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Quantification of severe liver iron overload using MRI offset echoes

Henric Rydén[1] and Mikael Skorpil[2,3]

Abstract

Magnetic resonance imaging (MRI) has become the clinical standard to estimate liver iron overload. The most commonly used method is to measure the transversal relaxation time, T2*, from a multi gradient recalled echo sequence (MGRE). While this technique is reliable in low to moderate liver iron concentrations (LIC), it will be inaccurate when it is severe. We report a case with severe liver hemochromatosis and show the benefit of using an easily implemented MRI offset echo sequence to more accurately estimate LIC. After adjusting treatment, both Ferritin and LIC decreased. Using standard MGRE this reduction could not have been detected.

Keywords

Abdomen/GI, magnetic resonance imaging (MRI), liver, adults and pediatrics, imaging sequences

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Introduction

Several magnetic resonance imaging (MRI) methods exist to non-invasively measure liver iron concentration (LIC), which have become standard in clinical practice (1,2). An often used and accurate method is T2* relaxometry, which correlates with LIC (3). It estimates LIC due to iron's T2* shortening effect, using a multi gradient recalled echo (MGRE) sequence (1). While not always apparent to clinicians, quantification of severe iron overload will be inaccurate, nor can hepatic steatosis be estimated in these patients.

Hereditary hemochromatosis, chronic hepatopathies, blood transfusions, and sickle cell disease can all cause liver iron accumulation (1). Iron is essential for the body, to the extent that there is no evolutionary developed mechanism to get rid of excess iron. Iron overload can be treated with phlebotomy and chelates (1). In thalassemia major and sickle cell disease a very high body iron accumulation can occur secondary to numerous blood transfusions. This may cause organ dysfunction of the liver, heart, and endocrine organs (4). Iron chelating therapy is used in these patients, since phlebotomy is not feasible due to anemia. Chelation therapy is effective, but potentially toxic, and clinical awareness of the inadequateness of standard MGRE sequences in severe iron overload estimation need to be emphasized. In severe iron overload, even combination therapy may be indicated and new iron chelators are evaluated in phase 3 clinical trials, all demanding precise and accurate LIC estimation (2).

T2* in healthy liver is approximately 20–50 ms (1,5). In severe iron overload T2* can be very short, less than 1 ms, resulting in signal amplitudes from the second echo close to the noise floor in a standard MGRE sequence optimized for minimum echo spacing (ΔTE) (3). Since at least two echoes are required to quantify T2*, it is necessary to decrease ΔTE considerably, which is not feasible with a standard MGRE sequence. Instead we used a modified method by Wood et al. to estimate severe liver iron overload (3). A multi breath-hold dual-echo sequence with each dual-echoes offset,

[1]Department of Medical Physics, Karolinska University Hospital, Stockholm, Sweden
[2]Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden
[3]Department of Radiology, Karolinska University Hospital, Stockholm, Sweden

Corresponding author:
Mikael Skorpil, Department of Radiology, Karolinska University Hospital, Solna 17176, Sweden.
Email: mikael.skorpil@ki.se

Table 1. MRI offset dual-echo (TE1 and TE2) sequence using 14 offsets. MGRE (multi gradient recalled echo sequence) with 12 TEs.

	Offset													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
TE 1	0.97	1.07	1.17	1.27	1.37	1.47	1.57	1.67	1.77	1.87	1.97	2.07	2.17	2.27
TE 2	2.37	2.47	2.57	2.67	2.77	2.87	2.97	3.07	3.17	3.27	3.37	3.47	3.57	3.67
	MGRE													
TE	0.99	2.4	3.81	5.22	6.63	8.04	9.45	10.9	12.3	13.7	15.1	16.5		

i.e. different TEs, were combined to allow calculation of very short T2*. We here report a case with severe liver hemochromatosis and show the benefit of instead using an easily implemented MRI offset echo sequence to estimate LIC.

Case report

A 20-year-old man with thalassemia major diagnosed at 2 years of age and secondary liver hemochromatosis was referred to a University Hospital due to continuously elevated serum Ferritin levels. In his childhood he was treated with Deferoxamine mesylate injections and now, since 5 years, has been on oral Deferasirox medication. Every third week he had blood transfusions. Ferritin was highly elevated, 1612 µg/L (normal range, 20–250 µg/L). To evaluate LIC a MRI examination (1.5 T) was performed with a standard MGRE sequence with 12 echoes (Table 1) and a ΔTE of 1.41 ms. Since the liver iron overload was severe, a complementary MRI offset echo sequence was acquired using a two-dimensional multi breath-hold (7.5 s) dual-echo sequence with the following parameters: flip angle, 24°; repetition time, 75 ms; and ΔTE, 1.4 ms. Fourteen offset acquisitions (Table 1) of the dual-echo sequence were acquired, reducing the actual ΔTE to 0.1 ms. Curve fitting was performed with a mono-exponential model with a plateau, P:

$$S(TE) = S_0 \exp(-TE/T2^*) + P$$

We added the plateau to the model to account for the noisy late echoes, as has previously been suggested (6). To increase the robustness of the fit, a fit was first performed without accounting for the plateau to roughly estimate T2*. A 50% deviation from this estimate was set as the upper and lower limits for the final curve fitting. The fitted curve for the MRI offset echo sequence is shown in Fig. 1, with a calculated T2* of 0.83 ms (95% confidence interval [CI], 0.76–0.89 ms). The calculated T2* for the standard MGRE sequence was 1.40 ms (95% CI, 1.07–1.73 ms). Note that in the standard MGRE sequence the signal amplitude of the second echo is close to the noise floor; while with the MRI offset echo sequence approximately 16 echoes have been collected prior to reaching the noise floor (Fig. 1). Due to the severe liver iron overload Deferasirox was increased from 1000 to 1500 mg per day and at follow-up 6 months later Ferritin had decreased to 1354 µg/L. A new MRI offset echo sequence was performed and the calculated T2* had increased to 1.00 ms (95% CI, 0.90–1.10 ms) (Fig. 1), i.e. iron overload had decreased.

Discussion

In order to quantify T2* robustly and accurately in liver iron overload diseases, the first echo should be acquired as quickly as possible and several echoes have to be acquired during the relaxation process (1). The echo spacing (ΔTE) is limited by the gradient system, and can be minimized by lowering the image resolution. On our full-body clinical scanner we optimized a dual-echo gradient recalled echo sequence for the shortest possible echo times, acquiring the first echo at 0.97 ms, with an intra-scan ΔTE of 1.4 ms. In cases of severe iron overload, T2* are very short and can be below 1 ms (3). Since the standard MGRE sequence can only acquire one echo before the signal has decayed close to the noise floor, T2* will be estimated incorrectly, as illustrated in Fig. 1. One approach to improve the sampling density of the echoes, i.e. shorten ΔTE, is to avoid sampling high spatial frequencies. However, lowering the spatial resolution will increase intra-voxel dephasing due to larger voxel volumes, resulting in even faster signal decay. This is also not optimal since a larger part of scan time is spent on ramp-up and ramp-down times of the gradient system. By using MRI offset echoes, i.e. combining several multi-echo scans where echoes in each scan are offset, there is no limit on the echo spacing. This enables high-resolution T2* quantification in patients with severe iron overload. A challenge in quantifying very short T2* is the confounding effect in the presence of fat. Since the signal has decayed before fat and water are returning to their in-phase state, there is an

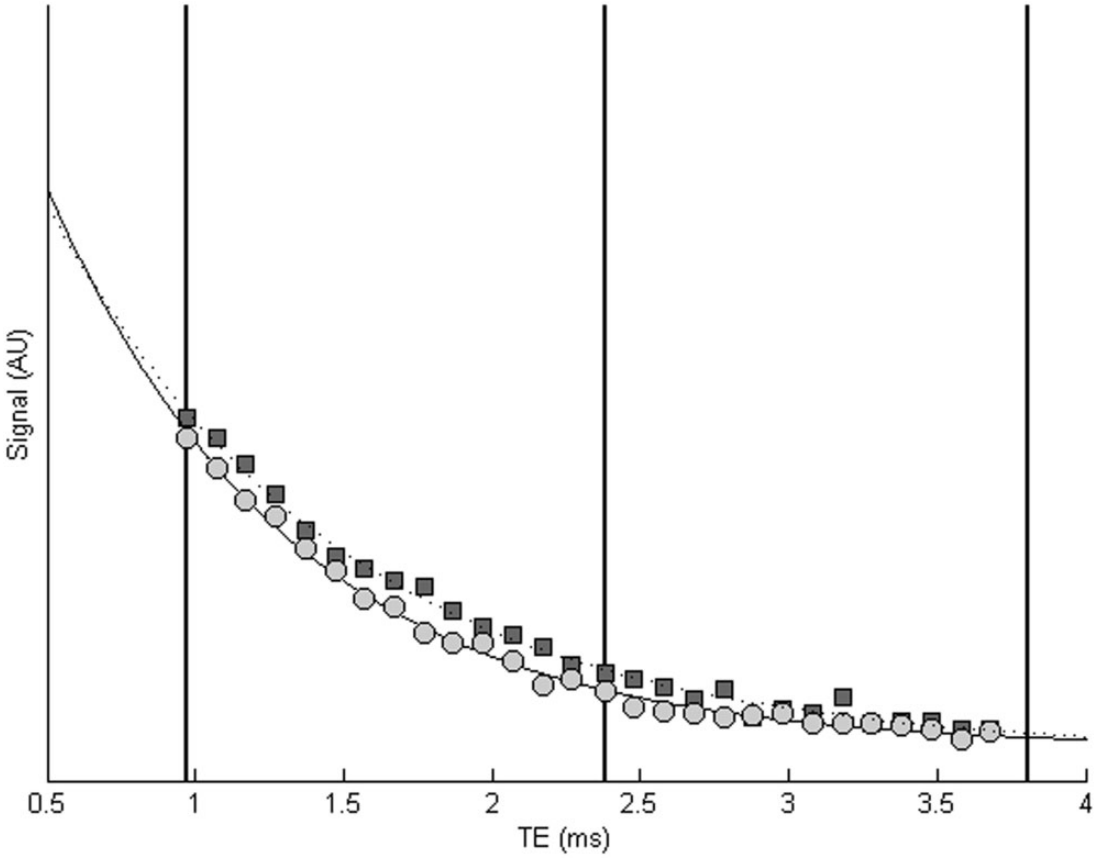

Fig. 1. The first MRI offset echo sequence (circles) with a calculated T2* of 0.83 ms. Follow-up MRI offset echo sequence after 6 months (squares) where T2* has increased to 1.00 ms, which could be detected due to the small variance in T2*. Lines represent the three first echoes of the 12 echo standard MGRE sequence. Note that the second echo amplitude (2.4 ms) is already close to the noise floor. AU, arbitrary units.

ambiguity as to whether the decay is caused by phase cancellation from the chemical shift between fat and water, or from T2* relaxation. This effect can be reduced by applying a fat suppression pulse, which increases scan time and SAR, but also reduces SNR, or by increasing the flip angle to increase the signal from liver tissue. We used an Ernst-optimized flip angle of 24° as it minimizes the noise floor, which extends the echo time window and reduces the confounding effect of fat. With the MRI offset echo sequence the patient's calculated T2* on the first examination was 0.83 ms. Calculating LIC from the T2* value is highly dependent on the choice of calibration model, especially in severe iron overload, and it is therefore often better to use T2* or its reciprocal value, R2* (7). Extrapolating LIC from a graph in a recent paper by Garbowski et al. T2* of 0.83 ms equals 39 mg/g dry weight (dw) (7). Using a standard MGRE the patient's T2* was 1.40 ms, i.e. 23 mg/g dw. Consequently there is a 69% misestimation of T2*. At follow-up, Ferritin had decreased and T2* had increased to 1.00 ms, i.e. 33 mg/g dw. This could be detected due to the small variance in T2* obtained with MRI offset echo sequences (Fig. 1), which is not possible with the standard MGRE sequence. While the implementation of MRI offset is simple, care must be taken to avoid bias from different receiver gains and shim parameters between scans. Estimation of severe iron overload is preferable on 1.5 T due to the faster signal decay at 3 T (1). Limitations of MRI offset, and all methods estimating very short T2*, is the uncertainty of the confounding effect of steatosis, and the requirement of multiple breath-holds, although 7.5 s is acceptable for most patients.

In conclusion, in order to quantify severe liver iron overload standard MGRE sequences are inadequate, in our patient underestimated by 69%. MRI offset echoes will more accurately estimate severe liver iron overload and also enables detection of small differences during follow-up.

Conflict of interest

None declared.

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