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Worsening of myocardial performance index in beta-thalassemia patients despite permanently normal iron load at MRI: A simple and cheap index reflecting cardiovascular involvement?

Umberto Barbero, MD [a,*], Filomena Longo, MD [b], Paola Destefanis, MD [a], Carmen Maria Gaglioti, MD [b], Roberto Pozzi, MD [a], Antonio Piga, MD, Prof [b]

[a] Cardiology Division, San Luigi Gonzaga Hospital, Orbassano, Italy
[b] Thalassemia Center, University of Turin, Orbassano, Italy

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ABSTRACT

Background: Iron Overload Cardiomyopathy (IOC) due to repeated transfusions still represents the main cause of death in Thalassemia major (TM) patients. Because iron overload remains asymptomatic for long time, it is important to stratify the patients based on the risk of developing IOC before the appearance of clinical signs of heart failure. The magnetic resonance imaging (MRI) T2* may be useful but it is expensive and its MRI software has limited availability; conventional echocardiographic parameters, although easy availability, remain normal until advanced stages of IOC. Tissue Doppler Imaging (TDI) opened a new way to explore systolic and diastolic function directly or through derived index such as myocardial performance index (MPI) which has a prognostic value in different cardiomyopathies.
Methods: We enrolled 46 consecutive β-TM patients without clinical signs of heart failure and we tested them with echocardiography in 2011 and again in 2015. MPI of left and right ventricular lateral wall was calculated by TDI. All TM patients had a T2* MRI evaluation of the heart in the year before.
Results: Despite the absence of significant changes in morphological data at echo and at T2* evaluation, S′ waves of the lateral ventricular wall decrease while time passed, MPI worsened during the follow-up period and the derived systolic pulmonary artery systolic pressure (PAPs) increased in 2015 with respect to 2011.
Conclusion: TDI and MPI may reveal very early myocardial dysfunction in TM patients despite a normal T2* value. Together with PAPs they should be periodically checked in these patients.

1. Introduction

Beta-Thalassemia major (TM) is an inherited chronic anaemia: affected patients are today treated lifelong with repeated blood transfusions but that therapy causes chronic tissue iron overload requiring intensive treatment with chelating agents [1]. Direct iron-related injury is responsible for different kinds of cardiovascular abnormalities, including progressive worsening of diastolic and systolic ventricular function, increased arterial stiffness and pulmonary hypertension [2,3]. Despite the improvement in survival, Iron Overload Cardiomyopathy (IOC) is still the main cause of death in thalassemia major (TM) patients: the main problem in the care of this illness is that once reduction in systolic function is observed with conventional echocardiography, patients are already in a late stage of the infiltrative cardiomyopathy. Therefore, it is important to discover signs of the disease while the cardiomyopathy is still reversible. The most important advancement in this field has been T2* magnetic resonance imaging (MRI) assessment, which has been used since 2000s: it is a non-invasive method for imaging the iron accumulation in vital organs such as the heart, liver, pancreas, and pituitary gland [4]. The impact of non-invasive techniques for the assessment of cardiac and hepatic siderosis before the appearance of clinical symptoms is well known [5–8]: T2* evaluation is able to early recognize patients with iron overload and it has gained a critical importance in the management of these patients, but in clinical practice echocardiography provides a bedside faster and cheaper technique to study the heart function.

In the last years some studies reported interesting results about the utility of Tissue Doppler Imaging (TDI) for the echocardiographic evaluation of patients with beta-thalassemia major, either directly either with derived index as the myocardial performance index (MPI) [9–11]. These echocardiographic evaluations could be useful for early detection of regional myocardial dysfunction before the occurrence of abnormal indices of global ventricular function and may be applied during clinical follow-up of these patients, especially in the period of time

* Corresponding author at: Cardiology Division, San Luigi Gonzaga Hospital, Regione Gonzole 10, 10043 Orbassano (TO), Italy.
E-mail address: u.barbero@gmail.com (U. Barbero).

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between MRI evaluations. The aim of our study is to collect echocardiographic data at baseline and after 4-years follow-up to look for changes especially concerning TDI and MPI.

2. Methods

From January to October 2011 we prospectively examined with echocardiography 46 consecutive patients with beta-thalassemia major (TM) on regular blood transfusion and iron chelation. Inclusion criteria were: a recent Biosusceptometry SQUID (Superconducting Quantum Interference Device) to quantify liver iron concentration (LIC); cardiac iron assessment by MRI T2* technique in the previous year. Exclusion criteria were: clinical signs of heart failure, valvular heart disease, pulmonary hypertension, arrhythmias, left ventricular ejection fraction (LVEF) <55%, ongoing pregnancy, age < 18 years or history of coronary artery disease. After four years, from February to June 2015 we repeated the exams in the same patients to compare data. The study protocol was approved by the local ethics committee, and all patients provided informed consent before participation. The study was conducted in compliance with the Declaration of Helsinki.

Transthoracic echocardiography was performed 4–9 days after blood transfusion to ensure hemodynamic stability, using an Aloka Prosound Alfa 10 ultrasound system (2,5–3,5 MHz), by two expert physicians that were blinded to clinical information about patients until the end of the study. Cardiac cycles were stored in a digital format. Chamber dimensions were determined by standard procedures [12] and valve flow Doppler and TDI were recorded in the apical 4-chamber view according to the guideline [13]. The systolic (S′), early (E′) and late (A′) diastolic peak velocities of TDI were assessed on three beats at septal and lateral mitral origin and at lateral tricuspid origin, and expressed as a mean. MPI was derived, both for left and right ventricle, from the measurement of intervals registered with TDI [14].

Pulmonary arterial systolic pressure (PAPs) was derived from the tricuspid regurgitation velocity and an estimate of the right atrial pressure based on the dimension of inferior vena cava [15–16]. For all the measurements, intervals from 3 consecutive cardiac cycles were stored and averaged [13]. A repeat MRI was performed in 2015 before echo. Compliance with each chelator (deferoxamine, deferasirox, deferiprone) was assessed by interviewing each patient at the transfusion visits, evaluating the signs of deferoxamine infusion at the infusion sites, and calculating the ratio prescribed chelation/pharmacy dispensing. For deferoxamine, compliance was also evaluated by number of infusions recorded by the electronic infusion pump. For patients on combination therapy, we considered as compliance the inferior between those with each of the two chelators.

2.1. Statistical analysis

All data were analyzed using the SPSS version 20.0 (IBM) and Statistica version 6.0 (Statasoft) statistical package. Categorical data are presented as frequency and percentage (%). Continuous variables were presented as mean ± standard deviation (SD), median, minimum and maximums. The comparisons among groups were made by unpaired Student *t*-test or Fisher's exact test for continuous variables with normal distribution, Mann–Whitney U tests for continuous variables with non-normal distribution and a Chi-squared test for categorical variables. Correlations of T2* MRI with LVEF, serum ferritin levels, and ages of patients were performed using the Pearson correlation test. A two-tailed *P* value <0.05 was considered statistically significant.

3. Results

The characteristics of patients in 2011 and in 2015 are summarized in Table 1. In all patients echocardiographic measurements were fully assessable. Although time passed, patients' weight and body surface area didn't change. In 2015 only 2 patients had cardiac iron overload at MRI versus 8 patients in 2011. Only 1 patient worsened from a good value to a pathological one. Globally, cardiac iron overload remained stable over time (37.7 ± 11 ms vs 41.0 ± 15.7 ms, $p = 0.23$) and substantially normal (i.e. a T2* > 20 ms), while SQUID revealed a worsening in hepatic value. Three patients (6.5%) had diabetes mellitus, while 9 (19.6%) had thyroid diseases. No patient had arterial hypertension. Five patients (11%) had dyslipidaemia.

Table 1
Characteristics of study population at baseline and after 4 years.

	2011	2015	*p*-Value
Age (years)	31,3 ± 6	36,1 ± 6,6	
Sex (M/F)	29/17	29/17	
Weight (kg)	58,7 ± 10,6	59,7 ± 10,2	NS
Height (m)	1,62 ± 0,07	1,62 ± 0,07	NS
BSA (m^2)	1,62 ± 0,16	1,62 ± 0,16	NS
HR (bpm)	84,6 ± 13	79,8 ± 18	NS
SBP (mmHg)	114 ± 17	112 ± 15	NS
Ferritin (ng/ml)†	1596 ± 1593	1472 ± 1178	NS
Hemoglobin (g/dl)†	11 ± 0,5	10.3 ± 0.5	<0,0001
Estimated value of hemoglobin in the echo's day (g/dl)	11,5 ± 1,1	11,3 ± 1.1	NS
Splenectomy (YES/NO)	30/16	30/16	
Iron input (mg/kg/die)†	0,32 ± 0,07	0,38 ± 0.08	0,0002
Chelators:			
DFO	8	11	
DFO + DFP	6	7	
DFP	13	10	
DFX	19	18	
Compliance (%)	97,2 ± 5,3	88,5 ± 13,3	0,0002
MRI-T2* of the heart†	37.7 ± 11	41 ± 15,7	NS
LIC by SQUID (mcg/g)†	1229 ± 1027	1476 ± 777	0,001

† = average of the previous year, BSA = body surface area, HR = heart rate, SBP = systolic blood pressure, DFO = deferoxamine, DFP = deferiprone, DFX = deferasirox, LIC = liver iron concentration, SQUID = Superconducting Quantum Interference Device, MRI = Magnetic resonance imaging.

Echo values are listed in Table 2. Morphological data are in normal ranges, without significant changes.

As regards systolic function EF is normal despite the left S′-waves by TDI are lightly but significantly reduced respect to the 2011 data (10.9 ± 2.73 cm/s vs 9.7 ± 2.32 cm/s, $p = 0.02$).

Interestingly MPI increased from 2011 to 2015 for left ventricle (0.52 ± 0.16 vs 0.65 ± 0.23 in LV, $p < 0.003$) and shows a similar trend as regards right ventricle (0.41 ± 0.16 vs 0.44 ± 0.17 in RV, $p = 0.48$). Regarding diastolic function there are no significant differences.

PAPs mean value was normal in 2011 and remained normal in 2015 but it increase (from 24.38 ± 3 mmHg to 27.7 ± 5.2 mmHg) due to an increase in tricuspid regurgitation jet velocity (TRV) from 2.16 ± 0.16 m/s to 2.38 ± 0.3 m/s ($p < 0.0001$). No differences in TRV were found between splenectomised and non-splenectomised patients (2.28 ± 0.32 m/s vs 2.41 ± 0.28 m/s).

No correlations were found between MPI with iron related parameters (left MPI 0.66 ± 0.24 in patients with T2* ≤ 20 ms and 0.62 ± 0.21 in patients with T2* > 20 ms, $p = 0,82$). Despite the little number of patients we performed a univariate analysis to check differences between chelating regimens but no significance emerged. An interesting association was noted when comparing the mean value of S′ wave in the left ventricle between patients with high (≥0.55 ms) and low (<0.55 ms) MPI index (8.80 ± 2.12 cm/s vs 10.32 ± 2.3 cm/s, $p = 0.03$, see Fig. 1).

4. Discussion

The main findings of our study are: 1. Left longitudinal systolic function measured with TDI (S′ waves of the lateral ventricular wall) has decreased over time; 2. The MPI index worsened during the follow-up period, irrespective of the MRI T2* value.

We started from the well diffused pulsed TDI, a simple and useful method of assessing ventricular longitudinal function. It has been

Table 2
Comparison of echocardiographic data at baseline and after 4 years.

	2011	2015	*p*-Value
LV mass (g/m^2)	77,6 ± 16,3	84,51 ± 19,7	NS
LA area (cm^2)	19,8 ± 3	20 ± 3,7	NS
Indexed LVEDD (mm/m^2)	29,7 ± 3	22,2 ± 3	NS
IVS (mm)	8,1 ± 1	8,4 ± 1,4	NS
LVPW (mm)	7,8 ± 0,8	8,7 ± 1,1	0,0002
RA area (cm^2)	16,4 ± 3	16,1 ± 3,3	NS
E mitral (m/s)	0,76 ± 0,15	0,87 ± 0,2	0,01
A mitral (m/s)	0,51 ± 0,12	0,61 ± 0,16	0,003
E/A mitral	1,55 ± 0,41	1,48 ± 0,46	NS
DecT (msec)	177 ± 29	182 ± 35	NS
E/E′ LV	4,3 ± 0,98	4,8 ± 1,35	NS
LVEF (%)	59,98 ± 2,7	61,5 ± 2,8	NS
S′ septal (cm/s)	9 ± 1,6	9,3 ± 1,2	NS
S′ LV (cm/s)	10.9 ± 2,7	9,7 ± 2,3	0,02
FAC RV (%)	50,2 ± 5,9	48,2 ± 7,7	NS
S′ RV	14 ± 2,4	14,9 ± 2,6	NS
TAPSE (mm)	23,9 ± 3	24,1 ± 3,5	NS
Left MPI	0.52 ± 0.16	0,65 ± 0,23	<0,003
Right MPI	0.41 ± 0.16	0,44 ± 0,17	0,48
TRV (m/s)	2.16 ± 0.16	2,38 ± 0,3	0,0001
PAPs (mmHg)	24.38 ± 3	27,73 ± 5,2	0,0005

LA = left atrium; RA = right atrium; LV = left ventricle; RV = right ventricle; EDD = end diastolic diameter; IVS = interventricular septum; PW = posterior wall; FAC = fractional area change; EF = ejection fraction; DecT = deceleration time of mitral E wave; TAPSE = tricuspidal annulus plain systolic excursion; MPI = myocardial performance index; TRV = tricuspidal jet velocity; PAPs = systolic pulmonary artery pressure.

widely studied in different cardiomyopathies over than in iron-related cardiomyopathy of thalassemic patients [9,10,17]. Different studies reported abnormal value of tissue Doppler waves, especially reduced S′ waves in TM patients matched to the healthy controls [18]; also in patients with low cardiac iron at MRI, a stress test may establish the fact of the reduced S′ wave's response for exercising, proving this parameter as a possible initial sign of ventricular dysfunction [11]. As it was previously described for other diseases, early abnormalities of cardiac function due to iron overloading first of all may involve longitudinal systolic function [19,20]. In our study S′ waves have been reduced with time despite the normal global systolic function, and this fact may reflect underlying iron damage to longitudinal fibres in spite of good chelation and low deposition of iron into cardiac tissue at the time of the last MRI investigation [19,20]. In clinical practice S′ waves of the right ventricular wall were widely used in all kinds of patients to assess the right ventricular function; we suppose that the similar explanation might be made for the left ventricle in TM patients.

MPI is a powerful index for the evaluation of both systolic and diastolic functions at the same time [21]. It represents a sensitive indicator for heart failure that also provides prognostic information in several different pathologies, as dilated cardiomyopathy, anthracycline toxicity, myocardial infarction and cardiac amyloidosis [14]. It is minimally affected by preload, and it is also independent from ventricular geometry, heart rate and blood pressure. A previous study reported higher MPI in TM children and in thalassemia intermedia patients, suggesting that MPI obtained by TDI may be an adjunctive parameter to conventional echocardiography for detecting early myocardial damage [22,23]. MPI is easy to obtain with TDI and in our study it was always assessable.

Probably according to the fact that our patient group showed high and normal values of MRI T2*, indicating absence of cardiac iron overloading, we were not able to show a linear relation between MPI and T2* value that could be useful to distinguish among patients with a major risk of having a cardiac overload. Furthermore, paying attention to the fact that ferritin levels, T2* levels and haemoglobin remained the same in 2011 and 2015 we suggest that the increase in MPI or in systolic PAPs might be attributed to a subtle and very early myocardial dysfunction not directly or only partially-related to myocardial iron deposition; or maybe MPI, as the reduced S′ wave, reflects the persistence of previous iron related damage on longitudinal fibres despite normalization of T2* at MRI evaluation. We should not forget that SQUID discovered a worsening in the hepatic iron overload that could precede the heart iron overload. Anyway, a pathological value of MPI should focus the attention on a TM patient history and actual therapy, irrespective of T2* time.

Finally, we reported an increase in estimated pulmonary artery systolic pressure over time. Today is we'll know how the development of pulmonary hypertension could affect long-term prognosis in β-thalassemia, but despite the fact that today the real prevalence seems to be lower than in previous reports, regarding <5% of patients [24], the underlying pathophysiology has not been completely understood. Several mechanisms have been proposed such as tissue hypoxia causing endothelial dysfunction and a high-output state due to anaemia. Furthermore, chronic hemolysis results in nitric oxide depletion that promotes vasoconstriction and hypercoagulability [25]. Lastly, oxidative

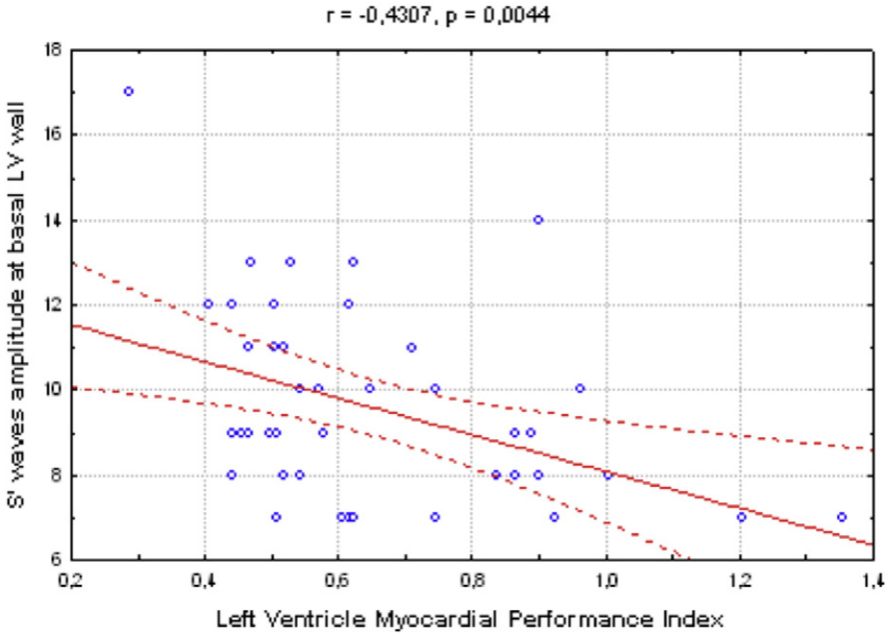

Fig. 1. Negative relation of S′ waves of the Left Ventricle (measured with Tissue Doppler Imaging) with left ventricular myocardial performance index (MPI).

tissue damage secondary to iron overload may result in pulmonary vascular remodelling and increased vascular resistance: endothelial dysfunction due to iron overload can cause an imbalance between vasodilator and vasoconstrictor substances in the pulmonary vascular endothelium, which induces smooth muscle cell proliferation, thereby leading to increased vascular resistance [3]. In our population, even in the presence of values of normal TRV at baseline and after 4 years of follow-up, we demonstrated a tendency to a statistically significant worsening. Despite new evidence stress the importance to confirm echocardiographic diagnostic value with right heart catheterization [24], this result puts the spotlight on the chronic nature of the iron-related damage also in the lungs, and the necessity to evaluate not only the estimated PAPs with regularly echocardiographic study, but also to compare it with the previous examinations in order to recognize as early as it is possible the sign of alarm before the appearance of clinical cardiac disease.

5. Limitations of this study

Although the original investigation about MPI used Doppler transvalvular velocities, TDI has been adequately validated and permits to study the index inside a single heartbeat. The increase in systolic PAP is significant but still within the normal range: because systolic PAP measurement should hide many sources of error we could not be sure of its worsening. Changes may reflect aging, although worsening seems to be too fast in just 4 years. We are in a lack of control group. The population is little and the following-up is short and the study is neither designed nor powered to detect clinical differences over time. However, enrolment of patients has still been continuing, and perhaps more follow-up studies would help better understand what is happening with the population. The strain technique has not been mentioned in this study because we would like to explore TDI and MPI potentiality, but correlation of our results with strain value could help to enforce our conclusions in the future studies. The strain technique is not widely diffused, especially in poorer countries, and often they need offline evaluations while MPI is faster to be checked during a normal echo examination.

6. Conclusions

Based on the results of our study, the tissue Doppler S′ wave and tissue Doppler derived MPI may be a simple and sensitive tools for the assessment of LV function. They are easy to get during a normal echocardiographic evaluation and it does not significantly prolong the examination time. Together with PAPs value they should be checked in every TM patient looking for worsening at follow-up.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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