# Improved Sensitivity of the Reversible Component of the Transverse Relaxation Rate (R2') in Iron-Overloading Diseases

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**Synopsis**

**MRI is an excellent tool for iron quantification in diseases causing its accumulation in the body. Although spin-echo sequences are sensitive to increased iron levels, other studies have shown that gradient-echo can often be more predictive. In this work, the various components of the transverse relaxation are measured using an efficient, single scan GESFIDE (gradient-echo sampling of free induction decay and echo) technique. Preliminary results in liver of a thalassemic mouse and in vivo in a patient with thalassemia suggest that R2' (=1/T2'), the reversible component of the transverse relaxation, may be the most sensitive parameter for determining iron content.**

## Introduction

In iron storage diseases such as hemochromatosis and thalassemia, excess iron levels accumulate in various organs of the body, predominately in the liver or heart, with potentially serious consequences of tissue injury, fibrosis, or cardiac failure at high levels. Accurate determination of iron levels could therefore greatly benefit the prognosis and help monitor effects of treatment. Among current non-invasive methods, the SQUID (superconducting quantum-interference device) technique is the only established technique for accurate iron quantification (1-2). Its limited availability and high cost, however, preclude its widespread clinical use. MRI offers an alternative for estimating iron content non-invasively. Although there is strong evidence that the spin-echo is sensitive to increased iron concentration (indicating enhanced relaxation rate $R_2$ ($=1/T_2$)) (3-5), studies have shown that under moderately iron-overloaded conditions, the gradient-echo sequence is significantly more sensitive (6). These observations may indicate that increased $R_2'$ ($=1/T_2'$), the reversible component of the transverse relaxation, may be the primary cause of signal loss in patients with smaller increases in iron. This work describes an application of the GESFIDE (gradient-echo sampling of free induction decay and echo) sequence (7), originally designed to estimate trabecular bone density, for an efficient single-scan technique for deriving $R_2^*$, $R_2$ and $R_2'$ in the liver. It is shown in both murine and in vivo examples of iron overload that $R_2'$ may be the most sensitive parameter for determining iron content.

## Methods

The GESFIDE technique is based on sampling the descending and ascending portions of the transverse magnetization with two trains of gradient-echoes (7). When fit to a decaying exponential, the echoes prior to the 180° yield $R_2^*$ ($= R_2 + R_2'$). Following the refocusing pulse, the magnetization evolves with a rate constant $R_2^-$ ($= R_2 - R_2'$). GESFIDE was implemented on a GE 1.5T Signa™ MR scanner, and a thalassemic mouse liver and a liver from a control mouse were imaged. The liver specimens were individually inserted into plastic vials filled with saline, and the tubes were oriented parallel to the magnetic field to minimize field perturbations. A single coronal slice was prescribed with the following parameters: 4 echoes per echo train (8 echoes total), 5 ms inter-echo spacing, TR = 500 ms, 3 mm slice thickness, 10 cm FOV, matrix size = 128x128, receiver bandwidth = ±32kHz, 2 averages. $R_2^*$ and $R_2^-$ maps were computed on a pixel-by-pixel basis from the two echo trains, and $R_2$ and $R_2'$ computed by subsequent linear combination. In vivo imaging of the liver was also performed in both a healthy subject (M, 38) and a subject with thalassemia (M, 41, serum ferritin = 4252 ng/ml). In the healthy volunteer, the sequence consisted of 6 echoes per echo train (12 total), with 3 ms inter-echo spacing. Three echoes per echo train were prescribed for the thalassemic patient in anticipation of enhanced $R_2^*$. Data from a single axial slice were acquired in a single breath-held period using a torso phased-array receive coil (TR = 200 ms, 10 mm slice thickness, 35 cm FOV, matrix size = 128x128, receiver bandwidth = ±64kHz, scan time = 25 sec).

## Results and Discussion

The relaxation rate maps for the murine liver are shown in **Fig. 1**. $R_2^*$, $R_2$ and $R_2'$ were all enhanced in the thalassemic liver but, as seen in the figure and **Table 1**, $R_2'$ was the most sensitive component, increasing by nearly 200%, while $R_2$ was enhanced by about 50% and $R_2^*$ just below 100%. These findings indicate that $R_2'$ may be the variable most sensitive to moderate changes in iron concentration levels, not as easily detected by either $R_2^*$ or $R_2$.

The relaxation parameter maps of the normal volunteer are shown in **Fig. 2**. The data show that $R_2$ in the liver is relatively homogeneous whereas $R_2'$ is considerably more heterogeneous. The GESFIDE technique allows isolation of the reversible component of the transverse relaxation rate, which is potentially more sensitive to small changes in iron concentration (as suggested by the data obtained from the thalassemic mouse). Notice in particular the region indicated by the arrow pointing to an area of reduced $R_2'$, suggesting reduced iron content. $R_2^*$, $R_2$, and $R_2'$ values in this region are 29.0, 26.3, and 3.9 $s^{-1}$, corresponding to a difference of -22%, 1.2%, and -65%, respectively, from the averages over the entire liver. The data also underscore the need for image-based measurement of relaxation parameters instead of localized single-voxel approaches, and suggest the potential advantage of the $R_2'$ parameter for enhanced detection sensitivity.

The temporal signal evolution averaged over the entire liver of the thalassemic patient is shown in **Fig. 3**. Because of the rapid signal decay, only the first two points (SNR > 2) were used to compute $R_2^*$ yielding an estimate of 256 $s^{-1}$. Since the SNR of the last echo (spin-echo) was also > 2, $R_2$ was also computed using an extrapolated value of signal at TE=0 from the first fit, yielding $R_2 = 67.3$ $s^{-1}$. From these two values, $R_2'$ was computed to be 189 $s^{-1}$. Compared to the normal volunteer, $R_2^*$, $R_2$, and $R_2'$ increased by factors of 6.9, 2.6, and 16.7, respectively (**Table 2**). Even with some level of uncertainty in these calculations, it is reasonable to conclude that $R_2'$ may be the more sensitive parameter than either $R_2^*$ and $R_2$ in detecting differences in iron levels.

## Conclusion

In this preliminary work, it is demonstrated that iron-induced relaxation rate enhancement in both human and murine tissues affects the rate parameter $R_2'$ to a greater degree than either $R_2$ or $R_2^*$, indicating that $R_2'$ may be the most sensitive parameter for iron quantification. It was shown that the GESFIDE sequence was capable of measuring these parameters efficiently in a single scan. Corroboration of our findings in a larger number of subjects is currently in progress.

**Table 1** Average relaxation rates in murine liver.

| | Wild-type | Thalassemia | Ratio |
|---|---|---|---|
| $R_2^*$ | 29.9 $s^{-1}$ | 57.3 $s^{-1}$ | 1.9 |
| $R_2$ | 19.7 | 28.2 | 1.4 |
| $R_2'$ | 10.2 | 29.1 | **2.9** |

**Table 2** Average relaxation rates in human liver.

| | Normal | Thalassemia | Ratio |
|---|---|---|---|
| $R_2^*$ | 37.2 $s^{-1}$ | 256 $s^{-1}$ | 6.9 |
| $R_2$ | 26.0 | 67.3 | 2.6 |
| $R_2'$ | 11.3 | 189 | **16.7** |

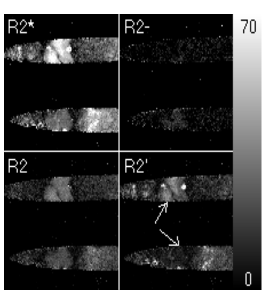


**Fig. 1**

**Fig. 1** Relaxation rate maps for the murine liver specimen. In each image, the thalassemic liver is the top specimen. The ratio of rates was greatest for the $R_2'$ values (see **Table 1**).

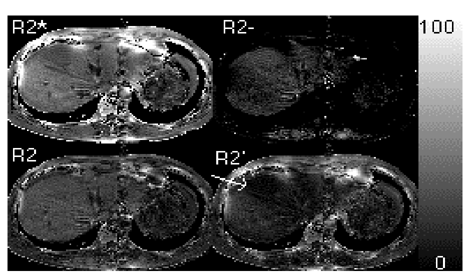


**Fig. 2**

**Fig. 2** Relaxation rate maps for the normal volunteer. The $R_2'$ map is more heterogeneous than $R_2$, possibly indicating higher sensitivity to local variations in iron content.

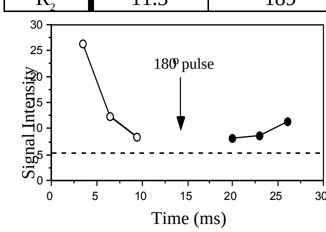


**Fig. 3** (Left) Signal evolution in the liver of the thalassemic subject. Three gradient-echoes before and three following the refocusing pulse were acquired, of which the last echo was also a spin-echo.

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**References**

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