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Original contributions

Assessment of liver fat quantification in the presence of iron

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Abstract

This study assesses the stability of magnetic resonance liver fat measurements against changes in T2* due to the presence of iron, which is a confound for accurate quantification. The liver T2* was experimentally shortened by intravenous infusion of a super paramagnetic iron oxide contrast agent. Low flip angle multiecho gradient echo sequences were performed before, during and after infusion. The liver fat fraction (*FF*) was calculated in co-localized regions-of-interest using T2* models that assumed no decay, monoexponential decay and biexponential decay. Results show that, when T2* was neglected, there was a strong underestimation of *FF* and with monoexponential decay there was a weak overestimation of *FF*. Curve-fitting using the biexponential decay was found to be problematic. The overestimation of *FF* may be due to remaining deficiencies in the model, although is unlikely to be important for clinical diagnosis of steatosis.

Keywords: Liver; Fat quantification; SPIO; Iron

1. Introduction

Fat quantification by magnetic resonance (MR) imaging typically refers to measurement of the fat fraction (*FF*), which is the ratio of signal from fat protons to the signal from all protons. Clinically, the *FF* allows quantification of abnormal retention of fat within a cell (steatosis). The *FF* from MR measurements should estimate the actual proportion of fat and water protons; however, there are several confounds to the accuracy. These include T1 relaxation, T2* relaxation and fat spectral complexity. T2* is particularly relevant for liver imaging since steatosis is frequently accompanied by iron accumulation, which causes T2* signal decay. While quantification methods incorporating T2* decay have been described for quantifying liver fat, it has not yet been established that these give reliable measurements in patients. The present study describes a novel methodology for using superparamagnetic iron oxide (SPIO) contrast agent as an *in vivo* mimic of iron overload. Under experimental perturbation of the T2* using SPIO, the consistency of *FF* measurements can provide an empirical test of fat quantification methods intended to correct for T2* decay.

The deleterious effects of T2* on accuracy have long been recognized [1,2] but are often neglected or considered small. However, a recent clinical study found that T2* shortening due to the presence of iron represents a limitation for the evaluation of fatty liver [3]. The "dual echo" method used in that study neglects T2* and attributes all changes in signal during the interval ΔTE to interference between water and fat, caused by differences in chemical shift.

Letting w and f represent the water and fat signals, respectively, the dual echo method acquired two images with w and f in-phase, IP=$|w+f|$, and out-of-phase, OP=$|w-f|$. Under these conditions, the fat fraction can be estimated from Eq. (1).

$$FF = \frac{\mathrm{IP} - \mathrm{OP}}{2\mathrm{IP}} \tag{1}$$

Clearly, T2* can be a source of error in this model, since the signal on the later echo is always systematically

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lowered by T2* decay. The consequences of neglecting T2* have been demonstrated in numerical simulations [4] and theoretically [5]. Rewriting Eq. (1) in terms of $FF_{true}=f/(w+f)$ and $\kappa=\Delta TE/T2^* \ll 1$ the following is obtained.

$$FF \approx FF_{true} - \left(\frac{1}{2} - FF_{true}\right)\kappa \tag{2}$$

From this, it can be seen that *FF* is a function of both FF_{true} and T2*. Since iron concentration is proportional to 1/T2*, the dual echo method typically results in underestimation of FF_{true} in patients with liver iron. This illustrates how neglecting a key physical property (T2*) can introduce systematic errors and create spurious correlation between unrelated parameters (*FF* and T2*).

To improve upon the dual echo method, a more realistic model of the MR signal must be developed that includes parameters to express the decay with echo time. Several ideas have been considered previously. The most simple approach is to assume water and a single fat peak with identical T2* for both. However, it is known that fat has a broad spectrum compared to water so it is more realistic to assign a shorter T2* to fat [6]. Models with separate T2* terms for water and fat have also been used and these confirm the short apparent T2* of fat [5,7], although this approach can fail at low *FF* since it becomes difficult to estimate the T2* of fat. In any case the short T2* is an artifact of approximating fat as a single peak, whereas in reality it is a superposition of multiple peaks with different resonant frequencies [5,8–11]. The relative proportions of the peaks are similar in different fats and oils, therefore it is reasonable to assume as prior knowledge a standard approximation of the fat spectrum. Whether it is necessary to include separate T2* terms for each peak is unclear at the present time. Differences in T2* are difficult to measure reliably, since discrepancies between the assumed and the true fat spectrum will manifest as T2*. Also, since T2s are generally long (see Table 1) it may be expected that differences in 1/T2*=1/T2+1/T2′ are small. Recent studies that have assumed a standard fat spectrum with the same T2* have reported good fitting of empirical data in phantoms [5,11] and excellent agreement between imaging and spectroscopy in patients [12,13].

Table 1
Chemical shifts (δ), peak areas (α) and T2 values in fatty liver taken from Refs. [24] and [27]

Chemical shift (ppm)	Peak area	T2 at 1.5 T (ms)	T2 at 3.0 T (ms)
5.3	0.047	–	–
4.2	0.039	–	–
2.75	0.006	–	51
2.1	0.120	39.2	52
1.3	0.700	75.5	62
0.9	0.088	45.0	83
4.7 (water)	–	35.2	23

Some values for the fat T2s are missing due to the difficulty in measuring peaks close to the water peak in vivo, and there is also large variability in the ranges of the T2s.

The motivation of the present study is to assess how the above model performs in correcting T2* with application to liver fat quantification. Imaging was performed in patients before, during, and after intravenous infusion of a SPIO contrast agent used to experimentally manipulate T2*. Since the fat in the liver should remain constant during the infusion (over 30 min), any systematic changes in *FF* can be attributed to errors in the modeling. This methodology follows on from previous work [5,14,15].

2. Theory

The water and fat signals are modeled as a function of echo time (TE) as in Eqs. (3) and (4)

$$w(\mathrm{TE}) = w \cdot exp(-\mathrm{TE}/\mathrm{T2}^*_w) \cdot \alpha(\mathrm{TE}) \tag{3}$$

$$f(\mathrm{TE}) = f \cdot exp(-\mathrm{TE}/\mathrm{T2}^*_f) \cdot \beta(\mathrm{TE}) \tag{4}$$

were *w*/*f* are the (real) proton densities of water/fat and $T2^*_w$/$T2^*_f$ represent their decays. Separate terms for $T2^*_w$ and $T2^*_f$ are included (biexponential model), although it may be reasonable to assume they are equal (monoexponential model). Prior knowledge of chemical shifts of water and fat is contained in the terms $\alpha(TE)=\exp(2\pi i\omega\delta_{water}TE)$ and $\beta(TE)=\sum a_j \exp(2\pi i\omega\delta_j TE)$, with specific values given in Table 1. The Larmor frequency ω is $42.576\times10^6 B_0$ Hz.

The amplitude of the signal $|s(TE)|=|w(TE)+f(TE)|$ is used to avoid having to model B_0 field inhomogeneities. This introduces ambiguity between fat and water but is considered an acceptable trade-off in the present study, since fat in the liver is almost always the minority component. Then $|s(TE)|$ is rewritten in terms of *FF* and $\eta=w+f$.

$$\begin{aligned}|s(\mathrm{TE})| = \eta\,|&(1-FF)\cdot exp(-\mathrm{TE}/\mathrm{T2}^*_w)\cdot\alpha(\mathrm{TE})\\ &+ FF\cdot exp(-\mathrm{TE}/\mathrm{T2}^*_f)\cdot\beta(\mathrm{TE})\,|\end{aligned} \tag{5}$$

The dual echo method makes the simplification $T2^*_w=T2^*_f=\infty$ and neglects all fat peaks except the CH_2 peak at 1.3 ppm. Then two TEs are chosen such that α(TE)/β(TE) is equal to ±1, which correspond to the IP and OP images, $|w+f|$ and $|w-f|$. Note that for the purposes of this work, the effect of T1 relaxation is assumed negligible, which can be accomplished by using a long repetition time (TR) and low flip angle.

3. Methods

There are two main parts to the study. The first part tests the feasibility of using a biexponential decay model. For this part, 16-echo data were acquired in 54 patients. Models assuming no decay, monoexponential decay, and