Peer reviewed article

Prognostic significance of right ventricular diastolic function in thalassaemia major

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Summary

While left ventricular (LV) restrictive filling pattern is an ominous echocardiographic finding in thalassaemia major (TM), the prognostic significance of right ventricular (RV) diastolic function in patients with TM has not been thoroughly investigated. We studied 45 TM asymptomatic transfusion-dependent patients with normal LV systolic function by Doppler echocardiography. The 15-year cumulative survival rate was 34% in patients with RV restrictive filling pattern (RFP) and 82% in patients with RV non-RFP (log-rank = 10.41, p = 0.0013). Doppler estimation of RV filling pattern is very important in evaluating the prognosis of TM patients and should be performed routinely and using a standardised follow-up protocol.

Key words: thalassemia major; Doppler-echocardiography; right ventricular restrictive filling pattern; cardiac mortality

Ventricular restrictive filling pattern due to decreased ventricular compliance is characterised by an inappropriate elevation of ventricular pressure in comparison with a minor augmentation of ventricular volume, during early diastole. Elevated ventricular pressure leads to an abrupt premature cessation of early filling in the first half of the diastolic period and to insufficient filling in late diastole due to elevated end diastolic pressure. The Doppler flow velocity recordings across the mitral and tricuspid valves in patients manifesting restriction are markedly different from those in normal subjects, showing shortened deceleration times across both valves and a high ratio (>2) of early to late filling [1]. Left ventricular (LV) restrictive filling (LVRF) pattern, as assessed by Doppler-echocardiography, is an old well-recognised feature in thalassaemia major (TM) patients with normal LV systolic function [2] attributed by some authors to iron deposition in the heart [3, 4]. In a recently published study by our group, LVRF pattern was found to predict a very poor long-term prognosis in TM patients [5]. The significance of the right ventricle (RV), in terms of clinical outcome, in patients with TM has not been adequately studied. The purpose of this longitudinal study was to investigate the impact of the Doppler-demonstrated RV filling pattern on survival in a cohort of asymptomatic TM adult patients with normal LV systolic function over a 15-year observation period.

Design and methods

Patients and study protocol

The protocol of this study was reviewed and approved by the institutional review board. Sixty-five consecutive TM patients, who were followed-up in the Thalassaemia Unit of AHEPA Hospital, were considered candidates for the analysis. All patients initially underwent: clinical evaluation, chest x-ray, 12-lead ECG and Doppler-echocardiography from May 1989 to August 1989, in order to obtain baseline data, and then they were examined periodically, by clinical examination and Doppler-echocardiography up to the end of the data collection (May 2004). The endpoint of the study was death from any cardiovascular cause. Patients' inclusion criteria were: 1) Age 14 years at initial examination, 2) Normal LV end-diastolic diameter (≤55 mm) with normal LV systolic function (LV fractional shortening ≥30%) and normal RV end-diastolic diameter

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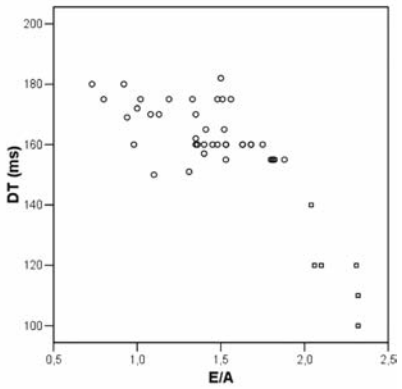

Figure 1

Scatter plot of baseline values of deceleration time of right ventricular early filling (DT) and peak early to peak late right ventricular filling velocity (E/A). Patients with right ventricular restrictive filling pattern are plotted with square symbols.

(≤30 mm) with normal RV systolic function (RV fractional area change ≥32%), as assessed by echocardiography and 3) Absence of any symptom of cardiac and/or pulmonary pathology. Among the 65 patients initially evaluated, 20 were excluded for the following reasons: 11 were <14 years of age; 4 had LV fractional shortening <30%; 5 died from non-cardiac causes during the follow-up period (2 in traffic accidents, 1 during non-cardiac elective surgery, 1 because of diabetic coma, and 1 from overwhelming septicaemia). The remaining 45 patients (23 female, 22 male) met the aforementioned criteria and comprised the final study cohort. All patients were on an iron–chelation regimen with subcutaneous infusion of desferrioxamine and none was on any cardioactive medication.

Echocardiography

The detailed study protocol is published elsewhere [5]. The patients underwent Doppler-echocardiography once or twice per year, unless otherwise required. RV diastolic filling pattern was assessed from the apical 4-chamber view by positioning a 2–4 mm sample volume at the tips of the mitral and tricuspid leaflets during diastole. The diastolic indices were calculated: peak velocity of E wave-representing early filling, peak velocity of A wave-representing late filling, ratio of peak early to peak late filling velocity (E/A), and deceleration time of early filling. Diastolic indices were measured at 6 consecutive beats and their values were averaged in order to avoid any influence of respiration on diastolic filling. RV function was assessed as a percent change in the cavity area from end-diastole to end-systole in a 4-chamber view. RV fractional area change was calculated using the following formula: (end-diastolic area – end-systolic area)/end-diastolic area×100 [6]. None of the patients studied had mitral and/or tricuspid regurgitation >1/4 as assessed by Doppler-echocardiography or pulmonary artery systolic pressure >30 mm Hg as assessed from the tricuspid regurgitant jet. RV restrictive filling pattern was considered present if the deceleration time of early filling was <150 ms or/and the peak early to peak late filling velocity ratio was >2. Figure 1 shows a scatter plot of baseline values of deceleration time of right ventricular early filling (DT) and peak early to peak late right ventricular filling velocity (E/A).

Depending on ventricular filling pattern of the baseline echocardiography, the patients were categorised into two groups: 1) Patients with RVRFP and 2) Patients with RV non-RFP.

Statistical analysis

Data are expressed as mean (standard deviation), except for the data concerning the age at start of regular transfusions, which are expressed as median [25th to 75th percentile]. T-test for independent parameters was used to estimate differences in mean values and the Mann-Whitney test was used to estimate differences in median values between groups. The differences between categorical data were assessed by the chi-square test. The Kaplan-Meier survival analysis was used to estimate survival, while differences in mortality between the groups were compared using the log-rank test. All reported p values are two-sided. P value <0.05 was considered statistically significant.

Results and discussion

At the time of the first examination haemoglobin levels ranged from 9 to 10.5 g/dl with a mean value of 10 [1]. There were no statistically significant differences between patients with restrictive and non-restrictive filling patterns regarding the mean values of age, height, weight, heart rate, age at start of chelation therapy, total blood units transfused, total iron burden and ferritin levels at the start of the study. There was also no statistically significant difference between patients with restrictive and non-restrictive filling pattern regarding the median age at start of transfusions. Six patients (13%) had a RVRFP, and 39 patients (87%) had a RV non-RFP. Patients who developed symptomatic systolic heart failure during follow-up were put accordingly on standard heart failure treatment.

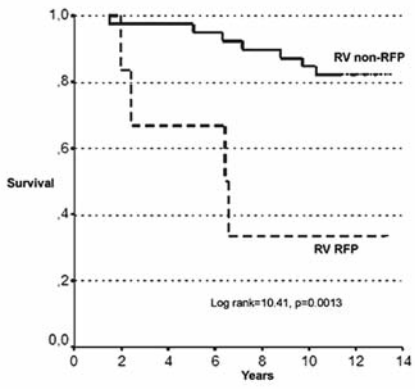

Figure 2

Kaplan-Meier 15-year survival estimates in thalassaemia major patients with right ventricular restrictive filling pattern (RV-RFP) and right ventricular non-restrictive filling pattern (RV-non RFP).

Relation between RVRFP and cardiac death

From the 6 patients with RVRFP at the beginning of the study, 4 (66%) were dead at the end of data collection, while from the 39 patients with RV non-RFP only 7 (18%) died at the end of the study. The cause of death in the former group was decompensated systolic heart failure in 3 patients and sudden cardiac death in 1 patient, while in the latter group end-stage systolic heart failure in 3 patients, sudden cardiac death in 2 patients and pulmonary embolism in 2 patients. Chi-square test of independence showed that RVRFP was significantly associated with mortality ($x^2 = 6.7$, $p = 0.01$). By Kaplan–Meier survival analysis, mean survival in patients with RVRFP was 7 (2) years (95% confidence interval: 4 to 11 years), while mean survival

Table 1

Comparison of baseline clinical and echocardiographic data in thalassaemia major patients with right ventricular restrictive filling pattern and right ventricular non-restrictive filling pattern.

Variable	RVRFP (n = 6)	RV non-RFP (n = 39)	p value
Clinical characteristics			
Age (y)	19 (3)	20 (±)	NS
Male gender	2	20	NS
Height (cm)	167 (8)	166 (7)	NS
Weight (kg)	55 (9)	54 (8)	NS
Systolic blood pressure	118 (10)	115 (9)	NS
Diastolic blood pressure	70 (8)	72 (8)	NS
Heart rate (bpm)	74 (7)	72 (8)	NS
Age at start of transfusions (y)	1.4 [0.7–1.8]	0.9 [0.5–1.5]	NS
Age at start of chelation therapy (y)	13 (3)	14 (4)	NS
Total blood transfused (units)	337 (68)	320 (61)	NS
Total iron burden (g)	78 (17)	73 (15)	NS
Ferritin (ng/ml)	5104 (1811)	4409 (1663)	NS
Echocardiographic characteristics			
Interventricular septum thickness, cm	0.94 (0.17)	0.92 (0.14)	NS
LV-posterior wall thickness, cm	0.87 (0.06)	0.86 (0.05)	NS
LV-end-diastolic diameter, cm	4.9 (0.5)	4.9 (0.4)	NS
LV-end-systolic diameter, cm	3.2 (0.3)	3.1 (0.5)	NS
LV-fractional shortening, %	35.8 (6.6)	34.8 (5.3)	NS
LV-mass index, g/m²	87.9 (10.4)	84.3 (9.6)	NS
Left atrium size, cm	3.4 (0.4)	3.2 (0.5)	NS
RV-end-diastolic diameter, cm	1.8 (0.4)	1.9 (0.3)	NS
RV-free wall thickness, cm	0.35 (0.04)	0.35 (0.05)	NS
RV fractional area change (%)	34.6 (8.6)	35.8 (9.1)	NS
Pulmonary artery systolic pressure, mm Hg	24.8 (5.9)	21.8 (3.9)	NS

Values are expressed as mean (standard deviation). Age at start of transfusion is expressed as median [25th to 75th percentile]. RVRFP: right ventricular restrictive filling pattern; LV: left ventricular; RV: right ventricular; NS: non-significant

in patients with RV non-RFP was 12 (1) (95% confidence interval: 12 to 13 years). The 15-year cumulative survival rate was 34% in patients with RVRFP and 82% in patients with RV non-RFP (log-rank statistic = 10.41, p = 0.0013) (fig. 2).

Cardiac function is the major determinant of survival in TM patients. Most TM patients are clinically stable for a long-life time, but when symptoms of heart failure appear, survival drops dramatically. Iron overload of the heart is the main cause of cardiac dysfunction and death in these patients [7, 8]. Myocardial iron deposition does not affect LV relaxation but directly causes LV myocardial restriction [2], while LV systolic function is still normal. In a recently published study we found that LVRF pattern predicted very bad prognosis in TM patients [5]. The 15-year cumulative survival rate was 58% in patients with LV restrictive filling pattern and 88% in patients with normal LV filling pattern. Being more compliant than LV, RV is affected by iron overload in latter stages. So, the development of RV restriction to filling denotes more advanced cardiac involvement and consequently worst prognosis. It is not surprising that the 15-year cumulative survival rate was 34% in patients with RVRFP and 82% in patients with RV non-RFP. Addition of oral deferiprone to standard chelation therapy with deferoxamine may improve cardiac function by removing myocardial iron, in such patients [9]. One limitation of this single centre study is the small number of patients with RV non-RFP and the limited number of mortality events. Moreover, myocardial iron loading with the use of cardiac magnetic resonance imaging, and myocardial tissue velocities with the use tissue Doppler imaging were not assessed, since these techniques were not available at the start of the study.

Further studies, perhaps of multicenter design, are needed in order to elucidate the importance of Doppler estimation of RV filling pattern in TM patients. More research is needed so that RV inflow Doppler may be performed routinely and in a standardised follow-up protocol for the risk stratification of these patients in the future.

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