Right ventricular cardiomyopathy in β-thalassaemia major


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Aims To evaluate right ventricular function in patients with β-thalassaemia major and congestive heart failure.

Background In patients with β-thalassaemia major a high incidence of cardiac involvement still exists despite improved prognosis with chelation therapy. Development of severe right heart failure is common and has been attributed to pulmonary hypertension secondary to lung haemochromatosis. However, the possibility of direct right ventricular myocardial involvement in the absence of significant pulmonary hypertension has not been adequately investigated.

Methods Twenty-nine consecutively screened patients with β-thalassaemia major and congestive heart failure were investigated by Doppler echocardiography, right ventricular first-pass radionuclide examination and cardiac catheterization. Haemodynamic data were obtained both before and after volume loading. A control group of 39 patients with β-thalassaemia major, free from cardiac disease, and matched for age, gender, body surface area and heart rate was used for comparison. A subset of the control thalassaemic group (n=15) underwent both radionuclide and haemodynamic assessment.

Results The majority of patients were on non-optimal chelation therapy. Only two of 29 patients were found to have cor pulmonale. One other patient suffered from constrictive pericarditis. A restrictive filling pattern in both ventricles and left ventricular systolic dysfunction were evident in the other 26 patients. Pulmonary artery pressure (systolic, 33 ± 8 vs 27 ± 5 mmHg, P<0.05) and pulmonary vascular resistance (114 ± 56 vs 65 ± 29 dynes . s . cm⁻³, P<0.01) were only mildly elevated in the heart failure group. After volume challenge, cardiac output remained unchanged although the increments of ventricular filling pressures were significant (Right atrial: 4.8 ± 2.2 mmHg, P<0.05; Pulmonary capillary wedge: 5.6 ± 2.9 mmHg, P<0.05) and correlated with each other (r=0.69; P<0.001) in heart failure patients, suggesting pericardial constraint and ventricular interaction. In these patients compared with the control thalassaemic group, a lower right ventricular ejection fraction (29% ± 9 vs 59% ± 6, P<0.0001) without correlation with pulmonary artery pressures was found. Haemodynamically significant right ventricular dysfunction defined as mean right atrial pressure >10 mmHg and ratio of mean right atrial-to-capillary wedge pressure >0.8 was evident in 15 of the 26 patients (58%), all with severe symptoms, representing three fourths of the patients in functional class III and IV. Simultaneous pressure recordings in six of these 15 patients showed equalization of ventricular end-diastolic pressures within 5 mmHg.

Conclusion The majority of patients with β-thalassaemia major and severe congestive heart failure demonstrated a unique haemodynamic pattern similar to that described in predominant right ventricular infarction, indicating severe right ventricular cardiomyopathy in addition to left ventricular dysfunction. The incidence of cor pulmonale as a cause of right heart failure seems to be much lower than previously hypothesized.

Key Words: Thalassaemia, heart failure, cardiomyopathy, right ventricle, right heart catheterization, Doppler echocardiography.

Introduction

In patients with β-thalassaemia major, cardiac abnormalities are important causes of morbidity and mortality. Lifelong blood transfusions, extra-vasal haemolysis and increased gastrointestinal iron
absorption lead to iron overload and toxicity in many organs including the heart[1-5]. Chelation therapy can dramatically improve, but not completely eliminate, cardiac involvement and prognosis[6,7]. Once congestive heart failure develops, a moderate or severe reduction of left ventricular systolic function usually exists, symptoms and signs of severe right-sided heart failure are common and the prognosis is considered poor.

Predominant right heart failure has been attributed to pulmonary hypertension, which was postulated to occur secondary to lung haemochromatosis, largely in patients with high ferritin levels[6-8]. Haemodynamic confirmation thereof has been reported in only a few patients with β-thalassaemia intermedia[9], while an old case-report suggested severe right ventricular involvement in haemochromatosis[10]. We recently reported our findings in patients with β-thalassaemia major and normal left ventricular systolic function, showing a disturbed right ventricular relaxation pattern but normal left ventricular filling characteristics and, in addition, the prognostic superiority of short tricuspid E deceleration time over other clinical and echocardiographic parameters in these patients[11].

In the current study, we prospectively investigated the right ventricular function in consecutive patients with β-thalassaemia major and congestive heart failure, testing the hypothesis that the right ventricular dysfunction is ‘primary’, i.e. mainly the consequence of right ventricular haemochromatosis and not secondary to pre- or post-capillary pulmonary hypertension.

Patients and methods

Study population and design

The study group included 29 consecutive patients with β-thalassaemia major (patient group) who presented with symptoms and signs of congestive heart failure (22 of whom were in New York Heart Association functional class III or IV) from October 1994 to January 2001. This corresponds to an annual incidence of heart failure of 3.8% in the adult population with β-thalassaemia major, who are being regularly transfused and clinically followed-up in the Thalassaemia Unit at our Institution. Patients were examined, while in a stable haemodynamic condition, with Doppler echocardiography, right heart catheterization and first-pass radionuclide right ventriculography, all performed within 1 week. All patients were on oral therapy with diuretics, digitalis and angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists. Echocardiographic findings were compared with those of 39 asymptomatic patients with β-thalassaemia major, normal ventricular systolic function and without a previous history of heart failure, matched for age, gender, body surface area and heart rate (control thalassaemic group). A subset of 15 patients from the control thalassaemic group underwent both haemodynamic and radionuclide examination for comparison with the patient group.

All thalassaemic patients were on a regular transfusion programme, every 2 to 3 weeks since their first months of life. They were receiving desferrioxamine 40 mg . kg\(^{-1}\) subcutaneously overnight and ascorbic acid orally. In advanced heart failure, chelation therapy was intensified and was periodically administered intravenously in haemodynamically stable patients. Serum ferritin values were obtained 4–5 times every year and all values in the last 4 years were taken into consideration. Adherence to desferrioxamine use was judged as good, moderate or insufficient if the patients followed the haematologist’s instructions with a compliance of >90%, 50-90% or <50%, respectively.

Doppler echocardiography

The echocardiographic examination was performed with a Hewlett-Packard Sonos 1000 echocardiography machine. All patients were in sinus rhythm at the time of the study. M-mode measurements were obtained according to previous recommendations[12]. Left ventricular mass was calculated from the corrected formula of Dereveux et al.[13]. Two-dimensional echocardiography was used for determination of left ventricular ejection fraction and volumes (single plane area-length method), for calculation of right ventricular end-diastolic area by planimetry at the onset of the R wave on the electrocardiogram from the four-chamber view and for qualitative assessment of global right ventricular systolic function as normal or depressed. Doppler examination included studies on both the right and left heart. Isovolumic right ventricular relaxation time was determined by the difference between the time interval from the peak of the R wave on the electrocardiogram and the onset of the tricuspid valve opening and the time interval from the peak of the R wave and the end of the pulmonary systolic flow. Flow velocities of the superior vena cava and right upper pulmonary vein were also recorded. Measurements are the averaged values over three to five cardiac cycles. Intra- and inter-observer variability of Doppler measurements in our laboratory, expressed as mean percent error, are respectively, 3% to 11% for the left heart and 4% to 15% for the right heart[11]. Severity of valvular regurgitation was estimated semiquantitatively with colour flow mapping from multiple views and graded from mild (=1) to very severe (=4).

Right heart catheterization

Haemodynamic measurements were obtained with a 7F triple lumen balloon-tipped thermocatheter introduced via the right femoral vein. All patients remained on their medications and gave a written informed consent. Pressure and cardiac output measurements were obtained both at baseline and in 23 patients after volume loading with leg elevation. In 20 clinically stable patients, rapid intravenous infusion of × 500 ml
Results

Patient characteristics and echocardiographic findings

Two female patients in New York Heart Association functional class IV with near normal left ventricular systolic function exhibited severe right ventricular dysfunction and dilatation due to pre-capillary pulmonary hypertension (pulmonary artery diastolic-to-mean capillary wedge pressure difference: 18 mmHg and 15 mmHg; pulmonary vascular resistance: 493 dynes.s.cm⁻⁵ and 167 dynes.s.cm⁻⁵, respectively). These patients with cor pulmonale and one other patient with constrictive pericarditis were excluded from subsequent analysis. The remaining 26 patients with heart failure had symptom duration of at least 1 month (mean ± 6 months), they tended to have higher ferritin values and were more likely to suffer from endocrinological disturbances and to be on non-optimal chelation therapy in comparison with control thalassaemic patients (Table 1). In fact, 18 (69%) patients with heart failure reported insufficient use of deferoxamine, while the youngest patient in our series had never undergone chelation therapy. Smoking (38.5% vs 40.2%) and heavy alcohol consumption (7.1% vs 6.9%) were equally prevalent between the patient and control thalassaemic group (P=ns). Liver biopsy, performed in 17 patients, revealed severe, grade III or IV organ haemosiderosis and cirrhosis in 10 (70%) and eight (47%) patients, respectively. Myopericarditis was evident in one patient and was suspected in another. Chamber enlargement, reduced left ventricular contractility and higher left ventricular mass, indicating advanced cardiac disease, were noted in the heart failure group along with higher early-to-late inflow velocity ratio and shorter deceleration time of early inflow across the atrioventricular valves (Table 2). The global right ventricular systolic function was estimated to be depressed in 21 patients (81%) but not in the control thalassaemic group (P<0.001). Mitral and tricuspid regurgitation were severe in 4 and 11 patients, respectively, with a respective average severity score of 1.85 ± 0.7 and 2.45 ± 1 (P<0.05). No patient in the control thalassaemic group had severe insufficiency across the atrioventricular valves.

Right heart catheterization

As expected, pressures were higher and cardiac output was lower in the heart failure group, although pulmonary artery and pulmonary capillary wedge pressures and vascular resistance were at best only modestly elevated (Table 3). Specifically, pulmonary vascular resistance was ≤150 dynes.s.cm⁻³ in 21 patients (with values ≤105 dynes.s.cm⁻³ found in 11 patients) and between 156 and 258 dynes.s.cm⁻³ in the remaining five patients. These five patients demonstrated reduced biventricular systolic function and a pulmonary artery

First-pass radionuclide angiography

Within 3 days of cardiac catheterization, first-pass radionuclide ventriculography was performed with the patients in a stable clinical condition. A single crystal gamma camera (Helix, El Scint, Israel), equipped with a high sensitivity parallel-hole collimator was used. With the head of the camera placed at a 40° right anterior oblique projection, a rapid sequence of images (at a rate of 25 frames per second) were acquired for a total of 30 s, starting simultaneously with the bolus injection of 925 MBq of ⁹⁹ᵐTc-Diethylenetriaminepentaacetic acid (DTPA). The manufacturer’s computer software was used for the processing of images. Briefly, region of interest was manually drawn over a summed image of the right ventricle and a time-activity curve was created to select cardiac cycles appropriate for use in calculations. Subsequently, separate regions of interest over end diastole and end systole were automatically generated. The right ventricular ejection fraction was obtained by averaging multiple, usually three to six, cardiac cycles[15]. The intra- and inter-observer variability of the calculated right ventricular ejection fraction was 7.9 ± 6.8% and 8.4 ± 5.1%, respectively.

Statistical analysis

Results are presented as mean ± SD. The two-tailed unpaired or paired Student’s t-test was used for comparison of continuous variables. Dichotomous variables were examined by the chi-squared test. Correlations between measured parameters of interest were determined with linear regression analysis. Statistical significance was defined as P<0.05.
diastolic-to-mean capillary wedge pressure difference of <3 mmHg. After volume loading, a good correlation was found ($r=0.69$, $P<0.001$) between the increments in right atrial pressures ($\Delta=4.8 \pm 2.2$ mmHg) and pulmonary capillary wedge pressure ($\Delta=5.6 \pm 2.9$ mmHg) in the heart failure group only (Fig. 1), although cardiac output failed to increase ($-0.3 \pm 0.61$ l.min$^{-1}$, $P=ns$). In contrast, volume challenge resulted in higher cardiac output ($+0.81 \pm 1.11$ l.min$^{-1}$, $P=0.05$) and stroke volume in the control group. Eleven (42%) and 15 (58%) patients, respectively, fulfilled the strict and less strict haemodynamic criterion of right ventricular dysfunction. These 15 patients were in functional class III and IV, representing three-fourths of the severely symptomatic patient subgroup (15 out of 20 patients). In all 15 patients the right ventricular ejection fraction was ≤44%, i.e. below the lower 95% confidence limits of the normal population, and volume loading in 14 of them resulted in a non-significant decline of cardiac output.

First-pass radionuclide ventriculography

A markedly reduced right ventricular ejection fraction was measured in the patient group as compared with the control thalassaemic group (29 ± 9% vs 59 ± 6%, $P<0.0001$). In fact, only one patient with heart failure exceeded the lower 95% confidence limits of the control group. There was no correlation between mean pulmonary artery pressure and right ventricular ejection fraction in the heart failure group (Fig. 2). In one patient with progressive clinical deterioration who underwent the radionuclide study twice, a decrease of right ventricular ejection fraction from 40% to 21%, along with...
worsening of his left ventricular ejection fraction and normal pulmonary artery systolic pressure were noted.

Follow-up
All six patients in functional class II at initial presentation, are still alive and in a stable clinical condition after a mean follow-up of 47 ± 7 months. In two of them with left-sided heart failure, symptoms disappeared after intensified desferrioxamine use. This was accompanied by more than doubling of their left ventricular ejection fraction over 37 to 42 months. Repeated liver biopsy in one of them showed a decline in haemosiderosis from grade 4 to grade 3, reflecting the decline of ferritin values from 4206 to 1690 ng . ml⁻¹ over a 3-year period. She is now in functional class III and her left ventricular ejection fraction has again deteriorated to 25%.

Over 9 ± 7 months, among the 20 severely symptomatic patients, death occurred in 11 (73%) of 15 patients with and in three (60%) of five patients without haemodynamic right ventricular dysfunction. One of them, a 25-year-old male patient developed acute, predominantly right heart failure, while being on treatment with

Table 3 Right heart catheterization results in patients with β-thalassaemia major with and without congestive heart failure before volume loading*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient group (n=26)</th>
<th>Control thalassaemic group (n=39)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAP (mmHg)</td>
<td>15.5 ± 8</td>
<td>6.6 ± 2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PAPs (mmHg)</td>
<td>33 ± 8</td>
<td>26.2 ± 5</td>
<td>0.01</td>
</tr>
<tr>
<td>PAPd (mmHg)</td>
<td>20 ± 6</td>
<td>14.6 ± 4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>PAPm (mmHg)</td>
<td>25.6 ± 7</td>
<td>19.9 ± 4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CWP (mmHg)</td>
<td>19.3 ± 7</td>
<td>13.3 ± 3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RAP/CWPm</td>
<td>0.73 ± 0.3</td>
<td>0.48 ± 0.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardiac output (l . min⁻¹)</td>
<td>4.9 ± 2.1</td>
<td>9.4 ± 1.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke volume (ml)</td>
<td>56 ± 37</td>
<td>114 ± 27</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVR (dynes . s . cm⁻⁵)</td>
<td>114 ± 56</td>
<td>65 ± 30</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SVR (dynes . s . cm⁻⁵)</td>
<td>980 ± 503</td>
<td>613 ± 96</td>
<td>0.07</td>
</tr>
</tbody>
</table>

* = two patients with cor pulmonale and one patient with constrictive pericarditis were excluded from the patient group; RAP= mean right atrial pressure; PAPs=systolic pulmonary artery pressure; PAPd=diastolic pulmonary artery pressure; PAPm=mean pulmonary artery pressure; CWP=mean capillary wedge pressure; PVR=pulmonary vascular resistance; SVR=systemic vascular resistance.

Figure 1 Correlation between the rise in mean capillary wedge pressure (ΔCWP) and in mean right atrial pressure (ΔRAP) after volume loading in 23 out of 26 patients with β-thalassaemia major and congestive heart failure.
daunorubicin with a cumulative dose of 300 mg m⁻² body surface area for lymphoblastic lymphoma. One other patient succumbed to his last episode of recurrent myopericarditis, leading to progressive right heart failure with initially preserved left ventricular contractility. In five patients with lethal outcome, all on poor chelation therapy with very high ferritin values and without evidence of perimyocarditis, the clinical course and the deterioration of ventricular systolic function were fulminant (i.e. within 0.5 to 5 months).

Clinical and echocardiographic improvement after intensified chelation therapy was noted in four patients in functional class III and IV (three with right ventricular dysfunction), all without evidence of myopericarditis. Moreover, complete atrioventricular block and runs of non-sustained ventricular tachycardia developed each in two patients.

Pump failure was the cause of death in all but one patient. There was one sudden death (7% of all deaths) in a 22-year-old male patient with left heart failure of 6 months’ duration, severe symptoms and high ferritin values. Of note, intractable ventricular tachyarrhythmias were not found in any of our heart failure patients. In fact, with the exception of the highly prevalent atrial fibrillation and flutter, these patients exhibited a remarkable electrical stability throughout the terminal phase of their disease.

**Discussion**

**Major findings**

In the present study, we found that the majority of patients with β-thalassaemia major and heart failure exhibited severe right ventricular dysfunction, independent of pulmonary artery pressures. The disproportional rise of right ventricular filling pressure, expressed in the right atrial-to-pulmonary capillary wedge pressure ratio, the not so severe elevation of pulmonary artery pressures and the slight decline of cardiac output after volume challenge, all imply severe right chamber involvement with inability to generate force and exhausted pre-load reserve (Fig. 3). This is underscored by the relative left ventricular underfilling, as expressed by the only modest increase in the pulmonary capillary wedge pressure, and by the more severe tricuspid than mitral regurgitation, potentially leading to overestimation of the right ventricular rather than the left ventricular ejection fraction. In addition, and contrary to prior beliefs, pulmonary vascular resistance was only mildly elevated, even in patients in the worst functional classes, ranging within the limits of healthy subjects without anaemia[16]. Pre-capillary pulmonary hypertension was found in only 7% of the screened population of consecutive thalassaemic patients presenting with heart failure.

**Previous studies**

In a previous study in paediatric patients with β-thalassaemia major studied with biventricular radionuclide angiography, profound right ventricular dysfunction in association with normal left ventricular systolic function was reported[9]. However, in this and another report showing more prevalent right ventricular than left ventricular systolic dysfunction[20], the patient groups were both inhomogenous in terms of clinical presentation (congestive heart failure was evident in
Figure 3  Echocardiographic and haemodynamic findings in a 22-year-old female patient with β-thalassemia major and congestive heart failure in New York Heart Association IV functional class who was not on optimal therapy with desferrioxamine. Two-dimensional end-diastolic echocardiographic images depict in (a) a D-shaped left ventricle at end-diastole, indicating high right ventricular filling pressures due to volume overload, and in (b) predominant right ventricular dilatation in the 4-chamber view. Doppler echocardiography shows a restrictive filling pattern across the tricuspid valve with a short deceleration time and high E/A inflow ratio (c) as well as in the superior vena cava with exclusively diastolic forward flow (d) and, in addition, a dagger-shaped, low-velocity, dense tricuspid regurgitation signal indicating high right atrial pressure and severe valve insufficiency (e). Simultaneous ventricular pressure tracings demonstrate elevation and equalization of end-diastolic pressures within 5 mmHg (right ventricle: 16 mmHg; left ventricular: 20 mmHg) (f). Note the low right ventricular systolic pressure. LV=left ventricle; RV=right ventricle; E=early tricuspid inflow; A=late tricuspid inflow; D=diastolic superior vena cava forward flow.
one-third to one-half of the patients) and did not undergo haemodynamic investigation\(^{16-17}\). In a recent study, a high incidence of pulmonary hypertension was found echocardiographically in a paediatric population\(^{17}\). Haemodynamic data were only recently provided in a small number of selected, non-consecutive patients with β-thalassaemia intermedia (i.e. with less severe phenotype), showing pre-capillary pulmonary hypertension in all patients\(^{19}\). Our findings are more consistent with the restrictive haemodynamic filling pattern described in a patient with haemochromatosis four decades ago\(^{11}\).

**Haemodynamic profile of right ventricular dysfunction**

The majority of patients with β-thalassaemia major and heart failure represent a unique group with a distinct haemodynamic profile. This haemodynamic profile resembles that of right ventricular infarction\(^{14,18}\) or that of subacute tricuspid insufficiency\(^{19}\), but these conditions are either acute or subacute, and there has been no prior report of a right ventricular pattern in the chronic state, such as the one herein observed in β-thalassaemia major patients. Furthermore, constrictive pericarditis or restrictive cardiomyopathy, which classically demonstrate a characteristic haemodynamic profile similar to the profile of our patient cohort, are associated with non-dilated ventricles, usually normal ventricular systolic function and higher pulmonary artery pressures\(^{19,20}\). Our catheterization data differ from those of heart failure studies, in which pulmonary artery and capillary pressures are at least 50% higher and the right-atrial-to-pulmonary capillary wedge pressure ratio at least one-third lower than our values\(^{21}\). Equalization of ventricular filling pressures within 5 mmHg in the majority of our patients with severe disease and their parallel increase after volume loading suggest severe pericardial constraint and ventricular interaction\(^{14,18,19}\), which was recently found to operate not only in acute but also in chronic heart failure\(^{22-24}\). The pathophysiologically more severe right ventricular involvement, possibly in association with faster functional derangement as compared with the left ventricle, may explain these findings\(^{14,18,22-24}\).

**Echocardiography and heart failure in β-thalassaemia major**

The Doppler echocardiographic filling characteristics in our heart failure patients indicate biventricular restrictive physiology\(^{25}\), a known independent risk factor for poor prognosis\(^{14,26,27}\). The disparate venous flow and isovolumic relaxation findings on either side of the heart probably reflect a differential behaviour of the two ventricles, the different regurgitation severity across the atrioventricular valves and/or ventricular interdependence\(^{28}\). Our data are at variance with a previous study in a small number of similar patients, showing no evidence of a restrictive transmitral inflow pattern\(^{29}\).

**Right ventricle and prognosis in β-thalassaemia major**

Right ventricular involvement in β-thalassaemia major is not surprising. According to necropsy studies, both ventricles are equally affected with hypertrophy and myocyte disruption, and focal necrosis is a common finding\(^{30,31}\). The thin-walled right ventricle may be more prone to earlier and rapid dysfunction, and right heart failure may be early and predominant or evolve after the onset of left heart failure. Similar to other cardiac diseases\(^{32,33}\) and as it has been experimentally shown, further deterioration of right ventricular performance can influence left ventricular function and vice versa, mediated by pericardial constraint and ventricular interaction\(^{34}\) in a volume and neurohumoural overload state such as in anaeamia\(^{19}\).

Regarding prognosis, mortality was high irrespective of the presence of haemodynamic right ventricular dysfunction; however, in 23% of patients, we also found evidence of clinical and echocardiographic improvement. In a preliminary observation\(^{25}\), prognosis in thalassaemic patients with predominant right heart failure seems more favourable than previously appreciated, thus contrasting previous studies on various right ventricular disease states\(^{35,36}\). Recently, the independent prognostic significance of pulmonary artery pressure and right ventricular ejection fraction in patients with heart failure has been demonstrated; however, reduced right ventricular ejection fraction coupled with normal pulmonary artery pressure, did not carry an additional risk\(^{38}\). Moreover, and in contrast to our results, a very low right-atrial-to-pulmonary capillary wedge pressure ratio of 0·16 was found in this subgroup of patients, 53% of whom were in functional class III or IV\(^{38}\).

Of note, the fulminant course in five patients with very high serum ferritin values suggests that very high cardiac iron burden may rapidly and irreversibly destabilize myocardial performance. Furthermore, anthracyclines, thought to exert an iron-mediated cardiotoxicity\(^{25}\), may disproportionaly increase cardiac risk in thalassaemic patients with known more-than-average incidence of malignancies\(^{33}\).

**Limitations**

Assessment of adherence to chelation therapy may have been imprecise due to its subjective nature. However, we felt confident in categorizing these patients according to desferioxamine use, since in most instances patients and/or their family members could provide reliable information in this regard due to their regular, year-long
In the last decade to 2895 Institution, average ferritin levels have dropped by 14% [10]. Ferritin values in our control thalassaemic group were obtained from the 1993—1997 time period. Among patients with β-thalassaemia major and without cardiac disease at our Institution, average ferritin levels have dropped by 14% in the last decade to 2895 ± 2573 ng ml−1 (Dr Th. Alexandrides, personal communication). Thus, more updated values in our control thalassaemic group would resulted in a greater divergence of serum ferritin levels between our study groups.

Doppler echocardiography permits only a global and indirect assessment of ventricular diastolic function, since it is affected, among other factors, by loading conditions. In addition, grading of valvular regurgitation by colour flow mapping is subjective, at best semiquantitative and may have led to erroneous information regarding the disparate severity of mitral and tricuspid insufficiency found in the current study.

Myopericarditis, a previously reported cause of left-heart failure in thalassaemia with variable course [11], was not investigated with endomyocardial biopsy in our patients, although it was clinically evident or suspected in two of them. Compared with the patients of that previous study [12], our patient population was older and more heterogenous. Although immunogenetic profile and myopericarditis seem to be associated with left heart failure [13–16], the iron-mediated generation of toxic reactive oxygen radicals at the molecular level [17], recent findings in the ultrastructural cardiac pathology in patients with β-thalassaemia major and heart failure [18,19], and the clinical evidence of improved prognosis conferred by chelation therapy [4,6,22] all imply a key role of iron in inducing cardiac damage. An alternative scenario might be postulated, with thalassaemic cardiomyopathy being a prerequisite for secondary myopericarditis, in analogy with arrhythmogenic right ventricular dysplasia cardiomyopathy [23].

Conclusions

We found that patients with β-thalassaemia major and congestive heart failure are usually on non-optimal chelation therapy and exhibit a distinct haemodynamic profile indicating severe right ventricular cardiomyopathy. Cor pulmonale seems to occur scarcely and it is only the exception in these patients.

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