

# A Single Breath-Hold Multiecho T2\* Cardiovascular Magnetic Resonance Technique for Diagnosis of Myocardial Iron Overload

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**Purpose:** To assess tissue iron concentrations by the use of a gradient echo T2\* multiecho technique.

**Materials and Methods:** We compared the results of measurements of heart T2\* from 32 patients using the established multiple breath-hold variable TR technique with a new multiecho sequence that acquires all images within a single breath-hold with constant TR.

**Results:** There was good agreement of myocardial T2\* values between both methods in the abnormal range of T2\* < 20 msec (mean difference 0.2msec, 95% CI -1.3 to 0.9 msec,  $r = 0.97$ ,  $P < 0.0001$ ). The coefficient of variability between the methods was 3.5%. The interstudy reproducibility using the multiecho sequence had a variability coefficient of 2.3% in the abnormal T2\* range and 5.8% over all T2\* values. There was good agreement between the techniques for the liver T2\* values.

**Conclusions:** The use of the single breath-hold, multiecho acquisition allowed reliable quantification of myocardial T2\*. The good reproducibility, speed, and T1 independence of this technique allows greater accuracy, faster patient throughput, and, therefore, reduced costs (which is important in developing countries where thalassemia is most prevalent).

**Key Words:** cardiomyopathy; thalassemia; magnetic resonance imaging; heart failure; diagnosis; anemia

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CARDIAC FAILURE DUE TO IRON OVERLOAD remains the most common cause of death in patients with thalassemia major in developed countries (1,2), with 60% of all patients dying of heart failure and 50% of patients with thalassaemia major dying before the age of 35 in the UK (3). However, iron-induced cardiomyopathy is both treatable and reversible if intensive chelation treatment is instituted in time (4–6). Attempts to measure myocardial iron loading using T2 have been reported but have not entered widespread use due to problems with artifacts and limited reproducibility (7). An alternative and reliable method to detect and evaluate the extent of cardiac iron deposition early, and before cardiac failure develops, has been described using T2\* measurements (8). This has been shown to have potential to guide chelation therapy (9). T2\* is an inherent property of any tissue or substrate which arises principally from local magnetic field irregularities that are increased by iron deposition. However, this method requires up to nine separate image acquisitions for the heart and liver, each of which require a breath-hold. This is quite time consuming, and can present problems in patients that are young, dyspneic, or claustrophobic. In the heart, it can also be difficult to assess the exact myocardial borders for each image, especially those with long echo times where there can be artifacts. As each image is acquired as a separate breath-hold, there are also differences in image registration. This can also introduce errors in T2\* measurements. The development of multiecho sequences that would allow all the images for the heart or liver to be acquired in a single breath-hold would significantly shorten scanning time, and may improve the reproducibility of the scan. Multiecho T2\* imaging has previously been used for the assessment of myocardial perfusion (10,11), but has not been previously applied to determine iron concentrations. The aim of this study was, therefore, to investigate the assessment of tissue iron levels using a single breath-hold T2\* multiecho sequence in comparison with the established multiple breath-hold sequence.

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## METHODS

### Study Population

A total of 32 patients with beta thalassemia major underwent MR scanning at the Royal Brompton Hospital Cardiovascular MR Unit. The patients included 16 males and the age range was 18 to 40 (mean 29.1) years. All patients had been regularly transfused since early childhood and had received chelation therapy since the mid-to-late 1970s. A broad range of compliance to chelation therapy was present, resulting in a wide range of tissue iron deposition. There were four diabetic patients. At the time of scanning, seven patients had cardiac symptoms (palpitations or atrial fibrillation causing symptoms). One patient was taking Amiodarone and two patients were taking beta blockers for arrhythmias. None of the patients were in decompensated heart failure at the time of scanning, but five patients had previous heart failure, for which three were continuing to take ACE inhibitors. In addition, 10 normal volunteers were scanned who had a mean age of  $49 \pm 26$  years. There were three males and seven females.

### Magnetic Resonance

Patients were first scanned using the multiple breath-hold method previously described by Anderson (8) as modified for a Siemens Sonata 1.5T scanner (Siemens Medical Solutions, Erlangen, Germany). For the measurement of myocardial  $T2^*$ , a single short axis mid-ventricular slice was acquired at nine separate echo times (5.6 – 18.0 msec). A spoiled gradient echo sequence was used, with a flip angle of  $35^\circ$ , a matrix of  $128 \times 256$  pixels, nine segments per view, a field of view of 35 cm, and a sampling bandwidth of 488 Hz per pixel. The repeat time (TR) between the nine radio-frequency pulses applied to each cardiac cycle varied with the echo time (TE) according to the equation  $TR = TE + 2.58$  msec. A delay time of 0 msec after the R wave trigger was chosen in order to obtain a high quality image when blood flow and myocardial wall motion artifacts are minimized. A homogeneous full-thickness region of interest was chosen in the left ventricular septum, encompassing both epicardial and endocardial regions. The signal intensity of this region was measured for each image using in-house designed software (CMRtools, © Imperial College, London), and this was then plotted against the echo time to form an exponential decay curve. To derive  $T2^*$ , an exponential trendline 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. The liver  $T2^*$  value was determined as follows: a single transaxial 10 mm slice through the center of the liver was scanned at a series of eight different echo times (2.3 – 20.0 msec). Each image was acquired during a breath-hold of approximately 20 seconds. A gradient-echo sequence was used with a TR of 200 msec with no cardiac gating, a flip angle of  $20^\circ$ , a matrix of  $96 \times 128$  pixels, a field of view of 35 cm, and a sampling bandwidth of 488 Hz per pixel. In the liver, a large

region of interest was chosen in a homogenous area of liver parenchyma without blood vessels. Analysis was then as described for the heart.

Patients were then scanned using the multiecho sequence. The mean time between scans was 20 minutes, with a range from 10 to 60 minutes. The multiecho sequence parameters were as follows: for the measurement of myocardial  $T2^*$ , a single short axis mid-ventricular slice was acquired at eight echo times (2.6 – 16.74 msec, which increased in 2.02 msec increments) in a single breath-hold. The even echoes were used to allow motion compensation. A gradient-echo sequence was used with a flip angle of  $35^\circ$ , a matrix of  $128 \times 256$  pixels, a field of view of 40 cm, and a sampling bandwidth of 810 Hz per pixel. The TR between the eight radio frequency pulses applied each cardiac cycle was 20 msec. As previously, a delay time of 0 msec was chosen. The analysis was the same as that detailed above.

The liver  $T2^*$  value was determined as follows: a single transaxial 10 mm slice through the center of the liver was scanned at a series of 20 different echo times (0.97 – 13.89 msec, which increased in 0.68 msec increments), using a multiecho gradient-echo sequence with a flip angle of  $20^\circ$ , a matrix of  $128 \times 128$  pixels, a field of view of 40 cm, and a sampling bandwidth of 1950 Hz per pixel. Both the even and odd echoes were used. The TR between two radio frequency pulses was 200 msec, with no cardiac gating. In the liver, a large region of interest was chosen in a homogenous area of liver parenchyma without blood vessels. Analysis was then as described for the heart multiecho. In both the liver and the heart, the same slice positions were used to compare the standard acquisition and the multiecho. Finally, a second scan was performed using the multiecho sequence in 20 patients, for both the heart and liver, after a period of up to one hour outside the scanner, to allow the assessment of interstudy reproducibility.

### Statistical Analysis

The variability between both methods was first compared using a Bland Altman Plot (12). In addition, for the variability between methods and interstudy reproducibility, the coefficient of variation was defined as the standard deviation of the differences between the two separate measurements, divided by their mean, and expressed as a percentage. Mean differences are also quoted. The analysis of variability and reproducibility was performed for the myocardial  $T2^*$  values in both the abnormal range ( $T2^* < 20$  msec), and in the normal range ( $T2^* > 20$  msec) (8). This was because the  $T2^*$  Cardiovascular Magnetic Resonance (CMR) acquisition sequences were optimized for low values (as would occur in patients at risk of heart failure) and there were a priori reasons, therefore, to suppose that the variability would be greater with higher  $T2^*$  values (patients with little or no iron loading). The range of echo times were chosen so that the most accurate measurements of  $T2^*$  would be expected in the range 5 – 20 msec for the heart and 2 – 20 msec for the liver. The measurement perfor-

mance in the abnormal range is of particular interest clinically. There was only one patient with a liver T2\* in the normal range and, therefore, liver figures are quoted for all patients combined. Figures are quoted as mean  $\pm$  1 SD.

## RESULTS

### Normal T2\* Values

The values for the T2\* in the normal subjects for the heart were: standard acquisition  $30.1 \pm 7.1$  msec, multiecho acquisition  $33.3 \pm 7.8$  msec. The lower limit of normal (mean  $-2$  SD) was 15.8 and 17.7 msec, respectively. The values for T2\* in the normal subjects for the liver were: standard acquisition  $26.6 \pm 4.7$  msec, multiecho acquisition  $26.7 \pm 4.2$  msec. The lower limit of normal (mean  $-2$  SD) was 17.2 and 18.2 msec, respectively. These values compare well with previously published normal lower limits of normal T2\* values (heart 20 msec, liver 19 msec) (8).

### Comparison of Techniques in Patients

For the heart in the *abnormal* T2\* range ( $<20$  msec), the Bland-Altman plot showed no significant skewing between the T2\* values obtained between both methods. The mean difference between the standard acquisition and the multiecho acquisition was 0.2 msec, which was not statistically significant ( $P = 0.10$ ), with 95% levels of agreement of  $-1.3$  to  $0.9$  msec (Fig. 1). The linear correlation was  $r = 0.97$  ( $P < 0.00001$ ). The coefficient of variability between the methods was 3.5%. In the *normal* range for the heart ( $>20$  msec) the mean difference was 3.8 msec, which was not statistically significant ( $P = 0.08$ ), with 95% levels of agreement of  $-17.8$  to  $10.4$  msec (Fig. 2). The coefficient of variability was also higher in the normal range (13.2%) and the correlation was  $r = 0.87$  ( $P < 0.00001$ ).

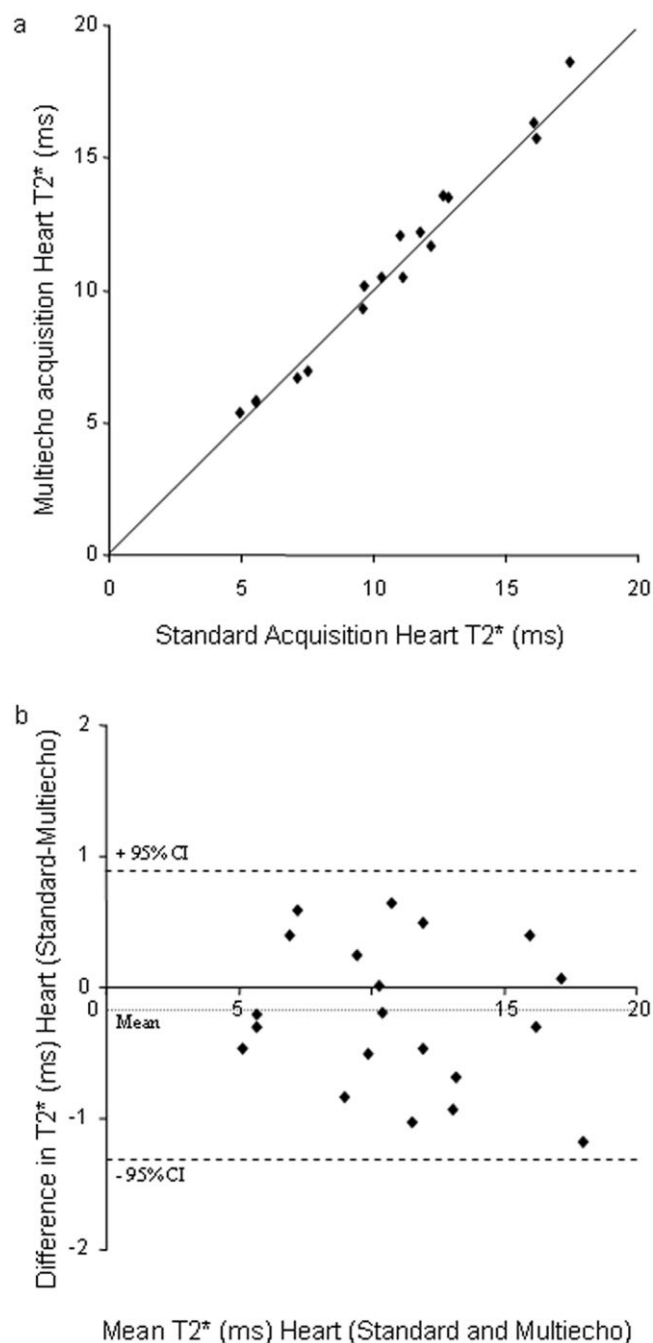
For the liver for all patients, the mean difference between both methods was  $-0.2$  msec ( $P = 0.001$ ), with 95% levels of agreement of  $-0.8$  to  $0.4$  msec (Fig. 3). The coefficient of variability between the methods was 4.8% and the linear correlation between T2\* values was  $r = 0.97$  ( $P < 0.00001$ ).

### Interstudy Reproducibility

For the heart, the coefficient of variation for the multiecho sequence was 2.3% (Fig. 4a) for patients with T2\* values in the abnormal range, 9.3% (Fig. 4b) for patients with T2\* values in the normal range, and 5.8% overall for all patients. The coefficient of variation for the multiecho sequence was found to be 2.9% for the liver over all values (Fig. 5). These results compared favorably with the interstudy reproducibility of the standard acquisition method that was previously reported over all T2\* values as 5.0% for the heart and 3.3% for the liver (8).

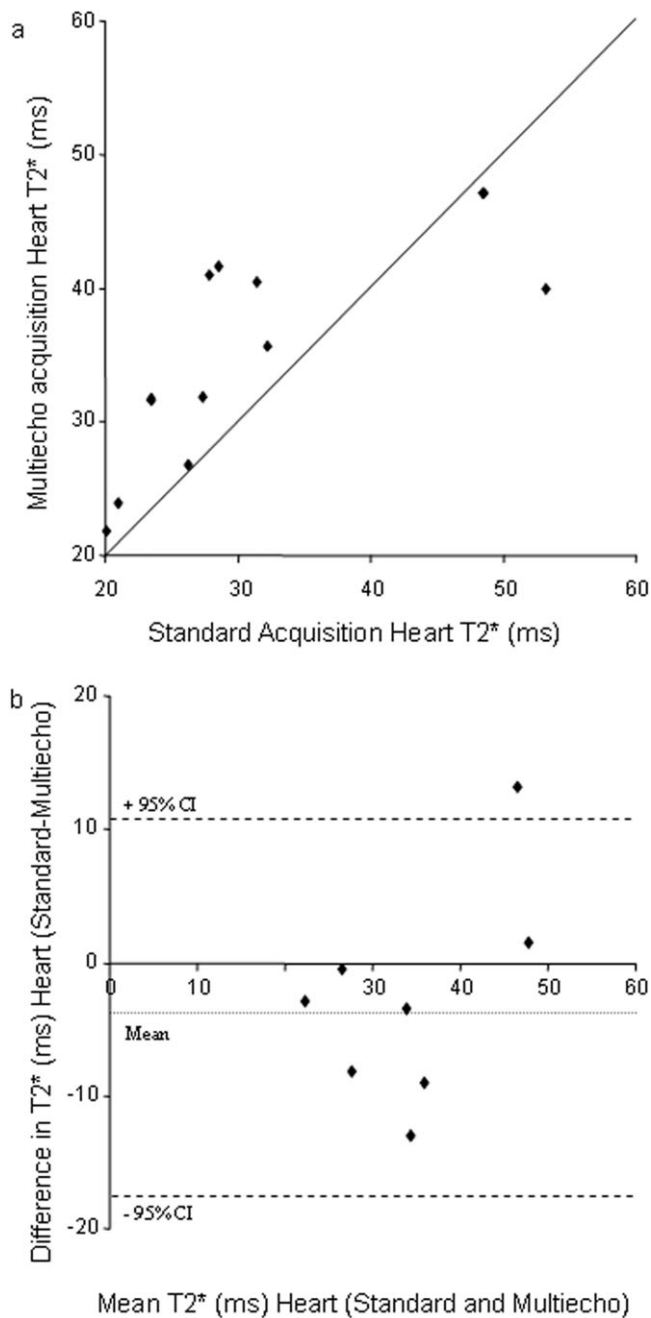
## DISCUSSION

We have shown that the multiecho technique for the measurement of T2\* for assessment of tissue iron con-



**Figure 1.** Comparison of heart T2\* values (in the abnormal T2\* range) between methods with the line of identity shown (a), and Bland-Altman plot of the heart T2\* values obtained between methods, with the 95% confidence intervals shown, and the mean value shown as a dotted line (b).

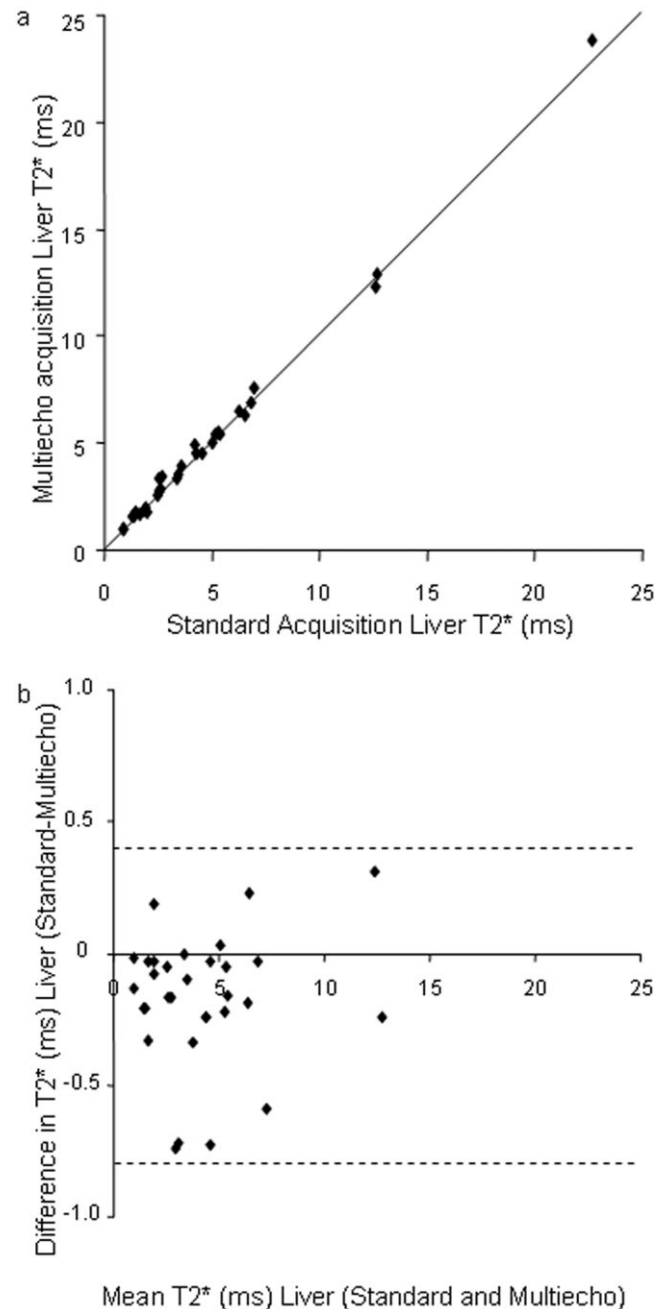
centration is fast, reproducible, and gives results consistent with the standard multiple breath-hold technique. Gradient echo techniques (because of their marked sensitivity to iron deposition and short acquisition times) have been used to reproducibly and reliably quantify myocardial and hepatic iron (8). The range of echo times that we used allows accurate quantification of T2\* values in severe iron overload and provides good sensitivity at low tissue iron levels. However,



**Figure 2.** Comparison of heart T2\* values (in the normal T2\* range) between methods with the line of identity shown (a), and Bland-Altman plot of the heart T2\* values obtained between methods, with the 95% confidence intervals shown, and the mean value shown as a dotted line (b).

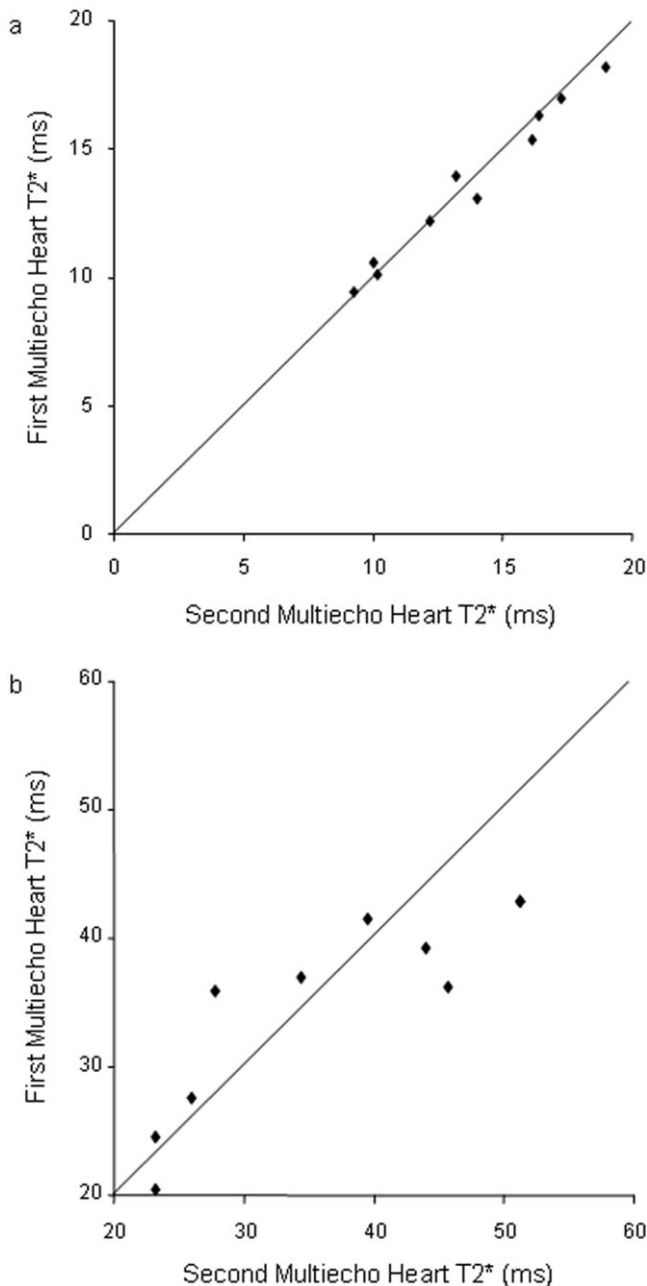
several images are required of both the heart and the liver to allow accurate and reproducible assessment of T2\*. We previously used a nine breath-hold image acquisition for the heart, and an eight breath-hold image for the liver. But, this is time consuming and may be difficult in some patients (especially in children or those who are claustrophobic or dyspneic). The use of the multiecho sequence described in this paper allows much faster scanning times. This has important impli-

cations in many countries where thalassaemia is prevalent, as resources are often scarce. This study also further demonstrates the robustness and reliability of T2\* imaging in the assessment of myocardial iron assessment. The results for the liver were also encouraging and, although there was a significant difference for the liver T2\* between the two techniques, the mean difference was very small ( $-0.2$  msec [4.1% of the mean value]), which is of little clinical importance.

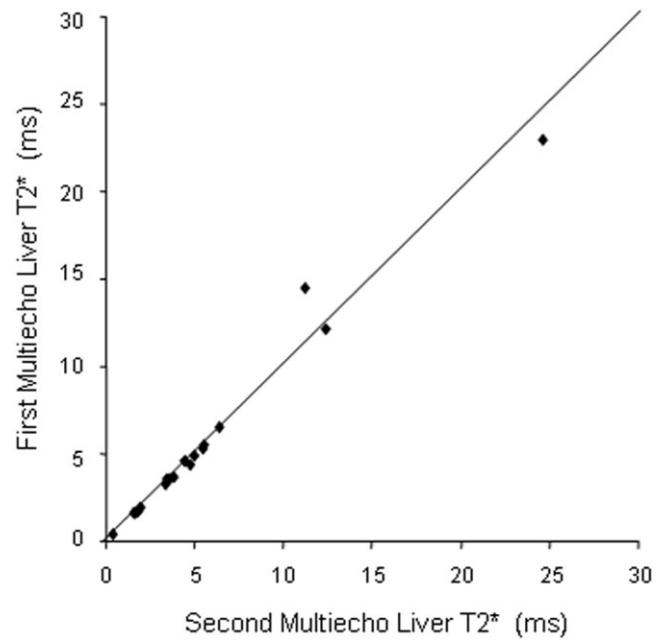


**Figure 3.** Comparison of liver T2\* values between methods with the line of identity shown (a), and Bland-Altman plot of the liver T2\* values obtained between methods, with the 95% confidence intervals shown, and the mean value shown as a dotted line (b).

The range of echo times chosen for the multiecho sequence were slightly shorter than those in used in previous work because we were able to make use of more powerful system gradients. Although the echo times could be altered to be over a longer range, we kept them as short as possible. This is because the main range of clinical interest for  $T2^*$  is 5–20 msec, as higher values indicate normality. As the  $T2^*$  value is, in effect, the time taken for the signal intensity to decay by about 63%, these echo times are ideal to provide accurate quantification in the most clinically important range, the abnormal range. In our study, no patient who had a



**Figure 4.** Interstudy reproducibility of the heart  $T2^*$  in the abnormal (a) and in the normal range (b) of  $T2^*$  values obtained by the multiecho method, with the line of identity shown.



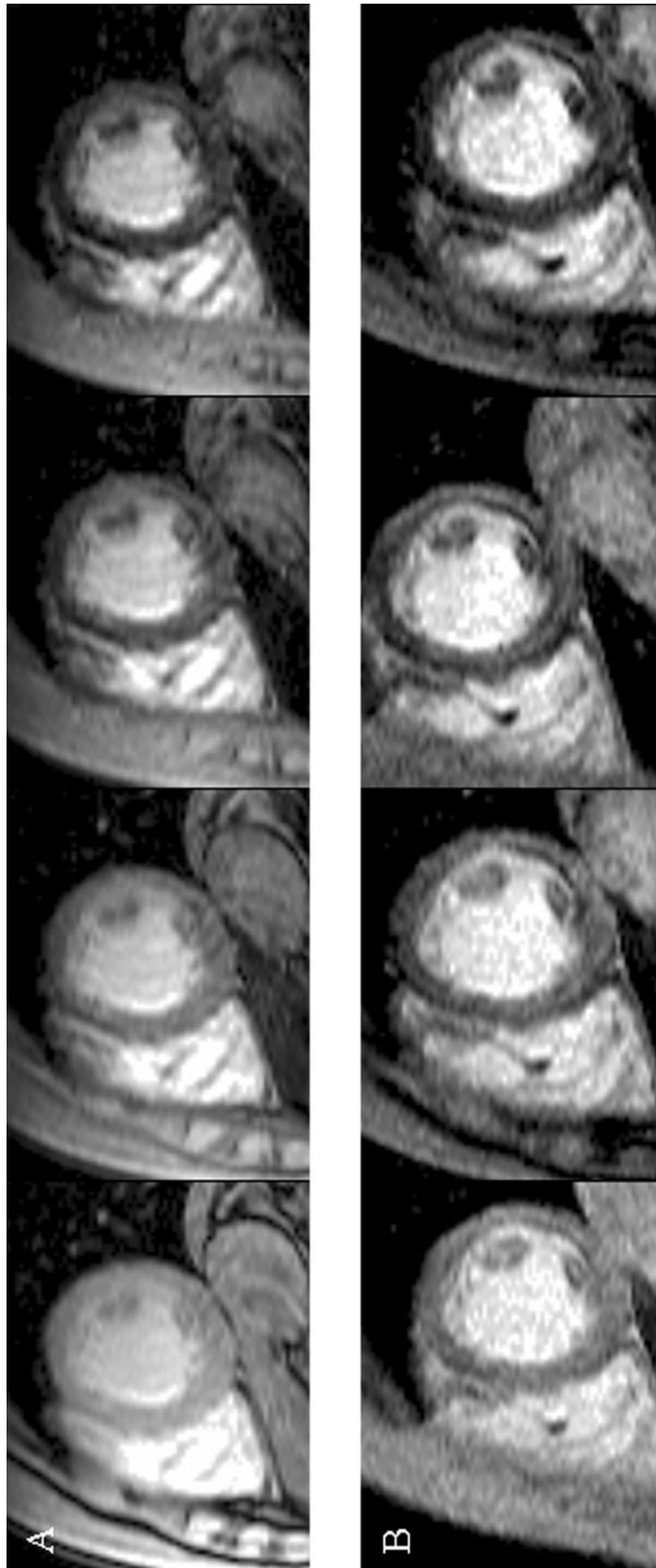
**Figure 5.** Interstudy reproducibility of the liver  $T2^*$  values obtained by the multiecho method, with the line of identity shown.

$T2^*$  of greater than 20 msec via one method had a  $T2^*$  of less than 20 msec via the other method. Also, the high degree of interstudy reproducibility means that the chances of a false positive are small, especially in the abnormal myocardial  $T2^*$  range.

There are some other considerations that give the multiecho sequence an advantage over the conventional sequence. For the multiecho sequence, the TR is constant between all echo times, but for the conventional sequence, the TR lengthened with increasing TE due to scanner programming limitations in the initial development and validation of the technique (8). The constancy of TR eliminates any T1 effects which might skew the data for longer TEs when using the conventional sequence, as T1 is shortened by increasing tissue iron. We have calculated the errors introduced by the T1 effects that occur in the standard sequence and they are low for  $T2^*$  values in the abnormal range, namely 4.4% for  $T2^* < 10$  msec, and 8.7% for  $T2^* < 20$  msec. This well understood and small error in the  $T2^*$  value was systematic, and, therefore, consistent, which still allowed good reproducibility for clinical monitoring. In addition, as the images are all acquired in the same breath-hold, they are well registered, making identification of the myocardial borders easier (Fig. 6), which is important for ease of analysis, reliability, and speed.

## CONCLUSIONS

Gradient-echo  $T2^*$  MR provides a rapid, non-invasive, reproducible means for assessing myocardial iron. In comparison with the standard multiple breath-hold sequence, the multiecho technique has similar reproducibility, reduces the time required to assess each patient, and eliminates errors from T1 effects.



**Figure 6.** Series of images showing myocardial T2\* acquisition with the multiecho (a) and standard acquisition (b) methods. The myocardial borders are more clearly identified and misregistration between images is eliminated with the multiecho method.

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