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Echocardiographic predictors of adverse cardiac events in asymptomatic beta-thalassemic patients

Ines Paola Monte[1], Sergio Buccheri[2], Stefano Leggio[3].

University of Catania, Catania.

Abstract

Aim of study was to identify echocardiographic parameters related to the development of future adverse events (AEs) in asymptomatic thalassemic patients (TM). A total of 74 TM patients (TM group) and 22 healthy subjects (HS group) were included in the study. All subjects underwent standard echocardiography with Tissue Doppler Imaging (TDI). The follow up was for 974 ± 275 days. When compared to HS, TM showed a significant increase of LV Mass index (LVMi), diastolic (LVEDV) and systolic (LVESV) volume (p=0.001, p=0.001 and p=0.023, respectively). TDI analysis identified a significant impairment of S', E' and A' wave mean values (p<0.001, p<0.001 and p=0.002 respectively). Left atrial volume index and the E/E' ratio were significantly increased in TM (p<0.001). LV ejection fraction was preserved. At follow up, 10 AEs were observed in TM: one death from cardiac cause, 6 patients developing heart failure, 3 new detected supra-ventricular arrhythmias. In TM, ROC curve analysis identified LVEDV>122 ml, LVESV >46 ml, LVMi >82.1 g/m^2, E/A ratio>2.09, S' wave≤6.2 cm/sec, E' wave≤10 cm/sec, A' wave≤5 cm/sec and E/E' ratio >7.82 as cut off-values differentiating TM patients with AEs. On multivariate logistic regression analysis, the E/E' ratio (Exp (B) = 1.623, p=0.038) and the A' velocity (Exp (B)=0.509, p=0.044) were independent predictors of AEs at follow up. The TDI derived parameters are useful for the prognostic stratification of asymptomatic TM and easy to use. Early identification of subclinical myocardial dysfunction based on these parameters could be useful for the optimization of therapeutic strategies and correct risk stratification.

Keywords: Beta-thalassemic patients; Cardiac dysfunction; Tissue Doppler

*Corresponding Author: Prof. Ines Monte, Clinical Echocardiography, A.O.U. Policlinic VE – PO G.Rodolico, Via Santa Sofia 78 – 95100 Catania. Telephone: +39 095 3781308, Email: inemonte@unict.it

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Introduction

Beta-thalassemia is an inherited blood disorder characterized by a combination of ineffective erythropoiesis and haemolytic anaemia secondary to impaired haemoglobin beta-chain output [1]. These features are responsible for a severe anaemic status incompatible with life and for this reason patients require periodic blood transfusions. Each transfusion is responsible for an estimated iron over-load of 0.3-0.5 mg/kg/d^2 that combined with increased iron absorption in the intestinal tract lead to secondary hemochromatosis [2]. This process can affect different organs including the liver, pancreas, gonads and hypothesis but cardiac dysfunction secondary to chronic iron overload and high output state actually represents the leading cause of mortality and morbidity in thalassemic patients [3].

Echocardiography is a fundamental tool for the close follow up that this group of patients requires. Even if quantification if myocardial iron overload by means of cardiac magnetic resonance imaging (MRI) represents the gold standard for the identification of myocardial iron burden. However, the risk of gadolinium contrast reactions using MRI and against low costs and the wide availability of echocardiography, are features favouring echocardiography routinely clinical use.

Several papers published in the literature have shown the usefulness of echocardiography for the assessment of early cardio-vascular dysfunction in thalassemic patients [5, 6]. However, few studies have been performed to assess echocardiographic predictors of cardiac adverse events (AEs). Accordingly, we sought to identify echocardiographic parameters related to the development of future AEs in a group of asymptomatic beta-thalassemic patients.

Materials and Methods

Study population

This was a single centre, prospective and observational study. A total of 74 asymptomatic beta-thalassemic patients (TM group) were included in the study. A control group of 22 healthy subjects (HS group) were randomly selected and volunteered in the study. The current study population included a subgroup of TM patients (n=21) enrolled in a previously published work [7]. Exclusions criteria in both groups were represented by: presence of sign and symptoms of heart failure, supra-ventricular arrhythmias, hypertension, moderate or severe valvular abnormalities. Figure 1 shows the flow-diagram of the study.

Thalassemic patients received blood transfusions every three weeks to keep haemoglobin values between 10.5 and 13.5 g/dl and were optimally treated with iron-chelating therapies (deferoxamine and/or deferiprone). All thalassemic subjects underwent blood sample analysis to assess ferritin levels.

The study complied with the declaration of Helsinki and a written informed consent was achieved from all the subjects included in the study.

Echocardiography

All subjects underwent standard echocardiography in left lateral decubitus by using a GE Vivid 7 (GE, Vingmed Ultrasound AS, Horten, Norway) equipped with a S3 multi-frequency probe. From the parasternal long axis view, the following 2D guided M-mode parameters were obtained: LV end-diastolic thickness of interventricular septum (LV_IVSd) and posterior wall (LV_PWd), LV systolic and diastolic diameters (LVDd and LVDs, respectively). LV Mass was then calculated with the Devereux's formula [8] and indexed for body surface area (BSA) to obtain LV Mass Index (LVMi). Left atrial volume was obtained from the apical 4-ans 2-chamber views and was also indexed for body surface area to obtain left atrial volume index (LAVi). The LV end systolic volumes (LVESV) and end diastolic volumes (LVEDV) were obtained according to the modified Simpson's rule. LV ejection fraction (LVEF) was calculated as in formula: (LVEDV – LVESV)/LVEDV.

The peak mitral inflow velocities during early diastole (E wave) and atrial filling (A wave), were obtained by placing the sampling volume of pulsed-wave Doppler imaging at the tip level of the mitral leaflets from the apical 4-chamber view; their ratio (E/A ratio) was then calculated.

Tissue Doppler Imaging (TDI) was performed using real-time pulsed Doppler TDI to obtain spectral recordings of annular myocardial peak velocities. The sampling volume of the pulsed wave Doppler was applied at the septal and lateral sides of the mitral annulus and the parameters, obtained by averaging the respective values at the two places of measurements, were: systolic myocardial velocity (S' wave), early and late diastolic myocardial velocities (E' and A' wave, respectively). For each acquisition, scan line direction was carefully aligned with the direction of motion and gain settings were optimized to obtain optimal digital traces. Finally, the ratio between E and E' (E/E' ratio) was calculated and considered as an index of LV filling pressure [9].

All measures were performed according to the recommendations of the American Society of Echocardiography and European Association of Cardiovascular Imaging [10] by a level III certified echo-cardiologist, blinded to clinical data.

Clinical follow up and definition of adverse events

All the thalassemic patients received a six months thorough clinical and echocardiographic follow up on an outpatient basis. A standard 12-lead electrocardiographic assessment was also performed at each control. Adverse events were considered in a composite endpoint including: death from all causes, cardio-vascular death, heart failure hospitalization, new detection of supra-ventricular arrhythmias (including only atrial fibrillation/flutter). To be counted as an AE, atrial fibrillation/flutter ought to be long lasting (at least > 48 hours) and symptomatic, including persistent or permanent form of the arrhythmia. Patients with detected supra-ventricular arrhythmias at the FU visits underwent Holter monitoring. AEs were confirmed by obtaining source documentation at follow-up visits. If necessary, patients were contacted for further information. Control subjects were clinically followed up mainly by telephone contacts.

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Reproducibility analysis

Intra- and inter-observer variability of Doppler measurements has been performed in a randomly selected group of 20 subjects (12 TM patients and 8 HS). For the assessment of intra-observer variability, the operator repeated Doppler measurements blinded to previous findings. For the evaluation of inter-observer variability, a second operator, also blinded to previous results, performed Doppler measurements in the same group of subjects. Reproducibility is expressed as Coefficient of Variability (COV) and infraclass correlation coefficient (ICC) with 95% confidence interval.

Statistical analysis: The normal distribution of the examined parameters has been tested with the Kolgomorov-Smirnov test. Continuous variables are presented as mean ± standard deviation while dichotomous parameters are presented as frequencies and percentages. Using the unpaired t-test or the Mann-Whitney U Test, as appropriate, compared continuous variables. Categorical variables were compared with the chi-squared test.

Receiver-operating characteristic analysis (ROC curve analysis) has been performed in TM group and used to identify cut-off values of echocardiographic parameters predicting adverse cardiac events. Based on ROC curve identified cut-off values, TM patients were subdivided in different subgroups; the cumulative incidences of clinical events at follow-up in these groups were assessed with the Kaplan-Meier method and compared with the log-rank test. Univariate logistic regression analysis was performed to assess the relationship between echocardiographic parameters and the development of AEs. Variables with a p value < 0.01 at univariate analysis were entered in a multivariate logistic regression analysis to assess independent predictors of AEs. All tests were two tailed. A p-value < 0.05 was considered statistically significant.

Results

The overall population was followed up for 974 ± 275 days. During the follow-up period 10 AEs were observed in TM group including one death from cardiac cause, 6 patients developing HF, 3 new detected supra-ventricular arrhythmias. One patient with atrial fibrillation required PM implantation due to slow ventricular response and atrial-ventricular block at time of sinusal rhythm. No AEs occurred in the HS group.

Clinical characteristics between the two groups are shown in Table 1. Subjects in TM group showed a significant reduction of BMI and BSA in respect to HS group (p=0.004 and p<0.001, respectively). The mean ferritin value in TM patients was 1907±1918 ng/ml (range 250 -8000 ng/ml). No differences in ferritin values were found between patients with AEs at follow up and patients without AEs(p=0.406).

Parameters	TM, n=74	HS, n=22	p-value
Age (years)	31.3±8.0	32.6±7.5	0.841
Sex (M/F)	33/41	7/15	0.286
BSA (m^2)	1.56±0.16	1.78±0.22	<0.001
BMI (kg/m^2)	22.0±2.8	24.1±3.4	0.004
Heart rate (beats/min)	74.3±9.6	74.7±12.1	0.814
Systolic blood pressure (mmHg)	107.3±12.8	110.9±10.5	0.248
Diastolic blood pressure (mmHg)	67.7±7.9	68.0±7.4	0.705

Table 1: Clinical characteristic between the two groups. Data are expressed as number of patients or mean ± standard deviation. BSA, body surface area; BMI, body mass index.

Echocardiographic parameters are shown in Table 2. When compared to HS, TM patients showed a significant increase of LVMi (p=0.001), LVDd and LVDs (p=0.002 and p=0.035, respectively), LVEDV and LV ESV (p=0.001 and p=0.023, respectively). LAVi was significantly increased in TM patients (p<0.001). Relative wall thicknesses mean value was significantly reduced in TM group (p=0.001). LV ejection fraction was preserved in TM group while TDI analysis identified a significant impairment of systolic and diastolic myocardial velocities with reduced S', E' and A' mean values (p<0.001, p<0.001 and p=0.002 respectively). The E/E' ratio was significantly increased in TM group (p<0.001).

	TM n=74	*HS n=22*	*Range*	*p-value*	*TM- AEs n=10*	*TM no AEs n=64*	*p-value*
LVIVSd (mm)	7.5±1.3	8.2±1.2	4-11	0.030	8.2±0.7	7.4±1.3	0.081
LVDd (mm)	50.6±5.7	46.0±6.1	37-62	0.002	55.1±3.3	49.9±5.7	0.01
LVDs (mm)	31.5±4.3	29.5±3.8	24-43	0.035	35.2±4.3	31.0±4.1	0.009
LVPWd (mm)	7.9±1.8	8.3±1.5	5-14	0.136	8.4±1	7.6±1.8	0.126
RWT	0.31±0.06	0.37±0.09	0.21-0.58	0.001	0.31±0.05	0.31±0.06	0.901
LVMi (g/m^2)	71±20	59±13	29-125	0.001	90±15	68±20	0.004
LVEDV (ml)	120±32	94±31	47-193	0.001	148±20	117±32	0.005
LVESV (ml)	40±14	33± 13	15-82	0.023	53±15	38±12	0.006
LAVi (ml/m^2)	25±9	18±4	10-63	<0.001	36±18	24±7	0.161
LVEF (%)	67±6	64±8	52-79	0.132	65±7	67±6	0.224
E wave(cm/sec)	94±14	86±19	54-129	0.039	100±15	93±14	0.166
A wave(cm/sec)	56±14	57± 15	21-112	0.933	47±16	58±13	0.026
E/A ratio	1.76±0.55	1.64±0.56	0.8-4.8	0.393	2.36±0.97	1.68±0.41	0.003
S' (cm/sec)	7.6±1.7	10.1±1.8	4-13	<0.001	6.0±1.5	7.8±1.7	0.006
E' (cm/sec)	12.8±3.1	15.2±2.2	6-22	<0.001	10.4±3.6	13.1±2.9	0.029
A' (cm/sec)	7.0±2.2	9.4±3.4	2-17	0.002	4.8±2.2	7.3±2	0.002
E/E'	7.8±2.4	5.9±1.1	4.3-15.0	<0.001	10.5±3.3	7.4±2	0.005

Table 2: Echocardiographic parameters in all subjects and in patients with and without adverse events. Data are expressed as mean ± Standard Deviation. LV, left ventricle; IVSd, diastolic inter-ventricular septum thickness; Dd, diastolic diameter; Ds, systolic diameter; PWd, posterior wall thickness; RWT, relative wall thickness; LVMi Mass index; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; LAVi, left atrium voulme index; E, early diastolic filling velocities and A, late diastolic velocity at mitral valve; S', systolic myocardial velocity, E', early diastolic myocardial velocity and A', late myocardial diastolic velocity at mitral annulus. TM-AEs, patients with adverse events. TM no AEs, patients without adverse events

	AUC	*p-value*	*Cut-Off Values*
LVEDV (ml)	0.79	<0.0001	122
LVESV (ml)	0.79	0.0001	46
LVMi (g/m^2)	0.80	<0.0001	82.1
LAVi (ml/m^2)	0.70	0.256	33.6
LVEF (%)	0.60	0.412	64
E/A ratio	0.81	<0.0001	2.09
S' (cm/sec)	0.78	0.0004	6.16
E' (cm/sec)	0.72	0.047	10
A' (cm/sec)	0.81	0.0009	5
E/E'	0.79	0.005	7.82

Table 3: ROC curve analysis in thalassemic patients. AUC, area under the curve**.** Abbreviations same as in table 2.

	Univariate analysis		
	Exp (B)-coefficient	*95% CI Exp (B)*	*p-value*
LVMi (g/m^2)	1.059	1.015 - 1.105	0.009
LVEDV (ml)	1.031	1.007 - 1.056	0.012
LVESV (ml)	1.065	1.017 - 1.116	0.008
LVEF (%)	0.928	0.823 – 1.047	0.225
E/A ratio	6.27	1.416 – 27.742	0.016
S' (cm/sec)	0.434	0.238 – 0.737	0.006
LAVi (ml/m^2)	1.116	1.007- 1.236	0.036
E' (cm/sec)	0.702	0.526 – 0.937	0.016
A' (cm/sec)	0.469	0.281 - 0.782	0.004
E/E'	1.538	1.172 – 2.018	0.002

Table 4: Univariate logistic regression analysis. Abbreviations same as in Table 2.

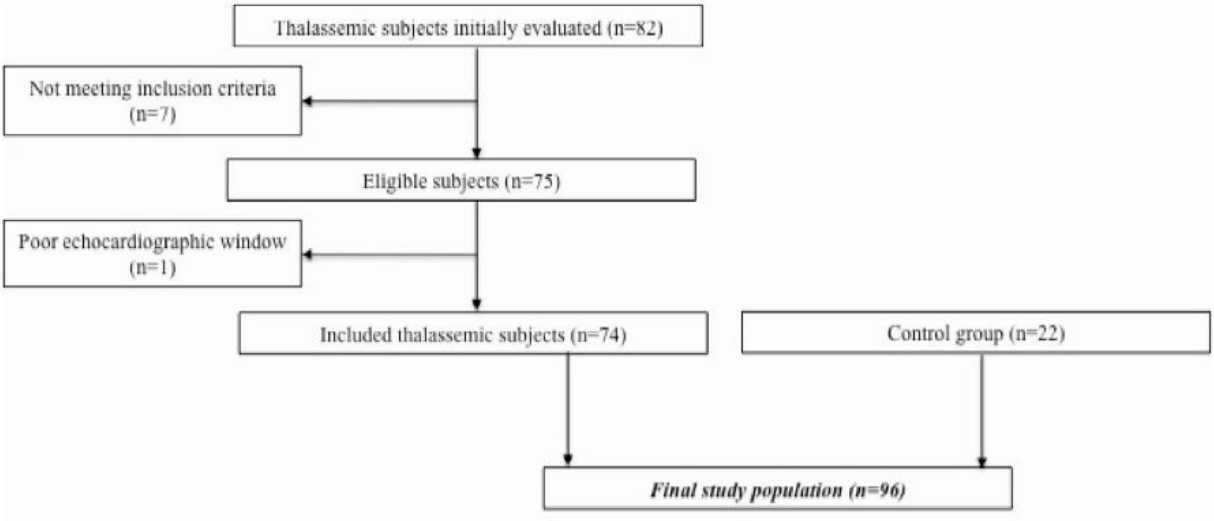

Figure 1: The flow-diagram of the study.

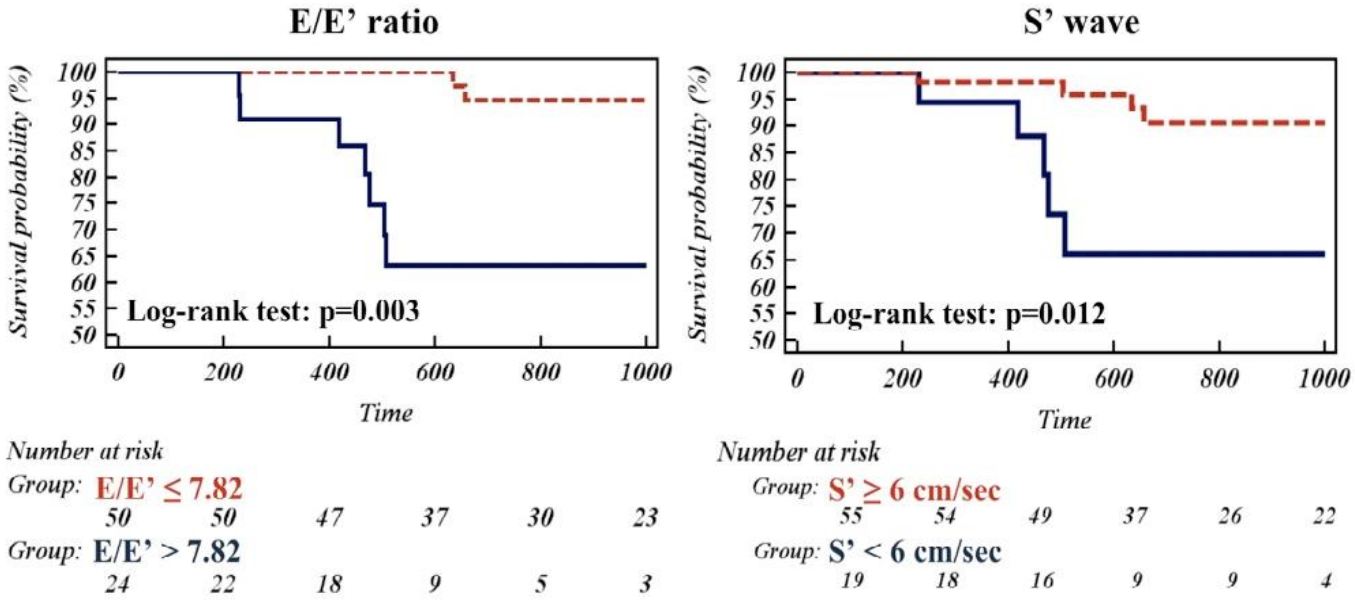

Figure 2: Kaplan-Meier curves in TM patients based on TDI cut-off values identified by ROC curve analysis.

The comparison between echocardiographic parameters in TM subjects with AEs at follow-up and patients without AEs, showed in TM with AEs a significant increase of LVDd (p=0.010), LVDs (p=0.009) and LVMi (p=0.004). Systolic and diastolic LV volumes were significantly increased in patients with AEs (p=0.006 and p=0.005, respectively); consequently LVEF was preserved between groups. Late diastolic filling velocity was significantly reduced in TM with AEs (p=0.026) and the E/A ratio was significantly increased in this group (p=0.003). All TDI derived parameters were significantly impaired in TM with AEs at follow up. The E/E' ratio was significantly increased in TM with AEs (p=0.005).

ROC curve analysis is shown in Table 3. TDI derived parameters were able to differentiate TM patients developing AEs at follow-up while LVEF was not useful for this purpose. In addition, morphological parameters including LVEDV, LVESV and LVMi were able to differentiate patients with cardiac AEs during the follow-up period.

Based on these findings TM patients were subdivided according to the identified cut-off values (S' values 6 cm/sec, E/E' ratio 7.82). Figure 2 shows Kaplan-Meier curves with log rank tests in these subgroups.

Univariate logistic regression analysis, performed in TM group and having the development of AEs as dependent variable, is shown in Table 4. Even in this case, morphological parameters, including LVEDV, LVESV, LAVi and LVMi were significantly related to the development of AEs. In addition, all TDI derived parameters were also related to the development of adverse events. Finally, diastolic functional parameters including the E/A ratio and the E/E' ratio were significantly related to the development of AEs at follow up.

On multivariate logistic regression analysis, the E/E' ratio (Exp (B)= 1.623, p=0.038) and the A' velocity (Exp (B)= 0.509, p=0.044) were independent predictors of AEs at follow up.

Discussion

Beta-thalassemia imposes to the heart morpho-functional adaptations that are secondary to the anaemic status and the progressive increase in myocardial iron concentration. Chronic anaemia is in fact responsible for cardiac chambers' dilatation that acts as a compensatory mechanism to increase cardiac output and provide adequate oxygen supply to body tissues and organs despite low haemoglobin blood levels. Enlargement in both the end-diastolic and end-systolic left ventricular volumes, rather than increased heart rate, has been demonstrated as the leading mechanism linked to the high-output state seen in this group of patients [11]. Cardiac hemochromatosis leads then to progressive myocardial dysfunction, characterized by overt systolic and diastolic functional abnormalities that are often seen when patients become symptomatic.

Despite improvements in chelating therapies, iron mediated cardiomiopathy actually represents the leading cause of morbidity and mortality in thalassemic patients [3]. The identification of subclinical markers of cardiac dysfunction with prognostic impact is therefore crucial because thalassemia heart disease could be even reversible in the first phases of the disease [12]. However, conventional echocardiographic parameters have poor sensitivity and specificity for the early identification and for the prognostic stratification of asymptomatic patients.

On this background, we looked at the identification of echocardiographic AEs predictors in the asymptomatic phases of the disease. The main findings of the current study are:

a) morphological parameters including LV hypertrophy and LV chamber dilatation are related to the development of future events;
b) Tissue Doppler Imaging is a useful echocardiographic tool for the identification of subclinical cardiac dysfunction and the prediction of future cardiovascular events in thalassemic patients;
c) features of restrictive physiology as identified by TDI abnormalities are related to the development of adverse events before impairment of conventional echocardiographic parameters like ejection fraction;
d) Diastolic dysfunction has a strong prognostic impact in TM patients.

In the current work we demonstrated that morphological remodelling of the LV has a poor prognostic impact. A combined and progressive increase in LV systolic and diastolic volumes, with a consequent near normal LVEF, could in fact represent a marker of incipient cardiac dysfunction. When LVEF is still in the normal range this reflects a condition of labile balance. The drop in LVEF, seen later and in advanced disease, is in fact a final marker of cardiac dysfunction and expresses the transition from a high to low-output stage.

Previously published works in the literature have shown that TDI analysis in TM patients is a useful technique for the identification of regional wall motion abnormalities that are probably secondary to patchy areas of fibrosis within the myocardium seen in the early phases of the disease[13]. In particular, the basal septum and lateral wall of the LV have been shown to be early affected in the course of the disease [6, 14]. This is in agreement with our findings and could also justify the superiority of sampling such regions with TDI for the prediction of AEs in respect to conventional parameters.

Our results are also in agreement with previous studies in the literature demonstrating the prognostic impact of TDI derived parameters. Marcì et al.[15] identified in fact an S' value below 7.9 cm/sec as a predictor of heart dysfunction in TM patients. In addition to S' values, we identified that a global impairment of TDI derived parameters is able to predict cardiovascular adverse events.

We also found that features of restrictive diastolic function represent a prognostic determinant in TM patients. We demonstrated that the E/E' ratio and the A' wave velocity are independent predictors of adverse events on multivariate analysis. Our findings are in agreement with previous published data in the literature[16] showing poor survival for patients with a Doppler detected restrictive filling pattern.

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Others predictors of clinical adverse events in TM patients have been studied in the literature. Ferritin has been largely used as a marker of increased iron load in this group of patients. A previously published work [17] showed increased risk of AEs for TM patients with a serum ferritin level above 2500 ug per litre. However, further literature showed the inconsistent nature of ferritin measurements for the prediction of myocardial iron overload and AEs [18]. Our results are in agreement with the recent acknowledgement of serum ferritin as an unreliable marker of cardiac iron overload and prognostic stratification tool [19]. We in fact showed that ferritin levels were not useful as predictors of AEs during follow up. Quantification of iron overload by means of T2* cardiac MRI has instead proven to be the gold standard technique for the assessment of myocardial iron burden. This technique has also shown the ability to predict heart failure development in this group of patients [20]. Moreover, previous studies in the literature showed that TDI analysis is directly related to myocardial iron concentration as assessed by T2* MRI values [21,22].

TDI and conventional echocardiography could therefore represent a cost-effective technique for the identification of subclinical myocardial dysfunction and the prediction of developing cardiac AEs. Such strategy to look at cardiac function could be of particular value in the poor countries where thalassemia is very frequent and cardiac MRI evaluation could be difficult to perform or too expensive [23]. Also the risk of anaphylaxis associated with gadolinium- based contrast agents is a limit of the MRI use [24].

Several published studies identified the prognostic value TDI analysis in other pathological conditions including hypertrophic cardiomiopathy and heart failure [25, 26] but also in asymptomatic subjects with cardiovascular risk factors [27]. We demonstrated that TDI analysis could be a simple and very useful tool with prognostic value in thalassemia heart disease. Given the strong prognostic value and the ease of obtaining such parameters, we believe that TDI analysis should be routinely used in the echo-lab for the assessment of cardiac function in TM patients. TDI could be in fact superior to conventional echocardiographic parameters because, as above said, impairment of LV EF often occurs when iron accumulated in the heart exhausts storage capacity of myocardial cells [12] and an irreversible myocardial dysfunction is present.

Findings of impaired velocity of myocardial contraction and relaxation velocities could be also of therapeutic interest. Garadah et al. [28] showed that the increment of oral chelating therapies in TM patients for a six months duration leaded to significant increments of systolic and diastolic tissue Doppler velocities with a significant reduction of E/E' ratio. Moreover, detection of diastolic abnormalities and chambers' dilatation could prompt the early use of low dose angiotensin converting enzymes inhibitors. Karvounis et al. [29] demonstrated in fact a significant reduction of the E/A ratio and LV diastolic volumes after treatment with enalapril.

Echocardiography is a continuously developing tool and new techniques, such as speckle tracking echocardiography, are improving the echocardiographic ability to detect subclinical cardiac functional abnormalities. Different studies have shown the usefulness of STE derived parameters, like longitudinal strain, for the early identification of myocardial dysfunction in TM patients [5,6,13-15,21,30]. We recently reported that rotational dynamics could be affected even before impairment of longitudinal function in TM patients [7]. However, this method requires a wider diffusion and technical expertise, as well further studies are needed to assess the prognostic value of such parameters in this group of patients.

In conclusion, early identification of patients at highest risk for the development of cardiovascular complications may offer the opportunity to change the natural course of the disease and improve prognosis. Early identification of subclinical dysfunction is mandatory because in thalassemia heart disease therapeutic strategies are more effective if undertaken in the correct time. Prognostic assessment can be performed using simple echocardiographic parameters and when subtle alterations of myocardial function are detected patients should be followed-up closely and managed with more aggressive therapeutic strategies.

Limitations

The current study has some limitations. Firstly, a relatively low number of AEs was noted during the follow up period of the study. Cardiac death was present in only one subject and a longer follow-up was probably needed to assess parameters related to mortality. However, heart failure onset often predicts short-term mortality and is therefore a strong prognostic end-point.

Few studies have been performed to assess functional implications of new detected supra-ventricular arrhythmias; we reported that in TM patients the development of arrhythmias is related to myocardial dysfunction [31] and for this reason were included in the composite end-point of the study.

Moreover, BNP values were not prospectively evaluated in the studied population and performed in a small number of these patients [32]. As previously stated, a more holistic echocardiographic approach, including speckle-tracking imaging, should have been of potential interest. Nevertheless, we aimed to identify a simple echocardiographic approach to be routinely used in clinical practice for the prognostic stratification of TM patients.

Finally, identified cut-off values should be applied in a prospective and different cohort of TM patients to validate sensitivity and specificity for the prediction of AEs.

Conclusions

Echocardiography with TDI analysis is useful for the prognostic stratification asymptomatic thalassemic patients. Early identification of subclinical myocardial dysfunction based on these parameters could be useful for the optimization of therapeutic strategies and correct risk stratification.

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