Relation of myocardial T2* to right ventricular function in thalassaemia major

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Aims
Myocardial T2* cardiovascular magnetic resonance (CMR) provides a rapid and reproducible measure of cardiac iron loading and is being increasingly used worldwide for monitoring of transfusion-dependent thalassaemia patients. Although myocardial siderosis (T2* >20 ms) is associated with impaired left ventricular (LV) function, little is known of its relation with right ventricular (RV) function. The aim of this study was to investigate the relationship between cardiac T2* and RV function.

Methods and results
A retrospective analysis of 319 patients with beta-thalassaemia major presenting for their first CMR scan was performed (45.1% male, mean age 25.6 years). In patients with normal myocardial T2* (<20 ms), the RV ejection fraction (EF) was within the normal range in 98% of patients. When myocardial T2* was <20 ms, there was a progressive and significant decline in RV EF. There was a linear relationship between RV and LV EF.

Conclusion
Myocardial iron deposition is strongly associated with RV dysfunction, which mirrors the decrease in LV function seen with worsening cardiac iron loading. Right ventricular dysfunction may play a significant role in heart failure associated with myocardial siderosis.

Keywords
Iron overload • Right ventricle • Heart failure

Introduction
For patients with beta-thalassaemia major, heart failure due to iron-overload cardiomyopathy is the main cause of mortality. In developed countries until recently,1 it has accounted for up to 71% of all deaths, with up to 50% of these patients dying before 35 years of age, despite iron-chelating therapy.2,3 This form of cardiomyopathy can be reversible if detected early and appropriately treated, but once heart failure develops, prognosis is poor. Conventional techniques to assess iron in the myocardium have either proven to be invasive or unreliable, and frequently the diagnosis is delayed due to the unpredictable nature of cardiac iron loading and the late development of symptoms, which usually only become apparent after significant iron deposition has occurred.

Cardiovascular magnetic resonance (CMR) has emerged as a useful non-invasive tool for evaluating the amount of iron in the heart. The technique relies on the measurement of T2* relaxation from gradient-echo sequences. When the storage capacity of ferritin is exceeded, iron is deposited in the myocardium as particulate haemosiderin, which is a form of ferrithedrite (hydrated iron oxide). This disrupts the local magnetic field homogeneity causing reduced T2* values in inverse relation to iron concentration. T2* CMR is an ideal technique for non-invasive measurement of iron concentration, because the acquisition for the validated single slice method requires only a single breath-hold and has good reproducibility making it valuable for serial monitoring over time. Calibration of the T2* technique has been reported in humans.4–6 It has been shown that lower myocardial T2* values are associated with an increased likelihood of left ventricular (LV) dysfunction,7 whereas an improvement in myocardial T2* results in improvement in LV ejection fraction (EF).8,9 These findings have been confirmed in observational, prospective, and randomized controlled studies of iron chelation in thalassaemia patients.8–12 However,
the relation between myocardial iron loading and right ventricular (RV) function has not been fully addressed. Right ventricular EF is an important predictor of outcome in other forms of cardiomyopathy, which is both independent of and incremental to LV EF.13 Accordingly, the effects of myocardial iron loading on RV function may be important in thalassaemia patients. As CMR is considered to be the most accurate and reproducible technique for assessing RV volumes and EF,14,15 Cardiovascular magnetic resonance provides an ideal opportunity to correlate myocardial iron loading with RV function. Therefore, the aim of this study was to evaluate the relationship between myocardial T2* and RV EF in patients with thalassaemia major.

Methods

Study population

We analysed a database of 323 consecutive patients with beta-thalassaemia major who were referred for their first myocardial T2* scan from 21 UK haematology centres. All the patients included in this analysis were treated with a single iron chelation agent (deferoxamine) at presentation. They had all received iron chelation therapy since the mid-to-late 1970s or from an early age if born after this. Any patient with suspected pulmonary hypertension (PHT) (defined as tricuspid regurgitant jet velocity of >3.0 m/s on transthoracic echocardiogram) or any other known or potential cause of RV abnormality was excluded (e.g. congenital heart disease, valve disease, lung disease).16 Four patients were excluded from the final analysis due to cardiac or vascular anomalies (one aortic stenosis, one subaortic shelf, one pulmonary artery stenosis, and one repaired tetralogy of Fallot). The residual cohort consisted therefore of 319 patients, (144 males and 175 females), with a mean age of 26.5 ± 8.9 years (Table 1). At the time of their first CMR scan, 21 of the patients were taking medication for LV dysfunction or heart failure (diuretics, beta-blockers, or angiotensin converting enzyme inhibitors). The data collection and analysis associated with this study were approved by Trent NHS Research Ethics Committee.

Magnetic resonance

Patients were scanned with a 1.5 T Sonata scanner (Siemens Medical Systems, Erlangen, Germany). Each scan included the measurement of heart T2* (mid-septum) together with LV and RV volumes, EF, and mass using previously published techniques.17–19 T2* measured in the mid-ventricular septum is a reliable estimation of cardiac iron loading.5,20,21 Scan duration was ~15–20 min. For the measurement of myocardial T2*, a single short-axis mid-ventricular slice was acquired using a single-breath-hold ECG-gated multi-echo technique. This T2* sequence generated a series of eight images with a range of echo times (TE = 2.54–17.9 ms).

Cardiovascular magnetic resonance analysis

For T2* analysis, a full-thickness region of interest was defined in the interventricular septum (routinely chosen to avoid T2* artefacts from the cardiac veins, liver, and lungs). Myocardial T2* decay was calculated from this region using semi-automated analysis (Thalassaemia tools, Cardiovascular Imaging Solutions, London, UK). Signal intensity was plotted against echo time for each image and T2* was calculated from the resulting exponential decay curve. To allow for background noise, a truncation method was used as previously described.22 The normal range for myocardial T2* has been previously published from a series of healthy volunteers (the median normal value is 40 ms with a lower cut-off of normality of 20 ms).7 This value of 20 ms is widely accepted in clinical practice and was therefore chosen to define the lower limit of the normal range in this study.

Right ventricular and LV volumes were determined from steady-state free precession cines, with contiguous short-axis slices from base to apex as previously described (7 mm slice thickness with 3 mm gap).18,19 Ventricular volumes and EF were analysed with CMRtools (Cardiovascular Imaging Solutions). Three main steps for volume analysis were performed. First, both RV and LV endocardial and epicardial borders were delineated in all phases of the cardiac cycle in the short-axis slices. Then, valve plane tracking of the tricuspid and mitral valves was used to correct for alteration in volume due to descent of the AV ring towards the apex during systole. Finally, blood pool thresholding was used to delineate the papillary muscles and RV trabeculations (which were excluded from ventricular volume measurements). Left ventricular and RV volumes were indexed to body surface area.18,19 The normal ranges for LV and RV volumes and function were taken from previously published data with the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographics and summary of cardiovascular magnetic resonance parameters</th>
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<tbody>
<tr>
<td>Patient demographics</td>
<td></td>
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<tr>
<td>Total number of patients</td>
<td>319 (144 male, 175 female)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>26.5 ± 8.9</td>
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<tr>
<td>Height (cm)</td>
<td>157 ± 12.8</td>
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<tr>
<td>Weight (kg)</td>
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<td>Body surface area (m²)</td>
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<td>T2* (geometric mean ± CV%)</td>
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<td>Cardiac T2* (ms)</td>
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<td>Liver T2* (ms)</td>
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<td>CMR parameters for all patients</td>
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<tr>
<td>RV ejection fraction (%)</td>
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<td>LV ejection fraction (%)</td>
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<tr>
<td>Annual red cell consumption (mL/kg/year)</td>
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<tr>
<td>ACE-inhibitors</td>
<td>18 (5.6%)</td>
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<tr>
<td>Beta-blockers</td>
<td>7 (2.2%)</td>
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</table>

Data are presented as mean ± SD or number (%), unless otherwise stated.
lower limit of normal for RV EF in healthy subjects being 54% and the lower limit of normal for LV EF in non-iron-overloaded thalassaemia patients being 59%.19,23

**Statistical analysis**

All parameters are presented as mean ± standard deviation, except T2* which is shown as geometric mean (antilog of the mean of the log data) and percent coefficient of variation (CV—equivalent to the variance of the mean in log scale) following log transformation of data to normalize the data distribution. Spearman’s rank test was used to assess the correlation between myocardial T2*, ferritin, RV volumes, and EF. Analysis of variance was used to assess differences across different ranges of myocardial T2*. Two-sided statistical significance was set at $P < 0.05$. All statistical analyses were performed using Stata 10.1 software (StataCorp, TX, USA).

**Results**

In thalassaemia patients with a normal myocardial T2* (>20 ms), RV EF was $65.0 ± 6.1\%$ and was distributed within the normal range of expected values in 98% of patients. In patients with myocardial siderosis (T2* <20 ms), there was a progressive and significant decline in RV EF ($r = 0.43, P < 0.001$; Figure 1) and an increase in the RV end-systolic volume ($r = −0.33, P < 0.001$; Figure 2). In contrast to EF and end-systolic volume index, there was no significant correlation of either RV end-diastolic volume index or RV mass index with T2*. Of the 165 patients with myocardial siderosis (T2* <20 ms), 23 (14%) were found to have an RV EF below the lower limit of the normal range. Of the patients with impaired RV EF, 82.6% also had an impaired LV EF. There were four patients with T2* <20 ms who had impaired RV EF but a normal LV EF. None of the patients had documented PHT. The mean RV EF for these patients was $49 ± 1.6\%$ and the mean LV EF was towards the lower limit of the normal range ($62 ± 3.8\%$). Both RV mass and the pulmonary artery diameter were normal (mean RV mass index $28 ± 4.6$ g/m², mean PA diameter $18 ± 3.7$ mm). No septal flattening or tricuspid valve regurgitation was seen on cine images. All four patients had severe myocardial iron loading with T2* ranging from 5.0 to 9.2 ms (mean T2* 7.0 ± 2.1 ms). All were on the same transfusion regime (2 U of packed red cells every 4 weeks, mean annual red cell consumption $129$ mL/kg/year), none had undergone previous splenectomy, and none had symptoms of heart failure. Apart from hypogonadotropic hypogonadism in one patient and osteoporosis in another, there were no other complications. Serum ferritin ranged from 723 to $4673$ µg/dL (mean ferritin $1772 ± 1937$ µg/dL).

LV EF was $69.5 ± 5.2\%$ and was within normal limits in 99% of thalassaemia patients with a normal T2*. Below 20 ms, LV EF showed a significant decline with lower T2* values ($r = 0.40, P < 0.001$; Figure 3). Of patients with myocardial siderosis (T2* <20 ms) 47 (28.4%) had reduced LV EF, of which, 19 (40.4%) also had a low RV EF. Linear regression between RV EF and LV EF showed a significant relation ($r = 0.69, P < 0.001$; Figure 4). A comparison of two representative patients is shown in Figure 5.
one with severe myocardial iron loading and poor biventricular function and the other with no evidence of myocardial iron loading and normal ventricular function.

A summary of the ventricular and haematological parameters in three different $T2^*$ ranges ($<10$, $10–20$, and $>20$ ms) is shown in Table 2. Differences between groups were found for RV and LV EF, RV end-systolic volume index, and serum ferritin. No difference was found between groups for RV end-diastolic volume index, RV mass index, pre-transfusion haemoglobin, yearly transfusion, or total units transfused. No correlation was found between any of the haematological parameters (including ferritin) and RV EF. There was a weak negative correlation between ferritin and myocardial $T2^*$ when the whole patient cohort was considered ($r = -0.22, P < 0.001$).

**Discussion**

Heart failure due to iron-overload cardiomyopathy is the dominant cause of mortality in patients with thalassaemia major. Iron overload in thalassaemia major occurs due to a combination of repeated blood transfusions, with each unit of blood containing 200–250 mg of elemental iron, and excessive gastrointestinal absorption. Excess body iron is stored in ferritin and its degradation product haemosiderin. In the heart, this results in impaired function of the mitochondrial respiratory chain, ventricular dysfunction, and the potential for progression to heart failure. In this study, we have evaluated the relationship between myocardial iron loading and RV function. Our data show mirror effects on both LV and RV volumes and EF. We found a normal RV EF in 98% of patients with normal myocardial $T2^*$ values, but progressive RV enlargement and dysfunction with increasing myocardial siderosis. The RV and LV EF showed significant correlation.

Aside from myocardial iron loading, we did not identify any clinical factors that could explain the observed effects on ventricular function.

![Figure 4](image)

**Figure 4** The relationship between right ventricular ejection fraction (RV EF) and left ventricular ejection fraction (LV EF).

![Figure 5](image)

**Figure 5** Comparison of two patients with different iron loading profiles and ventricular function. The top row of images (A–C) shows a patient with raised right and left ventricular volumes in end-diastole (A) and end-systole (B), poor biventricular ejection fraction (RV EF = 25% and LV EF = 22%) and severe iron overload. Myocardial $T2^*$ is 5.4 ms (C). The lower row shows end-diastolic (D) and end-systolic (E) images from a patient with normal biventricular ejection fraction (RV EF = 61% and LV EF = 66%) and no myocardial iron loading [$T2^*$ is 29.8 ms (F)]. The dotted line in each case denotes the level of the atrioventricular junction at end-diastole to illustrate the long-axis contraction of the heart in systole. TE, echo time.
In the original validation study by Anderson et al., myocardial T2* values in the normal range were associated with normal LV EF values, but when myocardial T2* fell below 20 ms, a progressive deterioration in LV EF was seen,7,9,10,12 and this finding has been reproduced once again in this large cohort. There is limited data examining the relation between cardiac T2* and RV function.25,26 The importance of the right ventricle as an aggravating factor in heart disease and a predictor of adverse cardiac outcomes has often been overlooked in the past. Studies have indicated the importance of RV function in conditions such as congenital heart disease,27–29 dilated cardiomyopathy,13,30 chronic systolic dysfunction,31 and ischaemic heart failure.32–34 In these studies, RV dysfunction was a strong predictor of mortality and outcomes in heart failure, irrespective of aetiology, and independent of the LV function. New York Heart Association (NYHA) functional class of heart failure, or peak oxygen consumption. This suggests that RV function may be a significant contributor to the clinical manifestation of heart failure seen in severe myocardial siderosis. The finding of a close correlation between LV and RV function suggests that there is diffuse myocardial toxicity due to excess iron and that this plays an important role in both LV and RV dysfunction in this type of cardiomyopathy. This pattern is typical of non-ischaemic cardiomyopathy, where RV dysfunction is the common and more closely parallels LV dysfunction in contrast with the predominant LV impairment seen in ischaemic heart failure.

The function of the right ventricle may be affected by PHT which can occur as a complication in patients with thalassaemia.25 Initial reports suggested that increased pulmonary systolic pressure was a common finding in thalassaemia major patients but some of these early results were based on a cohort of patients who were under-transfused and poorly chelated.36,37 Subsequent studies in well-treated Italian and Greek patients have not confirmed these findings, with PHT being practically absent in thalassaemia major patients with a high standard of care.38,39 In contrast, PHT is a prominent finding in patients with thalassaemia intermedia.40 While beta-thalassaemia major is a severe anaemia which presents within the first years of life and requires lifelong transfusions to prolong survival, thalassaemia intermedia is milder with a later clinical onset. In one series of 110 thalassaemia intermedia patients, PHT was found in nearly 60%, causing RV failure in ~5% although all patients had preserved LV systolic function.41 Despite this, a recent study has shown that patients with thalassaemia intermedia have a higher RV EF than those with TM.42 The current study included only thalassaemia major patients, all of whom had been transfused from an early age and none had evidence of PHT on transthoracic echocardiography. In the small number of patients where there was isolated RV impairment, all had severe myocardial iron loading with T2* values below 10 ms, and LV EF was at the lower end of the normal range. None of the patients had known PHT and there were no CMR features to suggest that the RV impairment was related to raised pulmonary artery pressure. It is likely that the RV impairment in these four cases is a precursor to LV impairment secondary to severe iron loading, since T2* values below 10 ms are a strong predictor of the development of heart failure.43

There is limited previous data on RV function in myocardial siderosis. Pepe et al.25 compared patients taking different iron-chelating agents and found no correlation between myocardial T2* and RV EF. This may be explained by the small study population and the small proportion of patients with significant myocardial iron loading. In a study of 26 patients with symptomatic heart failure (NYHA class III–IV), LV EF (measured by single plane area–length echocardiography) was compared with RV EF (measured by first-pass radionuclide angiography).26 Our findings not only confirm that RV and LV function are often correlated but also provide evidence that both RV and LV impairment are strongly related to myocardial iron overload. In addition, we have used CMR which is considered to be the gold standard for the assessment of both RV and LV volumes and function.14,15

**Limitations**

The data were analysed retrospectively from a prospectively accumulated database. Right ventricular EF is highly dependent on loading conditions and may not adequately reflect RV contractility; however, it is the most widely available method for assessing RV function. These T2* values only apply at a field strength of 1.5 T, as determined by transthoracic echocardiography.
and the relaxation parameters will be different at higher field strengths such as 3T which is becoming more widely available for clinical scanning. We measured myocardial T2* in the interventricular septum, using this value to give an assessment of global myocardial iron loading. Although this is an indirect measurement of RV iron, direct measurement of T2* in the RV free wall is not robust as the myocardium is very thin, close to the chest wall, and susceptible to artefact. Patients underwent regular cardiology assessment which included transthoracic echocardiography. We excluded patients with PHT (defined as tricuspid regurgitant jet velocity of >3.0 m/s on transthoracic echocardiography), but echocardiograms were not performed at the time of the CMR studies. We did not find any significant increase in RV mass index in this cohort (compared with normal reference values for healthy subjects) and there was no significant difference in RV mass between those patients with T2* <20 ms and those with a T2* of >20 ms. In this study, we did not assess biomarkers (such as brain natriuretic peptide or BNP) or the presence of late enhancement following gadolinium injection, both of which could give further insight into the mechanism of both RV and LV dysfunction in these patients.

Conclusions

Increasing myocardial siderosis as assessed by T2* CMR is associated with RV dysfunction, and this may be a significant contributor to heart failure in thalassaemia major. Further studies are required to determine the relative importance of RV function compared with LV function, and to establish whether novel treatment strategies targeted to the RV may prove useful.

Authors’ contribution

F.A. and J.P.C. both participated equally in the study design, data collection, and drafting of the manuscript; M.D. collected data and drafted the manuscript; P.K. collected the data; W.B. performed the statistical analysis; D.J.P. conceived the study, participated in its design and is responsible for the final manuscript.

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Conflict of interest: D.J.P. is a consultant to Novartis and ApoPharma, and a director of Cardiovascular Imaging Solutions. D.J.P. has research support and speakers honoraria from Siemens, Amgen, and ApoPharma. J.P.C. has received speaker’s honoraria has received research support and speakers honoraria from Siemens, ApoPharma, and a director of Cardiovascular Imaging Solutions. D.J.P. Conflict of interest: D.J.P. conceived the study, participated in its design and is responsible for the final manuscript.

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