Left and right atrioventricular coupling index in patients with beta-thalassemia major.

Antonella Meloni[1,2], Luca Saba[3], Vincenzo Positano[1,2], Laura Pistoia[2,4], Anna Spasiano[5], Maria Caterina Putti[6], Tommaso Casini[7], Antonella Cossu[8], Elisabetta Corigliano[9], Antonella Massa[10], Filippo Cademartiri[2], Riccardo Cau[3].

[1]Bioengineering Unit, Fondazione G. Monasterio CNR-Regione Toscana, Pisa, Italy.

[2]Department of Radiology, Fondazione G. Monasterio CNR-Regione Toscana, Pisa, Italy.

[3]Dipartimento di Radiologia, Azienda Ospedaliero-Universitaria di Cagliari - Polo di Monserrato, Cagliari, Italy

[4]U.O.C. Ricerca Clinica, Fondazione G. Monasterio CNR-Regione Toscana, Pisa, Italy.

[5]U.O.S.D. Malattie Rare del Globulo Rosso, Azienda Ospedaliera di Rilievo Nazionale "A. Cardarelli", Napoli, Italy.

[6]Dipartimento della Salute della Donna e del Bambino - Clinica di Emato-Oncologia Pediatrica, Azienda Ospedaliero-Università di Padova, Padova, Italy.

[7]SOC Oncologia, Ematologia e Trapianto di Cellule Staminali Emopoietiche, Meyer Children's Hospital IRCCS, Firenze, Italy.

[8]Ambulatorio Trasfusionale - Servizio Immunoematologia e Medicina Trasfusionale Dipartimento dei Servizi, Presidio Ospedaliero "San Francesco", Nuoro, Italy.

[9]Ematologia Microcitemia, Ospedale San Giovanni di Dio - ASP Crotone, Crotone, Italy.

[10]Servizio trasfusionale, Ospedale "Giovanni Paolo II", Olbia, Italy.

Corresponding author:

Prof. Dr. Filippo Cademartiri, MD, PhD

Department of Radiology, Fondazione G. Monasterio CNR-Regione Toscana

Via Moruzzi, 1 - 56124 Pisa, Italy

Email: fcademartiri@ftgm.it; Tel: +39 050-3152817

ABSTRACT

Purpose: The aim of this cross-sectional study was to investigate the relationship of left atrioventricular coupling index (LACI) and right atrioventricular coupling index (RACI) with demographics, clinical data, cardiovascular magnetic resonance (CMR) findings, and cardiac complications (heart failure, arrhythmias, and pulmonary hypertension) in a cohort of patients with beta-thalassemia major (β-TM).

Methods: We evaluated 292 β-TM patients (151 females, 36.72±11.76 years) consecutively enrolled in the Extension-Myocardial Iron Overload in Thalassemia (E-MIOT) project. Moreover, we assessed 32 sex- and age-matched healthy controls (12 females, mean age 40.78±14.35 years).

LACI was determined by calculating the ratio of the left atrium end-diastolic volume to the left ventricle end-diastolic volume, while RACI was defined by calculating the ratio of the right atrium end-diastolic volume to the right ventricle end-diastolic volume.

Results: Compared to healthy control, β-TM demonstrated increased LACI (22.99±13.58% vs. 16.05±5.28%; $p<0.0001$) and RACI (27.84±10.30% vs. 17.06±5.03%; $p<0.0001$). Aging, diabetes, splenectomy, and the presence of late gadolinium enhancement (LGE) showed a significant positive association with both LACI and RACI. In stepwise regression analysis, the presence of LGE was found to be an independent predictor of both impaired LACI and RACI (β coefficient=0.244, $p<0.0001$ and β coefficient=0.218, $p=0.003$; respectively). LACI and RACI were not correlated with myocardial iron overload. Patients with cardiac complications had significantly higher LACI and RACI than patients without cardiac complications.

Conclusion: In patients with β-TM, LACI and RACI were significantly associated with the presence of LV LGE. In addition, patients with cardiac complications had impaired LACI and RACI.

KEYWORDS: cardiovascular magnetic resonance; thalassemia major; iron overload; atrioventricular coupling index.

INTRODUCTION

Thalassemia stands as the most prevalent genetic disorder on a global scale. Beta-thalassemia major (β-TM) is characterized by either absent (β°) or reduced (β+) production of β-hemoglobin chains [1]. Individuals with β-TM necessitate lifelong, consistent transfusions to ensure their survival, which, in turn, lead to iron overload [1,2]. Iron-induced heart failure continues to be the primary cause of morbidity and mortality in β-TM patients [3-5]. However, the survival of patients has improved thanks to the non-invasive assessment of myocardial iron overload with cardiovascular magnetic resonance (CMR) [6,4]. Indeed, the CMR T2* technique has become a central and indispensable tool in tailoring chelation therapies to individual patients and evaluating the effectiveness of the chosen treatment [7]. Beyond the non-invasive evaluation of iron overload [8,9], CMR allows for highly reproducible and precise measurements of atrial and ventricular volumes [10-12]. Myocardial iron accumulation, in combination with volume overload stemming from chronic anemia, may lead to left ventricular systolic and diastolic dysfunction, which can subsequently result in atrial and ventricular dilatation and heart failure [13-15,5]. Similarly, right atrial and ventricular impairments have been described in patients with β-TM [16,17].

During ventricular diastole, atria and ventricles are directly linked, and their mechanism and filling pressure are closely coupled. In particular, the atria receive blood as the ventricles contract and pump it into the pulmonary and systemic circulation. They subsequently empty as ventricles relax. Therefore, a single parameter that takes into account atria and ventricles functions may better represent this physiological close relationship and more accurately reflect any impairment [18,19]. Recently, in a large cohort of patients without any cardiovascular disease at the enrollment (Multi-Ethnic Study of Atherosclerosis [MESA] study), the left atrioventricular coupling index (LACI) has demonstrated incremental prognostic role in predicting major adverse cardiac events along with ventricular and atrial volumes alone [20,21].

Currently, little is known about the importance of factors involved in the physiology of atrial/ventricular coupling in β-TM. Therefore, we aimed to systematically evaluate the cross-sectional relationship of the CMR-derived LACI and right atrioventricular coupling index (RACI) with demographics, clinical data, CMR parameters, and cardiac complications.

METHODS

Study population

We considered 292 β-TM patients (151 females, 36.72±11.76years) consecutively enrolled in the Extension-Myocardial Iron Overload in Thalassemia (E-MIOT) project. E-MIOT is an Italian network comprising 66 thalassemia centers and 15 magnetic resonance imaging (MRI) sites where CMR examinations are performed using homogeneous, standardized, and validated procedures [22,23]. A web-based database connects all centers, gathering participants' demographic, clinical, laboratory, and CMR parameters.

β-TM patients were regularly transfused since early childhood to maintain a pre-transfusion hemoglobin concentration above 9-10g/dl and started undergoing chelation therapy from the mid-to-late 1970s, while patients born after the 1970s received chelation therapy from early childhood. CMR scanning was performed within one week before a regular scheduled blood transfusion.

Moreover, we studied 32 healthy subjects (12 females, 40.78±14.35years) who constituted the control population. Inclusion criteria were: normal electrocardiogram, no history of cardiac diseases or symptoms, no cardiovascular risk factors, no known systemic diseases, 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 of the E-MIOT Network (Pisa) using a 1.5T scanner (Signa Excite HD or Signa Artist, GE Healthcare, Milwaukee, WI, USA). A 30-element cardiac phased-array receiver surface coil with breath-holding and ECG gating was used.

For myocardial iron overload (MIO) assessment, three parallel short-axis views (basal, medium, and apical) of the left ventricle (LV) were acquired at ten echo times by a T2* gradient–echo multiecho sequence [24]. Image analysis was performed using a custom-written, previously validated software (HIPPO MIOT®) [25]. The software provided the T2* value on each of the 16 LV segments, according to the standard AHA/ACC model [26]. An appropriate correction map was applied to correct the susceptibility artifacts [25]. The global heart T2* value was obtained by averaging all segmental values.

Cardiac anatomy and ventricular function were assessed using steady-state free procession (SSFP) sequences, with images acquired in two-, three- and four-chamber planes and short axis (slice thickness 8 mm, no gap) of the ventricles [27]. Thirty cardiac phases were acquired per heartbeat. Manual post-processing was performed by expert operators (>10years of experience in CMR) using a commercially available software system (cmr42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada). LV and right ventricular (RV) volumes were quantified from the stack of short-axis cine images, with the analysis based on the manual definition of the endocardial and epicardial borders of the wall in end-diastolic and end-systolic phases for each slice. Moreover, the papillary muscles were delineated and were considered myocardial mass rather than part of the blood pool. End-diastolic and end-systolic volumes (EDV and ESV, respectively) were calculated using Simpson's rule without the need for geometric assumption of the ventricle shape. Ejection fraction was calculated using the formula: (EDV-ESV) x 100/EDV. The LV mass was given by the volume of the myocardium multiplied by its specific weight of 1.05g/cm3.

The left atrial (LA) volume was assessed from two- and four-chamber views, while the right atrial (RA) volume was assessed from four-chamber views, as previously described [21,28,19].

Both LA and LV volumes were measured during the same end-diastolic phase, defined by the closure of the mitral valve. Both RA and RV volumes were measured during the same end-diastolic phase, defined by the closure of the tricuspid valve.

For each participant, the LACI value was determined by calculating the ratio of the LA end-diastolic volume to the LV end-diastolic volume, and the RACI value was determined by calculating the ratio of the RA end-diastolic volume to the RV end-diastolic volume (Figure 1). The LACI and RACI values were represented as a percentage. A higher atrioventricular coupling index indicates a more significant disparity between atrial and ventricular volumes at the end of diastole, implying a potentially increased impairment in atrioventricular coupling.

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 images were not acquired in patients with a glomerular filtration rate<30mL/min/1.73m2 and in patients who refused the contrast medium administration. Two experienced cardiologists or radiologists evaluated images qualitatively for the presence, pattern, and regional distribution of LGE areas. LGE was considered present when visualized in two different views [29].

Diagnostic criteria

A T2* measurement of 20ms was taken as a "conservative" normal value for the segmental and global heart T2* values [8,25].

Diabetes mellitus was defined as fasting plasma glucose≥126mg/dl or 2-h plasma glucose≥200mg/dl during an oral glucose tolerance test (OGTT) or random plasma glucose≥200mg/dl with classic symptoms of hyperglycaemia or hyperglycaemic crisis [30].

Heart failure (HF) was diagnosed by clinicians based on symptoms, signs, and instrumental findings, according to the current guidelines [31]. 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 [32]. Pulmonary hypertension was diagnosed if the trans-tricuspidal velocity jet by echocardiography was greater than 3.2m/s [33]. The term "cardiac complications" included HF, arrhythmias, and PH clinically active at the time of the CMR.

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 (SD), and categorical variables were expressed 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$\leq$50.

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

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 normalize the residual distributions and to equalize the residual variance.

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

Univariate and stepwise multivariate regression analyses were performed to identify determinants of LACI and RACI. 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 performed to examine the diagnostic ability of LACI and RACI, 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 probability value of 0.05 was considered statistically significant in all tests.

RESULTS

Comparison between TM patients and healthy subjects

Table 1 shows the comparison between TM patients and healthy subjects. No difference between the two groups was found in age and sex but TM patients showed a significantly lower body surface area (BSA) and significantly higher biventricular EDV and SV indexed by BSA, LV mass index, and bi-atrial EDV indexed by BSA. Biventricular ejection fractions were comparable between the two groups.

Compared to healthy subjects, β-TM patients exhibited significantly increased LACI (2299±13.58% vs. 16.05±5.28%; $p<0.0001$) and RACI (27.84±10.30% vs. 17.06±5.03%; $p<0.0001$) (Figure 2).

In healthy subjects, there was a significant correlation between LACI and RACI ($R=0.641$; $p<0.0001$), while only LACI exhibited a significant association with age ($R=0.379$; $p=0.032$). No difference between healthy males and females was found in LACI (15.38±5.09% vs. 17.17±5.61%; $p=0.460$) or RACI (16.19±4.05% vs. 18.49±6.28%; $p=0.392$).

Demographic and clinical correlates of LACI and RACI in TM patients

Demographic, clinical, and CMR characteristics of TM patients are summarized in Table 1.

A significant correlation was found between LACI and RACI ($R=0.430$; $p<0.0001$). Aging exhibited a significant positive association with both LACI ($R=0.472$; $p<0.0001$) and RACI ($R=0.289$;

p<0.0001). Males and females showed comparable LACI (23.51±14.66% vs. 22.51±12.53%; p=0.950) and RACI (28.63±11.37% vs. 27.11±9.18%; p=0.478).

LACI and RACI were not correlated with age at the start of regular transfusions or chelation, pre-transfusion hemoglobin levels, and mean serum ferritin over the previous year.

Compared to non-splenectomized patients, splenectomized patients showed significantly higher LACI (25.72±15.89% vs. 20.25±10.15%; p<0.0001) as well as RACI (29.16±11.53% vs. 26.52±8.76%; p=0.036).

Data about the presence of diabetes mellitus were available for 290 patients already diagnosed with diabetes or tested for blood glucose in the six months preceding the CMR scan. The prevalence of diabetes was 14.5%. When compared to patients without diabetes, patients with diabetes exhibited significantly increased LACI (33.21±21.76% vs. 21.24±10.85%; p<0.0001) as well as RACI (31.86±12.10% vs. 27.18±9.84%; p=0.015). Age significantly differed between patients with and without diabetes (44.93±7.23years vs. 35.21±11.77%; p<0.0001) and was therefore used as a covariate in the ANCOVA. After the correction for age, the difference in LACI remained significant (p<0.0001), while the difference in RACI lost the statistical significance (p=0.124).

Association of LACI and RACI with CMR parameters

A significant correlation was present between the underlying parameters of LA EDV and LV EDV (R=0.562; p<0.0001) and between the underlying parameters of RA EDV and RV EDV (R=0.643; p<0.001).

No association was found between LACI and LVEF (R=0.096; p=0.103) or between RACI and RVEF (R=-0.058, p=0.319).

There was no correlation of LACI with global heart T2* values (R=0.036; p=0.539) and number of segments with T2*<20ms (R=-0.003; p=0.954). Similarly, RACI was uncorrelated with both global heart T2* values (R=0.050; p=0.396) and number of segments with T2*<20ms (R=0.021; p=0.718).

The contrast medium was administered in 188 patients (64.4%), and LV LGE was detected in 75 (39.9%) of them. Two patients showed a transmural LGE, while the remaining 73 patients had a non-ischemic LGE pattern. 72% of patients had at least two foci of fibrosis involving the septum in the 80.0% of cases. Compared to LGE-negative patients, patients with LGE were significantly older (40.18±10.28years vs. 36.63±10.54years; p=0.029) and exhibited significantly higher LACI (27.23±17.04% vs. 19.39±8.51%; p<0.0001) and RACI (30.65±12.44% vs. 26.06±8.22%; p=0.026). In the ANCOVA model, LACI and RACI remained significantly different between patients without and with LGE, also adjusting for age (LACI: p<0.0001 and RACI: p=0.012).

Predictors of LACI and RACI

Table 2 shows the results of the stepwise regression analysis conducted, including all significant variables in univariate regression analysis with LACI/RACI as the dependent variable. No variable was excluded from the multivariable models due to excessive collinearity.

Age>75th percentile (44.4years), diabetes mellitus, and the presence of LGE were the strongest predictors of LACI (F=14.04; p<0.0001).

The presence of LGE emerged as the only independent predictor of RACI (F=9.26; p=0.003).

Association of LACI and RACI with cardiac complications

Twenty-seven patients had at least one cardiac complication. Specifically, nine patients had HF, 14 arrhythmias, 3 PH, and one both HF and arrhythmias. Among the detected arrhythmias, supraventricular arrhythmias (atrial fibrillation and atrial flutter) were the most common type (11/15=73.3). Three patients (20.0%) had ventricular arrhythmias, while one (6.7%) showed a hypokinetic arrhythmia.

Global heart T2* values were comparable between patients without and with cardiac complications (36.22±10.75ms vs. 35.52±10.81ms; p=0.373). Compared to patients without cardiac complications, patients with cardiac complications were significantly older (45.42±6.76years vs. 35.77±11.78years;

p<0.0001) and showed significantly higher LACI (40.29±22.38% vs. 21.19±10.97%; p<0.0001) (Figure 3A) and RACI (33.74±14.32% vs. 27.28±9.64%; p=0.015) (Figure 3B). The difference in LACI and RACI between patients without and with cardiac complications remained significant also after the adjustment for age (LACI: p<0.0001 and RACI: p=0.030).

At ROC curve analysis, a LACI>23.6% predicted the presence of cardiac complications with a sensitivity of 74.1% and a specificity of 75.8% (p<0.0001). The AUC was 0.79 (95%CIs= 0.73-0.83). At ROC curve analysis, a RACI > 36.7% predicted the presence of cardiac complications with a sensitivity of 37.0% and a specificity of 88.6% (p=0.014). The AUC was 0.64 (95%CIs= 0.58-0.69). The Delong's test showed a significant difference among the AUCs (p=0.015) (Figure 4).

DISCUSSION

This study highlighted important findings regarding the clinical correlates of LACI and RACI in β-TM patients: (1)β-TM patients demonstrated an increased atrioventricular coupling index in both left and right chambers, (2)increased age, diabetes, splenectomy, and presence of LGE were significantly associated with both LACI and RACI, (3)in stepwise regression analysis, the variables independently associated with LACI were age, diabetes, and LV LGE, while LV LGE was the only independent variable associated with RACI, (4)patients with cardiac complications demonstrated higher LACI and RACI after adjustment for age.

Atrioventricular coupling detects an early phase of atrium remodelling associated with compromised ventricular compliance [34]. In the MESA study, aging was one of the most important determinants of the atrioventricular coupling index [34]. Similarly, in our population with β-TM, an increase in age was significantly associated with LACI in a multivariable regression, regardless of demographic and clinical data, emphasizing the changes in LA function and LV filling during lifelong transfusions due to iron accumulation in atrial and ventricular walls [35]. Conversely, aging was not associated with

RACI after multivariable adjustment. This finding could be explained by less pronounced or delayed right cardiac chamber impairment [36], especially in patients with a good transfusional regimen.

The result about the significant association between diabetes mellitus and LACI is in line with the current literature that reports an increase in LA volume and a decrease in LV end-diastolic volume in patients with diabetes [37].

No correlation was found between LACI and RACI and left and right ejection fraction, as well as iron myocardial overload. This is likely due to the fact that 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 also described the independent association between the presence of LGE as a marker of LV replacement fibrosis and the LACI and RACI values. Considering the anatomic interaction of atria and ventricles, LV LGE can influence both right and left cardiac chambers [38,39,12,40,41]. Indeed, the accumulation of fibrotic tissue with a change in collagen quality and spatial organization is associated with ventricular stiffness and diastolic dysfunction [42].

In patients with β-TM, LV LGE is more prevalent in septal localization [43]. As previously reported, septal LGE determines a predominant impairment in subepicardial and transmural myocardial fibers, with an impairment in myocardial stiffness and LV filling that subsequently influences LA function [39], leading to a potential abnormal atrioventricular coupling index. In addition, LV LGE is also related to right ventricular impairment [44].

Considering the link between myocardial replacement fibrosis and adverse outcomes in β-TM patients [43,45], identifying factors associated with myocardial fibrosis could aid in risk-stratifying patients.

Our study also demonstrated for the first time a link between atrioventricular coupling in both cardiac chambers and cardiac complications. No association was found between cardiac complication and global heart T2* values [46]. As previously demonstrated, in patients not heavily loaded at the cardiac level, global heart T2* values are not a sensitive marker for the presence of cardiac complications.

The relationship between LACI and RACI and cardiac complications remained significant after adjustment for age, suggesting a potential role of the atrioventricular coupling index as an additional tool to improve the management of patients with β-TM. Importantly, the LACI was demonstrated to provide a superior discriminatory ability compared with the RACI, and the introduced LACI cut-off of 23.6% may help to identify the patients at high risk for cardiac complications.

Of interest for clinical practice, LACI and RACI can be readily calculated from standard CMR images without the need for additional acquisition or time-consuming post-processing software.

Limitations

The sample size was relatively small, and the study was cross-sectional in nature. Although our study yielded promising results, it is essential to conduct further prospective studies involving a larger patient cohort to validate our findings.

We did not measure atrial and ventricular strain parameters, which could offer a more accurate evaluation of cardiac chamber function [47-49].

CONCLUSION

In β-TM patients, LACI and RACI demonstrated higher values in comparison with age- and sex-matched healthy subjects. Aging and diabetes emerged as independent factors contributing to increased LACI in β-TM patients. Both LACI and RACI showed independent associations with LV LGE but displayed no significant correlation with myocardial iron overload. In addition, LACI may serve as an additional non-invasive marker in detecting cardiac complications.

ACKNOWLEDGEMENTS

We would like to thank all the colleagues involved in the E-MIOT project (https://emiot.ftgm.it/). We thank all patients and healthy volunteers for their cooperation.

This work is generated within the European Reference Network on Rare Hematological Diseases (ERN-EuroBloodNet).

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to privacy reasons. The data will be shared on reasonable request to the corresponding author.

STATEMENTS & DECLARATIONS

Funding

The E-MIOT project received "no-profit support" from industrial sponsorships (Chiesi Farmaceutici S.p.A. and Bayer).

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Author contributions

A.M. and R.C.: conceptualization, formal analysis, investigation, methodology, writing - original draft; L.S. and F.C.: methodology, supervision, writing - review & editing; V.P.: methodology, investigation, writing - review & editing; L.P.: data curation, writing - review & editing; A. S., M. C. P., T.C., A.C., E.C., A.Ma., resources, writing - review & editing.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Area Vasta Nord Ovest (Pisa)"

Consent to participate

Informed consent was obtained from all individual participants included in the study.

REFERENCES

1. Cao A, Galanello R (2010) Beta-thalassemia. Genet Med 12 (2):61-76

2. Shander A, Cappellini MD, Goodnough LT (2009) Iron overload and toxicity: the hidden risk of multiple blood transfusions. Vox Sanguinis 97 (3):185-197. doi:https://doi.org/10.1111/j.1423-0410.2009.01207.x

3. Borgna-Pignatti C, Rugolotto S, De Stefano P, Zhao H, Cappellini MD, Del Vecchio GC, Romeo MA, Forni GL, Gamberini MR, Ghilardi R, Piga A, Cnaan A (2004) Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica 89 (10):1187-1193

4. Pepe A, Pistoia L, Gamberini MR, Cuccia L, Lisi R, Cecinati V, Maggio A, Sorrentino F, Filosa A, Rosso R, Messina G, Missere M, Righi R, Renne S, Vallone A, Dalmiani S, Positano V, Midiri M, Meloni A (2022) National networking in rare diseases and reduction of cardiac burden in thalassemia major. Eur Heart J 43 (26):2482-2492. doi:10.1093/eurheartj/ehab851

5. Akiki N, Hodroj MH, Bou-Fakhredin R, Matli K, Taher AT (2023) Cardiovascular Complications in β-Thalassemia: Getting to the Heart of It. Thalassemia Reports 13 (1):38-50

6. Modell B, Khan M, Darlison M, Westwood MA, Ingram D, Pennell DJ (2008) Improved survival of thalassaemia major in the UK and relation to T2* cardiovascular magnetic resonance. J Cardiovasc Magn Reson 10 (1):42

7. Pennell DJ, Udelson JE, Arai AE, Bozkurt B, Cohen AR, Galanello R, Hoffman TM, Kiernan MS, Lerakis S, Piga A, Porter JB, Walker JM, Wood J (2013) Cardiovascular function and treatment in beta-thalassemia major: a consensus statement from the American Heart Association. Circulation 128 (3):281-308

8. Anderson LJ, Holden S, Davis B, Prescott E, Charrier CC, Bunce NH, Firmin DN, Wonke B, Porter J, Walker JM, Pennell DJ (2001) Cardiovascular T2-star (T2*) magnetic resonance for the early diagnosis of myocardial iron overload. Eur Heart J 22 (23):2171-2179

9. Wood JC, Noetzli L (2010) Cardiovascular MRI in thalassemia major. Ann N Y Acad Sci 1202:173-179

10. Maceira AM, Cosin-Sales J, Roughton M, Prasad SK, Pennell DJ (2010) Reference left atrial dimensions and volumes by steady state free precession cardiovascular magnetic resonance. J Cardiovasc Magn Reson 12:65

11. Kawel-Boehm N, Hetzel SJ, Ambale-Venkatesh B, Captur G, Francois CJ, Jerosch-Herold M, Salerno M, Teague SD, Valsangiacomo-Buechel E, van der Geest RJ, Bluemke DA (2020) Reference ranges ("normal values") for cardiovascular magnetic resonance (CMR) in adults and children: 2020 update. J Cardiovasc Magn Reson 22 (1):87. doi:10.1186/s12968-020-00683-3

12. Cau R, Pisu F, Suri JS, Mannelli L, Scaglione M, Masala S, Saba L (2023) Artificial Intelligence Applications in Cardiovascular Magnetic Resonance Imaging: Are We on the Path to Avoiding the Administration of Contrast Media? Diagnostics (Basel) 13 (12). doi:10.3390/diagnostics13122061

13. Kremastinos DT (2001) Heart Failure in β-Thalassemia. Congestive Heart Failure 7 (6):312-314. doi:https://doi.org/10.1111/j.1527-5299.2001.00259.x

14. Wood JC, Enriquez C, Ghugre N, Otto-Duessel M, Aguilar M, Nelson MD, Moats R, Coates TD (2005) Physiology and pathophysiology of iron cardiomyopathy in thalassemia. Ann N Y Acad Sci 1054:386-395

15. Kremastinos DT, Farmakis D, Aessopos A, Hahalis G, Hamodraka E, Tsiapras D, Keren A (2010) Beta-thalassemia cardiomyopathy: history, present considerations, and future perspectives. Circ Heart Fail 3 (3):451-458

16. Alpendurada F, Carpenter JP, Deac M, Kirk P, Walker JM, Porter JB, Banya W, He T, Smith GC, Pennell DJ (2010) Relation of myocardial T2* to right ventricular function in thalassaemia major. Eur Heart J 31 (13):1648-1654

17. Hahalis G, Manolis AS, Apostolopoulos D, Alexopoulos D, Vagenakis AG, Zoumbos NC (2002) Right ventricular cardiomyopathy in beta-thalassaemia major. Eur Heart J 23 (2):147-156. doi:10.1053/euhj.2001.2709

18. Pezel T, Venkatesh BA, Vasconcellos HDD, Kato Y, Shabani M, Xie E, Heckbert SR, Post WS, Shea SJ, Allen NB, Watson KE, Wu CO, Bluemke DA, Lima JAC (2021) Left Atrioventricular Coupling Index as a Prognostic Marker of Cardiovascular Events: The MESA Study. Hypertension 78 (3):661-671. doi:doi:10.1161/HYPERTENSIONAHA.121.17339

19. von Roeder M, Kowallick JT, Rommel K-P, Blazek S, Besler C, Fengler K, Lotz J, Hasenfuß G, Lücke C, Gutberlet M, Thiele H, Schuster A, Lurz P (2020) Right atrial–right ventricular coupling in heart failure with preserved ejection fraction. Clinical Research in Cardiology 109 (1):54-66. doi:10.1007/s00392-019-01484-0

20. Pezel T, Ambale Venkatesh B, Kato Y, De Vasconcellos HD, Heckbert SR, Wu CO, Post WS, Bluemke DA, Cohen-Solal A, Henry P, Lima JAC (2021) Left Atrioventricular Coupling Index to Predict Incident Heart Failure: The Multi-Ethnic Study of Atherosclerosis. Front Cardiovasc Med 8:704611. doi:10.3389/fcvm.2021.704611

21. Pezel T, Ambale-Venkatesh B, Quinaglia T, Heckbert SR, Kato Y, de Vasconcellos HD, Wu CO, Post WS, Henry P, Bluemke DA, Lima JAC (2022) Change in Left Atrioventricular Coupling Index to Predict Incident Atrial Fibrillation: The Multi-Ethnic Study of Atherosclerosis (MESA). Radiology 303 (2):317-326. doi:10.1148/radiol.210315

22. Ramazzotti A, Pepe A, Positano V, Rossi G, De Marchi D, Brizi MG, Luciani A, Midiri M, Sallustio G, Valeri G, Caruso V, Centra M, Cianciulli P, De Sanctis V, Maggio A, Lombardi M (2009) Multicenter validation of the magnetic resonance t2* technique for segmental and global quantification of myocardial iron. J Magn Reson Imaging 30 (1):62-68

23. Meloni A, De Marchi D, Pistoia L, Grassedonio E, Peritore G, Preziosi P, Restaino G, Righi R, Riva A, Renne S, Schicchi N, Vallone A, Peluso A, Gerardi C, Positano V, Pepe A (2019) Multicenter validation of the magnetic resonance T2* technique for quantification of pancreatic iron. Eur Radiol 29 (5):2246-2252

24. Meloni A, Restaino G, Borsellino Z, Caruso V, Spasiano A, Zuccarelli A, Valeri G, Toia P, Salvatori C, Positano V, Midiri M, Pepe A (2014) Different patterns of myocardial iron distribution by whole-heart T2* magnetic resonance as risk markers for heart complications in thalassemia major. International Journal of Cardiology 177 (3):1012-1019

25. Positano V, Pepe A, Santarelli MF, Scattini B, De Marchi D, Ramazzotti A, Forni G, Borgna-Pignatti C, Lai ME, Midiri M, Maggio A, Lombardi M, Landini L (2007) Standardized T2* map of normal human heart in vivo to correct T2* segmental artefacts. NMR Biomed 20 (6):578-590

26. Cerqueira MD, Weissman NJ, Dilsizian V, Jacobs AK, Kaul S, Laskey WK, Pennell DJ, Rumberger JA, Ryan T, Verani MS (2002) Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 105 (4):539-542

27. Meloni A, Righi R, Missere M, Renne S, Schicchi N, Gamberini MR, Cuccia L, Lisi R, Spasiano A, Roberti MG, Zuccarelli A, Ait-Ali L, Festa P, Aquaro GD, Mangione M, Barra V, Positano V, Pepe A (2021) Biventricular Reference Values by Body Surface Area, Age, and Gender in a Large Cohort of Well-Treated Thalassemia Major Patients Without Heart Damage Using a Multiparametric CMR Approach. J Magn Reson Imaging 53 (1):61-70

28. Lange T, Backhaus SJ, Schulz A, Evertz R, Kowallick JT, Bigalke B, Hasenfuss G, Thiele H, Stiermaier T, Eitel I, Schuster A (2023) Cardiovascular magnetic resonance-derived left atrioventricular coupling index and major adverse cardiac events in patients following acute myocardial infarction. J Cardiovasc Magn Reson 25 (1):24. doi:10.1186/s12968-023-00929-w

29. Pepe A, Positano V, Capra M, Maggio A, Lo Pinto C, Spasiano A, Forni G, Derchi G, Favilli B, Rossi G, Cracolici E, Midiri M, Lombardi M (2009) Myocardial scarring by delayed enhancement cardiovascular magnetic resonance in thalassaemia major. Heart 95:1688-1693

30. De Sanctis V, Soliman AT, Elsedfy H, Yaarubi SA, Skordis N, Khater D, El Kholy M, Stoeva I, Fiscina B, Angastiniotis M, Daar S, Kattamis C (2016) The ICET-A Recommendations for the Diagnosis and Management of Disturbances of Glucose Homeostasis in Thalassemia Major Patients. Mediterr J Hematol Infect Dis 8 (1):e2016058

31. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, Burri H, Butler J, Celutkiene J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, Group ESCSD (2021) 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 42 (36):3599-3726. doi:10.1093/eurheartj/ehab368

32. Buxton AE, Calkins H, Callans DJ, DiMarco JP, Fisher JD, Greene HL, Haines DE, Hayes DL, Heidenreich PA, Miller JM, Poppas A, Prystowsky EN, Schoenfeld MH, Zimetbaum PJ, Goff DC, Grover FL, Malenka DJ, Peterson ED, Radford MJ, Redberg RF (2006) ACC/AHA/HRS 2006 key data elements and definitions for electrophysiological studies and procedures: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (ACC/AHA/HRS Writing Committee to Develop Data Standards on Electrophysiology). Circulation 114 (23):2534-2570

33. Cogliandro T, Derchi G, Mancuso L, Mayer MC, Pannone B, Pepe A, Pili M, Bina P, Cianciulli P, De Sanctis V, Maggio A (2008) Guideline recommendations for heart complications in thalassemia major. J Cardiovasc Med (Hagerstown) 9 (5):515-525

34. Pezel T, Venkatesh BA, Vasconcellos HD, Kato Y, Post WS, Wu CO, Heckbert SR, Bluemke DA, Cohen-Solal A, Logeart D, Henry P, Lima JAC (2022) Determinants of left atrioventricular coupling index: The Multi-Ethnic Study of Atherosclerosis (MESA). Arch Cardiovasc Dis 115 (8-9):414-425. doi:10.1016/j.acvd.2022.04.011

35. Kostopoulou AG, Tsiapras DP, Chaidaroglou AS, De Giannis DE, Farmakis D, Kremastinos DT (2014) The pathophysiological relationship and clinical significance of left atrial function and left ventricular diastolic dysfunction in beta-thalassemia major. Am J Hematol 89 (1):13-18. doi:10.1002/ajh.23581

36. Carpenter JP, Alpendurada F, Deac M, Maceira A, Garbowski M, Kirk P, Walker JM, Porter JB, Shah F, Banya W, He T, Smith GC, Pennell DJ (2010) Right ventricular volumes and function in thalassemia major patients in the absence of myocardial iron overload. J Cardiovasc Magn Reson 12 (1):24

37. Zoppini G, Bonapace S, Bergamini C, Rossi A, Trombetta M, Lanzoni L, Bertolini L, Zenari L, Bonora E, Targher G (2016) Evidence of left atrial remodeling and left ventricular diastolic dysfunction in type 2 diabetes mellitus with preserved systolic function. Nutr Metab Cardiovasc Dis 26 (11):1026-1032. doi:10.1016/j.numecd.2016.05.004

38. Imai M, Ambale Venkatesh B, Samiei S, Donekal S, Habibi M, Armstrong AC, Heckbert SR, Wu CO, Bluemke DA, Lima JA (2014) Multi-ethnic study of atherosclerosis: association between left atrial function using tissue tracking from cine MR imaging and myocardial fibrosis. Radiology 273 (3):703-713. doi:10.1148/radiol.14131971

39. Cau R, Muscogiuri G, Pisu F, Mannelli L, Sironi S, Suri JS, Pontone G, Saba L (2023) Effect of late gadolinium enhancement on left atrial impairment in myocarditis patients. Eur Radiol. doi:10.1007/s00330-023-10176-3

40. Spiewak M, Klopotowski M, Mazurkiewicz L, Kowalik E, Petryka-Mazurkiewicz J, Milosz-Wieczorek B, Klisiewicz A, Witkowski A, Marczak M (2020) Predictors of right ventricular function and size in patients with hypertrophic cardiomyopathy. Sci Rep 10 (1):21054. doi:10.1038/s41598-020-78245-x

41. Lisi M, Cameli M, Righini FM, Malandrino A, Tacchini D, Focardi M, Tsioulpas C, Bernazzali S, Tanganelli P, Maccherini M, Mondillo S, Henein MY (2015) RV Longitudinal Deformation Correlates With Myocardial Fibrosis in Patients With End-Stage Heart Failure. JACC: Cardiovascular Imaging 8 (5):514-522. doi:https://doi.org/10.1016/j.jcmg.2014.12.026

42. González A, Schelbert EB, Díez J, Butler J (2018) Myocardial Interstitial Fibrosis in Heart Failure: Biological and Translational Perspectives. Journal of the American College of Cardiology 71 (15):1696-1706. doi:https://doi.org/10.1016/j.jacc.2018.02.021

43. Pepe A, Meloni A, Rossi G, Midiri M, Missere M, Valeri G, Sorrentino F, D'Ascola DG, Spasiano A, Filosa A, Cuccia L, Dello Iacono N, Forni G, Caruso V, Maggio A, Pitrolo L, Peluso A, De Marchi D, Positano V, Wood JC (2018) Prediction of cardiac complications for thalassemia major in the widespread cardiac magnetic resonance era: a prospective multicentre study by a multi-parametric approach. Eur Heart J Cardiovasc Imaging 19 (3):299-309

44. Bogaard HJ, Voelkel NF (2019) Is Myocardial Fibrosis Impairing Right Heart Function? Am J Respir Crit Care Med 199 (12):1458-1459. doi:10.1164/rccm.201812-2307ED

45. Meloni A, Pistoia L, Gamberini MR, Cuccia L, Lisi R, Cecinati V, Ricchi P, Gerardi C, Restaino G, Righi R, Positano V, Cademartiri F (2023) Multi-Parametric Cardiac Magnetic Resonance for Prediction of Heart Failure Death in Thalassemia Major. Diagnostics (Basel) 13 (5). doi:10.3390/diagnostics13050890

46. Meloni A, Martini N, Positano V, De Luca A, Pistoia L, Sbragi S, Spasiano A, Casini T, Bitti PP, Allò M, Sanna PMG, De Caterina R, Sinagra G, Pepe A (2021) Myocardial iron overload by cardiovascular magnetic resonance native segmental T1 mapping: a sensitive approach that correlates

with cardiac complications. Journal of Cardiovascular Magnetic Resonance 23 (1):70. doi:10.1186/s12968-021-00765-w

47. Cau R, Bassareo P, Deidda M, Caredda G, Suri JS, Pontone G, Saba L (2022) Could CMR Tissue-Tracking and Parametric Mapping Distinguish Between Takotsubo Syndrome and Acute Myocarditis? A Pilot Study. Acad Radiol 29 Suppl 4:S33-S39. doi:10.1016/j.acra.2021.01.009

48. Cau R, Pisu F, Porcu M, Cademartiri F, Montisci R, Bassareo P, Muscogiuri G, Amadu A, Sironi S, Esposito A, Suri JS, Saba L (2023) Machine learning approach in diagnosing Takotsubo cardiomyopathy: The role of the combined evaluation of atrial and ventricular strain, and parametric mapping. Int J Cardiol 373:124-133. doi:10.1016/j.ijcard.2022.11.021

49. Cau R, Bassareo P, Suri JS, Pontone G, Saba L (2022) The emerging role of atrial strain assessed by cardiac MRI in different cardiovascular settings: an up-to-date review. Eur Radiol 32 (7):4384-4394. doi:10.1007/s00330-022-08598-6

Table 1. Demographic, clinical, and CMR data of TM patients.

Variable	TM patients (N=292)	Healthy subjects	p-value
Females, N (%)	151 (51.7)	12 (37.5)	0.127
Age (years)	36.72±11.76	40.78±14.35	0.312
Age at start of regular transfusions (months)	20.99±36.54		
Chelation starting age (years)	5.24±5.66		
Splenectomy, N (%)	146 (50.0)		
Body surface area (m2)	1.58±0.23	1.78±0.23	<0.0001
Pre-transfusion hemoglobin (g/dl)	9.67±0.52		
Serum ferritin (ng/ml)	1272.96±1652.20		
Diabetes, N (%)	42/290 (14.5)	0 (0.0)	0.013
Global heart T2* (ms)	36.15±10.72		
Global heart T2*<20 ms, N (%)	32 (11.0)		
Number of segments with T2* < 20 ms	2.11±4.66		
LV end-diastolic volume index (ml/m2)	85.69±16.99	78.46±10.53	0.041
LV end-systolic volume index (ml/m2)	32.16±10.87	31.90±10.67	0.751
LV stroke volume index (ml/m2)	53.68±9.93	47.59±7.10	0.001
LV mass index (g/m2)	61.23±12.60	51.24±12.71	<0.0001
LV ejection fraction (%)	62.57±7.02	61.82±4.79	0.497
RV end-diastolic volume index (ml/m2)	85.35±19.87	76.19±12.52	0.029
RV end-systolic volume index (ml/m2)	33.28±13.08	30.38±8.95	0.256
RV stroke volume index (ml/m2)	51.89±10.48	43.28±9.05	<0.0001
RV ejection fraction (%)	61.16±6.84	60.34±5.45	0.433
LA end-diastolic volume index (ml/m2)	19.60±12.18	12.88±4.16	<0.0001

RA end-diastolic volume index (ml/m2)	23.53±9.87	13.09±3.87	<0.0001
LACI (%)	22.99±13.58	16.05±5.28	<0.0001
RACI (%)	27.84±10.30	17.06±5.03	<0.0001
Replacement myocardial fibrosis, N (%)	75/188 (39.9)		

TM=thalassemia major, N=number, LV=left ventricular, RV=right ventricular, LA=left atrial, RA=right atrial, LACI=left atrioventricular coupling index, RACI=right atrioventricular coupling index.

Table 2. Univariate and multivariate linear regression analysis for the prediction of the LACI and RACI.

	Univariate		Multivariate	
	β	**p-value**	**β**	**p-value**
Left atrioventricular coupling index				
Age>75th percentile	0.343	<0.0001	0.254	<0.0001
Splenectomy	0.202	0.001		
Diabetes	0.310	<0.0001	0.144	0.041
Replacement myocardial fibrosis	0.292	<0.0001	0.244	<0.0001
Right atrioventricular coupling index				
Age>75th percentile	0.169	0.004		
Splenectomy	0.128	0.028		
Diabetes	0.160	0.006		
Replacement myocardial fibrosis	0.218	0.003	0.218	0.003

FIGURE LEGENDS

Figure 1. Schematic illustration of left atrioventricular coupling index and right atrioventricular coupling index in a healthy control and a patient with beta-thalassemia major.

β-TM=beta-thalassemia major, LACI=left atrioventricular coupling index, LA=left atrial, EDV=end-diastolic volume, LV=left ventricular, RACI=right atrioventricular coupling index, RA=right atrial, RV=right ventricular.

Figure 2. Mean left atrioventricular coupling index (**A**) and right atrioventricular coupling index (**B**) in healthy subjects and in beta-thalassemia major patients. The bars in the boxes represent the standard deviation.

TM=thalassemia major.

Figure 3. Mean left atrioventricular coupling index **(A)** and right atrioventricular coupling index **(B)** in beta-thalassemia major patients without and with cardiac complications. The bars in the boxes represent the standard deviation.

Figure 4. ROC curve analysis of left atrioventricular coupling index (pink) and right atrioventricular coupling index (blue) to identify the presence of a cardiac complication.

LACI=left atrioventricular coupling index, RACI=right atrioventricular coupling index.