significantly differed between groups and was associated with the assessed outcome. When necessary, outcomes were log-transformed to normalise the residual distributions and to equalise the residual variance.

Linear univariate and stepwise multivariate regression analyses were performed to identify determinants of LA deformation parameters. Multivariate regression was performed using only variables with a $p<0.05$ in univariate regression analyses. The collinearity of variables tested in the multivariate model was assessed using the variance inflation factor (inflated if >5) and its tolerance statistic (inflated if <0.20).

The receiver operating characteristic(ROC) analysis was made to evaluate the diagnostic ability of the LA parameters in detecting the presence of cardiac complications, and the results were presented as areas under the curve(AUCs) with 95%confidence intervals(CIs). The optimal cut-off value was calculated using the Youden index method. The Delong's test was used to compare the statistical differences between AUCs.

A 2-tailed $p<0.05$ was considered statistically significant.

RESULTS

Comparison between healthy subjects and β-TM patients

Table 1 shows the comparison between healthy subjects and β-TM patients. Age and sex were comparable between the two groups. Compared to healthy individuals, TM patients exhibited

significantly lower LA reservoir strain and booster strains and LA reservoir and booster SR. In contrast, there was no difference in LA conduit functions.

In healthy subjects, all LA strains and SRs were comparable between males and females, and only LA conduit functions showed a significant association with age (strain: R=-0.460, p=0.005 and SR: R=0.600, p<0.0001).

Demographic and clinical correlates of LA strain parameters in TM patients

Table 2 shows the demographic, clinical, and CMR characteristics of TM patients and their associations with LA strains and SR.

All LA strains and strain rates were significantly lower in females than males. LA reservoir, conduit strains, and strain rates significantly correlated with age, age at the start of chelation therapy, and body surface area, whereas LA booster strain and SR did not. LA reservoir, conduit strains, and strain rates were significantly reduced in splenectomised patients compared to non-splenectomised patients and patients with diabetes compared to diabetes-free patients. Age significantly differed between splenectomised and non-splenectomised patients (41.77±9.01years vs. 31.81±12.47years; p<0.0001) and between patients with and without diabetes (45.03±7.37years vs. 35.32±12.03years; p<0.0001) and was therefore used as a covariate in the ANCOVA. After the correction for age, all differences in strain and strain rates between splenectomised and non-splenectomised patients, as well as between patients with and without diabetes, lost statistical significance.

All LA strains and strain rates were independent of age at the start of regular transfusions, pre-transfusion haemoglobin levels, and mean serum ferritin over the previous year.

Association of LA strain with CMR parameters

All LA strains and SRs were significantly correlated with each other (coefficients of correlation ranging from 0.412 to 0.925).

No LA strain or SR parameter was associated with global LV T2* values and number of segments with T2*<20ms.

LA reservoir and conduit strains and strain rates exhibited a significant association with LV end-diastolic volume index and ejection fraction, while LA booster strain and SR did not.

All LA strain and strain rates were significantly correlated with LV mass index and LA end-diastolic volume index.

One-hundred and seventy-three(65.5%) patients were injected with the contrast medium, and LV LGE was detected in 66(38.2%) of them. Only two patients presented a transmural LGE pattern, while the remaining 64 patients had a non-ischemic LGE pattern (**Figure 2**). The 72.7% of patients had at least two foci of fibrosis, and the septum was involved in 80.3% of the cases. All LA strains and strain rates were comparable between patients without and with LGE. In the subgroup of LGE-positive patients, the number of segments with LGE (mean:2.59±1.78; range:1-9) significantly correlated with all LA strain parameters, with the exception of the LA conduit rate (LA reservoir strain: R=-0.299, p=0.015; LA conduit strain: R=-0.264, p=0.032; LA booster strain: R=-0.314, p=0.010; LA reservoir SR: R=-0.233, p=0.049; LA booster SR: R=0.308, p=0.012).

Predictors of LA strain parameters

Univariate and multivariable determinants of LA reservoir, conduit, and booster strains and strain rates are shown in **Table 3**. For each tested dependent variable, there was no collinearity between independent variables in the final multivariate model.

Female sex emerged as an independent predictor of all LA deformation parameters except for the LA booster SR. Age at scan was independently associated with LA reservoir and conduit strains and strain rates. Among the LV functional parameters, LV end-diastolic and end-systolic volume indexes remained significantly associated with LA reservoir and booster strains, while the LV end-diastolic volume index emerged as the only CMR determinant of LA reservoir and booster strain rates.

Association of LA strain parameters with outcome

Twenty-three(8.7%) patients had at least one cardiac complication. Specifically, 9 patients had HF (5 with preserved ejection fraction), 13 arrhythmias, and one both HF and arrhythmias. Supraventricular arrhythmias (atrial fibrillation and atrial flutter) were the most common type of arrhythmias (11/14=78.6%).

Table 4 shows the comparison between patients without and with cardiac complications. No difference between the two groups was detected in terms of sex, haematological parameters, cardiac iron levels, and LV size and function. In contrast, patients with cardiac complications were significantly older, more frequently splenectomised, and affected by diabetes. Moreover, patients with cardiac complications presented more often with LGE and exhibited higher LA end-diastolic volume index and worse LA strains and strain rates. For all LA deformation parameters, the difference between patients without and with cardiac complications remained significant also after the adjustment for age ($p<0.0001$ for all parameters).

Figure 3 shows the ROC curves and the best-cut-offs of LA strain parameters for predicting the presence of cardiac complications. According to Delong's test, there was no statistical difference between AUCs.

DISCUSSION

This study highlighted important findings regarding the LA strain parameters in β-TM patients: 1)LA reservoir and booster strains and SR parameters were significantly lower when compared to values detected in healthy individuals; 2)increased age, sex, and LV volume-indexed by body surface area were significantly associated with LA strain parameters; 3)the number of segments with LGE significantly correlated with all LA strain parameters, with the exception of the LA conduit rate; 4)patients with cardiac complications demonstrated impaired atrial functions after adjustment for age.

LA is an active cardiac chamber that centrally regulates cardiac output by modulating LV fillings, and it is strongly related to LV diastolic parameters[11,12,28]. Moreover, LA dysfunction is associated with adverse outcomes in various cardiovascular diseases[11,29,30]. However, impact of LA strain in β-TM patients is poorly understod.

Patients with β-TM demonstrated an impaired LA reservoir and booster strain and SR compared to the control group. This result is in line with previous echocardiography studies[13,29]. One might speculate that the impairment in atrial strain could be associated with the compromised diastolic properties of the LV. Indeed, diastolic dysfunction is a prevalent myocardial disorder in β-TM patients, often preceding systolic dysfunction and HF[9,30]. Another hypothesis suggests direct damage of thin LA wall due to iron overload and inflammation, leading to a potential "atrial cardiomyopathy"[13,29]. Conversely, LA conduit strain and SR showed no significant differences among β-TM patients and healthy individuals. These findings may be attributed to the effectiveness of optimal transfusion and chelation programs in our enrolled patient cohort, resulting in lower iron overload and myocardial stiffness. Indeed, LA conduit parameters depend on both LV relaxation and LV stiffness[10].

The finding regarding the significant association between ageing and LA strain parameters aligns with current literature describing a trend of age-related changes in strain parameters[31,32]. These changes may be linked to structural remodelling of the LA myocardium with advancing age, resulting in impaired compliance and relaxation of the LA[31,32]. Nielsen et al. also reported a more pronounced impairment in atrial strain parameters in women than in males[32], which is confirmed by our results.

The reduction in LA reservoir, conduit strains, and strain rates found in diabetic versus non-diabetic patients or in in splenectomised versus non-splenectomised patients can be attributed to the older age of diabetic or splenectomized patients.

LV end-diastolic and end-systolic volume indexes were independent determinants of LA reservoir and booster strains. For LA reservoir and booster strain rates, LV end-diastolic volume index was the

only CMR determinant. These findings are expected because the ventricle and the atrium are anatomically linked. LA reservoir reflects LA relaxation and filling during systole. A complete LA relaxation results in reduced LA pressure, promoting increased forward flow of pulmonary venous blood into the LA and facilitating greater LA expansion[10]. The correlation between LA reservoir strains and LV volume index may be in part explained by volume overload from the hyperkinetic circulation and anaemia in β-TM patients, resulting in increased LA pressure with reduced LA expansion[33,34]. In addition, the elevated LA pressure induced increased atrial wall stress, that leads to increased atrial stiffness[34] with impairment of both LA reservoir and booster[35].

No correlation was found between LA strain parameters and left and right ejection fraction, as well as MIO. This is likely because most of our patients exhibited normal or only mild abnormalities in these parameters, which can be attributed to optimal transfusion and chelation programs.

The current study showed a relationship between the number of segments with LGE as a marker of replacement fibrosis and atrial mechanism. The association between LGE and atrial strain was examined in the Multi-Ethnic Study of Atherosclerosis, revealing that the existence of LV LGE resulted in altered LA functionality[36]. Overall, our results suggest that it is the extent of LGE the main determinant of atrial function impairment in β-TM patients. The association between LGE extension and atrial mechanism has also been reported in previous studies on patients with different diseases, including hypertrophic cardiomyopathy hypertrophic cardiomyopathy[37] and myocarditis[38]. These findings suggest that the number of segments involved by LV LGE may have a different effect on cardiac chamber functions, resulting in impaired myocardial stiffness and LV filling, subsequently leading to left atrial dysfunction. Considering the association between LGE and unfavourable outcomes in β-TM patients[39,40], identifying factors linked to myocardial fibrosis could assist in stratifying the risk for these patients.

Finally, we here demonstrated, for the first time, an independent association between decreased LA mechanism and a history of cardiac complications. The ROC curve analysis demonstrated that all LA strain parameters were good predictors of cardiac complications, with satisfying sensitivity and

specificity. Conversely, global LV T2* values showed no significant difference between patients without and with cardiac complications. Therefore, in our cohort of well-treated β-TM patients, LA strain parameters emerged as a sensitive marker of cardiac complications, stronger than cardiac iron levels. Our data support the hypothesis that LA strain parameters could serve as an additional non-contrast CMR parameter, which may potentially improve the risk stratification of β-TM patients.

Limitations

The patient sample size was relatively small. It is essential to conduct further studies involving a larger patient cohort to validate our promising findings.

Only a limited number of healthy subjects was included in our study. However, the detected strains and SR values are in line with those reported in large-sized groups of healthy subjects[41,42].

The study was cross-sectional in nature, and we did not evaluate the predictive value of LA parameters for adverse cardiovascular events in β-TM patients, nor did we investigate the changes in LA function at follow-up. Future longitudinal studies are required to explore these aspects.

Myocardial T1, T2, or extracellular volume values were not quantified, due to the unavailability of these CMR mapping techniques at the time of patient enrollment in the E-MIOT project. In particular, incorporating T1 mapping analysis could have enhanced the ability to detect mild or early MIO, while also providing a more comprehensive evaluation of myocardial fibrosis [43].

We did not acquire three-dimensional high-resolution LGE sequences, which could have enabled us to accurately detect and quantify LGE in the left atrium.

CONCLUSION

In β-TM patients, LA reservoir, LA booster, and LA booster SR demonstrated lower values in comparison with age- and sex-matched healthy subjects. LA strain parameters showed a significant correlation with the number of segments with LV LGE but displayed no significant correlation with

myocardial iron overload. In addition, LA strain parameters may serve as an additional non-invasive marker for detecting cardiac complications.

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DISCLOSURES

The authors have nothing to disclose.

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TABLE AND FIGURE LEGENDS

Table 1. Comparison of LA longitudinal strains and strain rates between healthy subjects and β-TM patients.

Table 2. Demographic, clinical, and CMR correlates of left atrial deformation parameters.

Table 3. Univariate and multivariate regression showing determinants of LA strains and strain rates in β-TM patients.

Table 4. Comparison between patients without and with cardiac complications.

Figure 1. Comparison of LA strain parameters in a control subject (a) and a patient with β-TM (b). The endo- and epicardial borders of the LA were manually depicted, and the curves of the LA function were automatically obtained. Corresponding LA reservoir, conduit, and booster strain curves in the control subject (c) and the patient with β-TM (d) are shown.

Figure 2. Patterns of late gadolinium enhancement in thalassemia patients. Short-axis (panels a and c, white arrow) and long-axis (panels b and d, white arrow) images demonstrate intramyocardial infero-lateral enhancement at mid-ventricular and basal level, respectively. Short-axis images exhibit antero-septal intramyocardial enhancement (red arrowhead in panel e) and infero-septal junction mid-ventricular area (yellow arrow in panels e and f) of late enhancement.

Figure 3. ROC curve analysis of LA deformation parameters to identify the presence of a cardiac complication.