



Multi-center validation of the transferability of the magnetic resonance T2* technique for the quantification of tissue iron

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The transferability of the T2* technique for measurement of tissue iron between magnetic resonance (MR) scanners is unknown. Heart and liver multi-breath-hold T2* sequences were installed on MR scanners at six different sites. T2* was assessed locally in five or more patients with thalassemia major (n=39), and subjects were re-scanned at the standardization center in London. Inter-center reproducibility of T2* in heart and liver was 5.0% and 7.1%, with mean absolute differences in T2* of 1.3ms and 0.45ms, respectively. The MR multi-breath-hold T2* technique for tissue iron quantification is transferable between scanners with good reproducibility.

Key words: T2*, magnetic resonance, thalassemia, reproducibility, heart

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The main cause of mortality in thalassemia major is heart failure secondary to myocardial iron overload.^{1,2} Symptomatic heart failure occurs late in the disease process and is very hazardous.^{3,4} Indirect markers of current cardiac iron loading, namely single measurements of serum ferritin and biopsy-determined liver iron concentration, are inadequate for identifying myocardial iron deposition in the chronically transfused patient.^{5,6} Hence there is a need for a reliable test to allow identification of pre-symptomatic cardiomyopathy, but conventional assessment of ventricular function with echocardiography and cardiac nuclear techniques have not proven adequate.^{7,8} Magnetic resonance (MR) can exploit the paramagnetic properties of tissue iron to provide direct, non-invasive iron assessments, and clinically this has been achieved by assessing the T2 and T2* relaxation parameters.⁶ In the heart, T2 MR assessment of myocardial iron is possible^{9,10} but in practice the gradient echo T2* technique is simpler and more robust, allowing rapid and reproducible quantification of myocardial and hepatic iron and therefore allows the pre-symptomatic detection of myocardial siderosis,¹¹⁻¹³ and assessment of chelation.¹⁴⁻¹⁶ The T2* technique has potential to become the gold standard in assessing myocardial iron, but is not yet widely available.¹⁷ For maximal healthcare impact, its transferability must be established between scanners of different manufacture and between sites, but only limited data on this are available.^{18,19} With support and funding from the Thalassemia International Federation, we initiated a validation study to establish this technique internationally.

Design and Methods

The standard center in London used a 1.5 Tesla Siemens Sonata (Erlangen, Germany) MR scanner. Six international sites were involved in the study and all major MR manufacturers were represented. Ethical approval was granted at the standard center and all sites involved. All patients gave written informed consent.

Study population and sites

All thalassemia major patients (n=39, mean age 30±6.8 years) had been regularly transfused since early childhood or since the introduction of deferoxamine, and were receiving regular iron chelation. They had a wide range of serum ferritin values (180-7050, median 1660 ug/L).

The following sites and scanners were involved in this study: *Philips Intera (Turin, Italy); Siemens Sonata and Siemens Avanto (Philadelphia, USA); GE Signa (Limassol, Cyprus); Philips Intera (Nicosia, Cyprus); GE Signa (Cagliari, Sardinia) and Philips Intera (Genova, Italy)*. The multi-breath-hold T2* sequence was installed on each scanner. Full sequence details and methods of T2* calculation have been previously detailed.^{11,18} In brief, for the heart a single mid-ventricular short axis slice was imaged at eight echo times (3.6 to 16ms). The TR between each radiofrequency pulse was 20 ms. Total scanning for liver and heart T2* assessment was completed within 10 minutes (16 breath-holds). For analysis, the signal intensity of a full-thickness region of the left ventricular septum,^{11,20} was measured for each echo time using Thalassemia-Tools (Cardiovascular

Imaging Solutions, London). Correction for positional changes between breath-holds was made to ensure regions of interest were within the myocardium. To derive T2*, a mono-exponential trend-line was fitted with an equation in the form $y=Ke^{-TE/T2^*}$ where K represents a constant, TE represents the echo time and y represents the image signal intensity. Analysis of heart and liver T2* can be completed within 2 minutes. In heavily iron-loaded tissues, signal decay occurs rapidly with noise dominating the signal at later echotimes.⁶ To minimize the potential for noise to cause over-estimation of T2* in heavily iron loaded tissues these later points are not used for curve fitting for very low values of T2*. For the measurement of liver T2*, a single trans-axial slice through the center of the liver was imaged at eight echo times (2.3 to 16ms). The TR was set to 200ms without cardiac gating. Signal intensity analysis was performed in the periphery of the liver away from the large central vessels. All analyses were performed by a single observer, with all scans assessed independently. Owing to inherent differences in scanner performance and software at the various sites, the sequence parameters (TE and TR) were not identical in all sites, but these variations were kept to a minimum, and would not be expected to affect the T2* estimation:

Cagliari- Heart (TE 4.5-14ms, TR 23ms);
Liver (not applicable)
Genova- Heart (TE 2.7-16.7ms, TR 24ms);
Liver (TE 2.3-18ms, TR 200ms)
Limassol- Heart (TE 2.6-16.7ms, TR 23ms);
Liver (TE 2.3-20ms, TR 200ms)
Nicosia- Heart (TE 3.6-16ms, TR 30ms);
Liver (TE 2.3-20ms, TR 200ms)
Philadelphia (Sonata)- Heart (TE 3.6-16ms, TR 20ms);
Liver (TE 2.3-16ms, TR 200ms)
Philadelphia (Avanto)- Heart (TE 2.6-17ms, TR 20ms);
Liver (TE 1.3-16ms, TR 200ms)
Turin- Heart (TE 3.4-16ms, TR 30ms);
Liver (TE 2.1-16ms, TR 200ms)

Five subjects were scanned (nine subjects at one site) for myocardial and liver T2* at each site. Local site inter-study reproducibility was assessed by repeating the scan within 1 hour. Inter-scanner (site to standard) reproducibility was assessed by repeating the scan within 1 month by flying the patients to the standard scanner in London.

Statistics

Reproducibility (both inter-scanner and inter-study) is expressed as the coefficient of variation (standard deviation of the differences between the two separate measurements, divided by their mean). Mean absolute differences in T2* between scans are also quoted as a measure of accuracy using the standard scanner results as *cor-*

Table 1. Summary of heart and liver T2* values at the different sites.

Site	Heart T2* (ms)			Liver T2* (ms)		
	Mean	SD	Range	Mean	SD	Range
Cagliari	11.0	3.8	7.0-18.7	Na	Na	Na
Genova	10.8	8.5	4.5-24.8	6.5	7.7	1.6-19.5
Limassol	15.7	10.8	8.0-34.3	1.2	0.2	1-1.48
Nicosia	21.9	18.7	5.7-51	6.1	6.4	1.4-16.1
Philadelphia 1	16.9	12.1	3.7-32.3	3.6	2.8	1.2-8.3
Philadelphia 2	26.8	10.1	13.6-39.7	4.9	3.2	2.0-9.8
Turin	11.5	12.4	3.6-33	2.5	1.9	1.0-5.6

SD: standard deviation; Na: not available.

rect. Summary data are displayed graphically using scatter plots with Spearman's rank correlation coefficient and Bland Altman plots.

Results and Discussion

Myocardial T2* ranged from severe iron loading to normal (3.6 to 51ms; mean 15.8 ±11.6ms), the lower limit of normal T2* in myocardium being 20ms.¹¹ There was good agreement between the standard center scanner and the local scanners at each site (Figure 1A). Overall inter-scanner reproducibility for myocardial T2* was 5.0%. The mean absolute difference in myocardial T2* between scanners was 1.3ms (7.1% mean difference). Local site inter-study reproducibility was 5.8% (Figure 2A). Liver T2* ranged from severe iron loading to normal (1.0 to 19.5 ms; mean 4.2 ±4.5ms), the lower limit of normal T2* in liver being 6.3ms. There was good agreement between the standard center and the peripheral scanner (Figure 1C). Overall inter-scanner reproducibility for liver T2* was 7.1%. The mean absolute difference in liver T2* between scanners was 0.5ms (10.2% mean difference). Local site inter-study reproducibility was 4.4% (Figure 2C).

This study shows that the T2* values in both heart and liver compare very well between 1.5 Tesla scanners in different locations and of different manufacturers. This demonstration of transferability suggests that there is real potential to disseminate the technique more widely. More recently a single breath-hold multi-echo T2* technique has been described. This was not investigated in this study because at the time the study was designed a significant proportion of scanners were not capable of supporting the single breath-hold sequence. The single breath-hold multi-echo technique has the advantage of being faster (single vs. many breath-holds) and permitting shorter echotimes.¹² In this study, the minimum achievable TE was particularly relevant in the case of severe hepatic iron loading in which an under-estimation of tissue iron can occur due to the rapid signal decay.¹⁷ As mentioned above, to minimize the

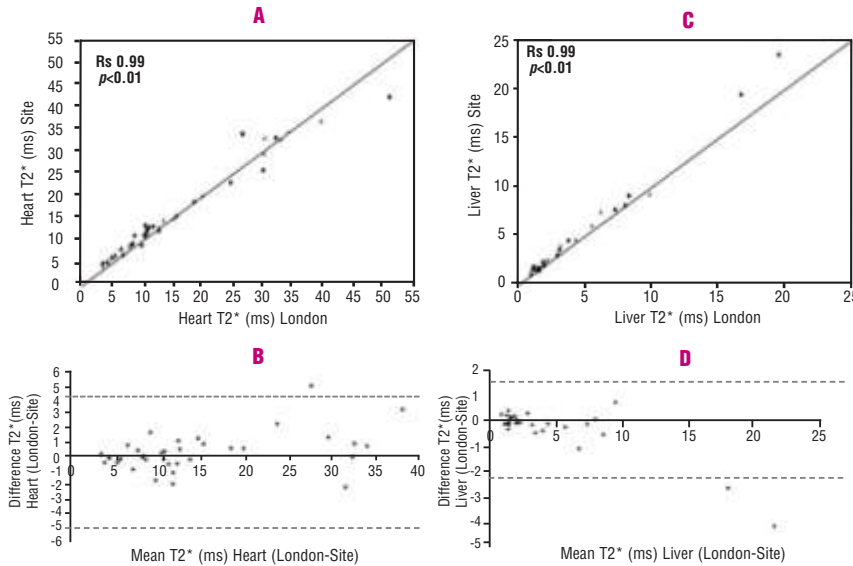
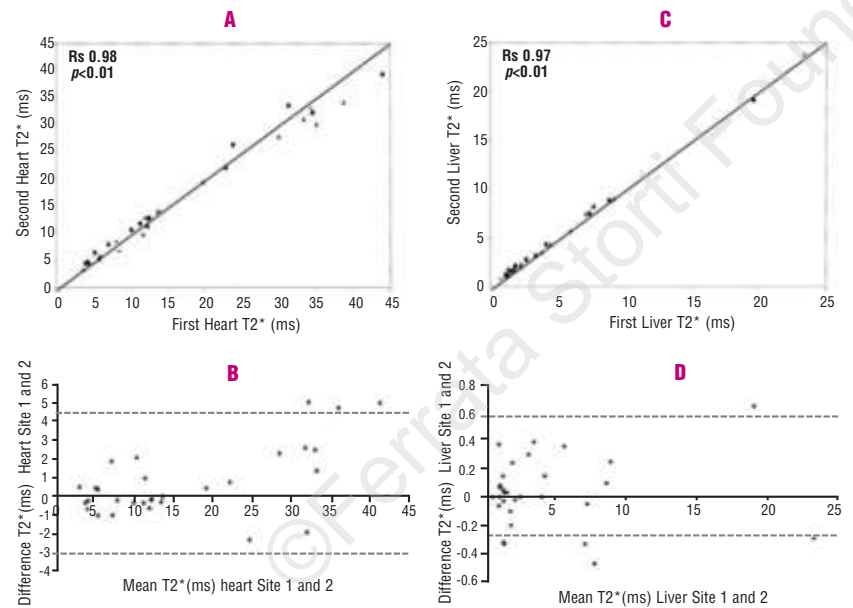


Figure 1. A. Myocardial T2* was assessed in 39 patients who were scanned locally and at the standard center in London. Overall, the inter-scanner reproducibility was 5.0%. The diagonal line shown is the line of identity. Each of the 7 scanners validated are represented by different symbols. B. Bland-Altman plot of the heart T2* values obtained between London and visited sites, with the 95% confidence intervals shown as a dotted line. C. Liver T2* was assessed in 30 subjects who were scanned locally and at the standard center in London. Overall, the inter-study reproducibility was 7.1%. D. Bland-Altman plot of the liver T2* values obtained between London and visited sites, with the 95% confidence intervals shown as a dotted line.



Key: ♦ Cagliari, ▲ Genova, — Limassol
• Nicosia, ■ Philadelphia I, ▲ Philadelphia 2
◆ Turin

Figure 2. A. Assessment of heart interstudy reproducibility at the sites (n=30). Subjects were scanned twice at the local site. The heart T2* reproducibility was 5.8%. The diagonal line shown is the line of identity. B. Bland-Altman plot of the liver T2* values (n=30) obtained between the two scans of the visited sites, with the 95% confidence intervals shown as a dotted line. C. Assessment of liver interstudy reproducibility at the sites (n=30). Subjects were scanned twice at the local site. The liver T2* reproducibility was 4.4%. The diagonal line shown is the line of identity. D. Bland-Altman plot of the liver T2* values obtained between the two scans of the visited sites, with the 95% confidence intervals shown as a dotted line.

potential for noise to cause over-estimation of T2* in heavily iron-loaded tissues, we routinely remove the later points of the decay curve caused by background noise. A valid alternative approach to dealing with this noise is to add a constant offset to the exponential curve.⁶ We have previously explored this latter approach in our unit, but our experience was that the T2* results so obtained were less robust than that obtained with our truncation approach, and created outlier results. There are complex technical reasons for this problem, and our established preference in clinical practice is to continue with the truncation approach. It should also be noted that in tissues with high T2* values (i.e. tissues with no iron loading) inaccuracies also increase.

One important advantage of the multi breath-hold sequence used in this study is that it can be run on scanners with only moderate gradient performance, ensuring that it can be run on scanners in most areas of the world where thalassemia is most prevalent and not only in those with advanced high-end performance. Although it was not possible to install identical sequences on all scanners, the variations in sequence parameters did not have significant effects.

To conclude, gradient-echo T2* MR provides a non-invasive means for assessing tissue iron which is accurate and reproducible and may be transferred between MR scanners in different centers from different manufacturers. Through the widespread application of this

technique it should be possible to improve management of tissue iron overload, and in particular aid the pre-symptomatic detection of myocardial siderosis, allowing earlier chelation intensification with its potential for reduced cardiac events.

MAT: performed research, collected data, analyzed data, and wrote the paper; TH: performed research, collected data; MAW: designed research; DNF: designed research; DJP: designed research, wrote the paper.

Thalassemia International Federation Heart T2 Investigators* were involved with data collection at the sites visited.*

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