Use of fat suppression in R_2 relaxometry with MRI for the quantification of tissue iron overload in beta-thalassemic patients

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Abstract

Purpose: To assess the performance and results of R_2 relaxometry using a fat-suppressed (FS) multiecho sequence and compare these to conventional R_2 relaxometry in estimating tissue iron overload.

Materials and Methods: Relaxation rate values ($R_2=1/T2$) of the liver, spleen, pancreas and vertebral bone marrow (VBM) were estimated in 21 patients with β-thalassemia major, using a respiratory-triggered 16-echo Carr-Purcell-Meiboom-Gill (CPMG) spin-echo sequence before (R_2) and after (R_2 FS) the application of chemically selective fat suppression.

Results: Hepatic and splenic R_2 FS values correlated with respective R_2 values ($r=0.98$ and $r=0.96$, $P<.001$), whereas correlations between R_2 FS and R_2 values for pancreas and VBM were not statistically significant. Bland–Altman plots show disagreement between R_2 and R_2 FS values, particularly for pancreas and VBM. Hepatic, pancreatic and VBM R_2 FS values correlated with serum ferritin ($r=0.88$, $P<.001$; $r=0.51$, $P<.003$; and $r=0.75$, $P<.002$, respectively). Hepatic R_2 FS values correlated with splenic R_2 FS ($r=0.77$, $P<.03$), pancreatic R_2 FS ($r=0.61$, $P<.006$) and VBM R_2 FS values ($r=0.70$, $P<.001$), whereas pancreatic R_2 FS values correlated also with VMB R_2 FS values. On the contrary, among the R_2 values of the above tissues, obtained without fat suppression, only hepatic R_2 values correlated with serum ferritin, whereas no correlation was documented between hepatic and pancreatic or VBM R_2 values. The application of fat suppression did not improve breathing or flow artifacts.

Conclusion: Application of fat suppression in the standard CPMG sequence improved the capability of MRI in noninvasive quantification of iron, particularly in lipid-rich tissues, such as vertebral bone marrow (VBM) and pancreas.
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1. Introduction

Over the past two decades, MRI has emerged as a noninvasive, safe and readily available method for estimation of iron concentration in liver and myocardium in patients with β-thalassemia major. A variety of MR techniques have been employed for this purpose including signal intensity ratio (SIR) measurements and relaxometry methods, namely, R_2 or R_2^* with satisfactory success rates [1-14]. Coexistance of fat and iron in the liver is not uncommon in patients with iron

overload pathologic conditions [15], hampering the ability of relaxometry or SIR methods to estimate iron [16,17]. Moreover, in extrahepatic tissues with iron overloaded and large amounts of fat, such as the pancreas and vertebral bone marrow, MR determination of iron cannot be representative of the degree of iron deposition due to severe fat influences. This may explain why MR measurements for pancreas and bone marrow with any method have yielded no correlation or poor correlations with indices of iron stores such as serum ferritin or hepatic siderosis so far, even in studies with large numbers of patients with iron overload pathologic conditions [18-26]. Recent research studies report methods of R_2^* quantification of liver iron after correction for fat [27] or allow discrimination of fat and water by separate reconstruction on opposed-phase images [28]. All these methods need sophisticated calculation algorithms and have not been

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applied yet in clinical practise in multiple transfused patients with β-thalassemia with a wide range of iron overload.

In this study, we hypothesize that the application of fat suppression in the standard CPMG sequence will improve the accuracy of R_2 estimation as well as subsequent iron estimation, particularly in lipid-rich vertebral bone marrow and pancreas. In patients with β-thalassemia, the pancreas may be frequently affected by severe fatty replacement and siderosis simultaneously [17,23,24,26]. To the best of our knowledge, fat suppression, although simple and easy, has not been applied so far in relaxometry methods in order to overcome fat influences in tissue iron determination with MRI in patients with iron overload syndromes.

The aim of our study was to assess the capability of R_2 relaxometry with application of fat suppression (R_2 FS) to estimate iron in the liver, pancreas, bone marrow and spleen in patients with β-thalassemia and a wide range of iron overload. For this purpose, we (a) correlated the R_2 FS values of the liver, spleen, pancreas and vertebral bone marrow between them and with serum ferritin, as a marker of iron stores, and (b) compared with respective correlations yielded by R_2 values of the same tissues.

2. Materials and methods

2.1. Patient population

Our study was composed of 21 consecutive patients with β-thalassemia major (7 males and 15 females, age 9–41 years, mean 35.6 years) who underwent MRI of the upper abdomen for the evaluation of hepatic siderosis over a 2-year period. This study was conducted with the approval of the hospital ethics committee, and informed consent was obtained from all subjects studied. All patients were under systematic red blood cell transfusions every 2–3 weeks and chelation therapy either with per os deferiprone or with subcutaneous desferrioxamine. Serum ferritin levels, obtained up to 3 months from the MR exam, were recorded and ranged from 75 to 7800 ng ml^{-1} (mean 2203 ng ml^{-1}, normal values 20–200 ng ml^{-1}). Thirteen of the 21 patients were splenectomized.

2.2. MRI Technique

All studies were performed on a 1.5-T MR unit (Philips NT Intera; Philips Medical Systems, Best, The Netherlands) using a quadrature radiofrequency (RF) body coil for both signal excitation and reception. For calculating R_2 values, a single-slice Carr-Purcell-Meiboom-Gill (CPMG) spin-echo sequence was obtained with 16 equidistant echoes and a short echo spacing of 5 ms (TR=2000 ms; TE_1, TE_2, ..., TE_{16}=5, 10, ..., 80 ms; flip angle=90°; acquisition matrix 192×256; slice thickness 10 mm), according to a previously published methodology [3,4]. The sequence was triggered on end-expiration phase in order to minimize breathing motion artifacts. Subsequently,

the same sequence with identical parameters was obtained with additional application of chemically selective fat suppression. Axial images were obtained, which included the right liver lobe, part of the pancreas, spleen (in the nonsplenectomized patients) and vertebral body or arch of the first or second lumbar vertebra.

The presence of artifacts and its influence on image quality were rated by an experienced investigator using a four-point scale for both breathing and flow artefacts (0=no artifacts, 1= some artifacts present not interfering with measurements, 2=artifacts present possibly interfering with measurements, 3=artifacts present resulting in unreliable measurements). If the overall conspicuity of the T2 map was not grossly degraded and the boundaries of the organs were clearly demarcated, then we proceeded to T2 calculations for regions of interest (ROIs) that were not affected by the artifacts, in each individual organ. Overall, two sequence acquisitions were repeated due to significant artifacts or poor respiratory signal detection. Additional multislice T1- and T2-weighted sequences were obtained in axial and coronal planes as part of our regular upper abdominal MRI protocol for investigation of the upper abdomen.

2.3. Image analysis

A monoexponential function of the form $S(TE) = So*exp(-TE*R_2)+C$ was assumed to describe the signal decay with echo time (TE), where $S(TE)$ is the SI at TE, So is the signal amplitude at TE=0 and C is a constant offset parameter added to compensate for background noise [3]. T2 values and, subsequently, T2 FS values were calculated automatically on the scanner's console and T2 map images reconstructed for abdominal scans. The fitting procedure for T2 calculations was incorporated in the Philips Intera MR system and was based on a weighted ratios least-squared (RLSQ) algorithm, where all 16 image echoes were fitted in order to calculate T2 [29]. T2 values without and with fat suppression of all examined organs were obtained on the T2 and T2 FS maps, respectively. The boundaries of the organs were more clearly depicted on T2 images. For hepatic measurements, two ROIs (diameter 1–2 cm^2) were placed in the right lobe and one ROI in the left lobe on the T2 map images. These ROIs were carefully drawn in order to avoid vascular structures, motion or pulsation artifacts. For splenic measurements, two or three ROIs were applied in the periphery of the organ. For pancreas, one or two ROIs were placed within its parenchyma, away from its boundaries. Vertebral bone marrow (VBM) values were obtained by two ROIs placed either at the anterior part of L1/L2 vertebral body or at their neural arch. Subsequently, using the same coordinates, we placed ROIs for all organs on T2 fat suppression maps at exactly the same locations as we did for T2 map images (Fig. 1). All the above measurements along with the standard deviations (S.D.) were recorded, and the average for each organ for R_2 and R_2 FS, respectively, was used for statistical analysis.