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Session: Iron Detection & Quantification

Tissue Iron Detection & Quantification with MRI

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Introduction

Endogenous tissue iron, other than that in blood, occurs primarily in two MRI detectable forms: ferritin iron and hemosiderin iron [1]. Ferritin is a water soluble protein with an iron core and is the body's main iron storage protein. Hemosiderin iron is water insoluble and consists largely of ferrihydrite. Ferritin may either be diffusely dispersed or localized in specific cells, depending on the tissue type. Hemosiderin is often the result of ferritin degradation and typically occurs in micron-sized aggregations. Ferritin is the predominant iron form in most healthy tissues, but hemosiderin may be present in high concentrations as a result of pathology (e.g., iron overload disorders).

The MRI detectability of ferritin and hemosiderin is a result of both their relative abundances as well as their high magnetic susceptibilities. As a consequence of their susceptibilities, they generate substantial magnetic field inhomogeneities when placed in the strong magnetic field of an MRI scanner. These field inhomogeneities cause proton spin dephasing and increase the transverse relaxation rate. Thus ferritin and hemosiderin act effectively as natural contrast agents. Iron-sensitive MRI techniques provide useful non-invasive approaches for the diagnosis and monitoring of a variety of diseases with associated changes in iron concentration and the spatial pattern of iron deposition.

MRI Methods for Tissue Iron Detection and Quantification

Several methods have been proposed for MRI detection and quantification of tissue iron. These are based either on the effect of iron on the magnitude and/or phase of the water proton MR signal. Some are intended primarily to generate iron-weighted contrast for the qualitative assessment of tissue iron. More commonly, the methods are designed to quantify tissue iron concentration or some other property of the iron distribution.

All such methods are approximate, since the MR signal is always influenced by other tissue properties (e.g., dipolar interactions and the water diffusion coefficient) that are difficult to fully account for. Quantification is further confounded by the fact that the spatial pattern of tissue iron deposition is often complex and varies with tissue type and pathology [2,3]. In addition, ferritin and hemosiderin iron can alter the MR signal in significantly different ways [4], implying that a single MR parameter may not always be sufficient for accurate quantification. Caution should therefore be exercised in applying any of these techniques, and their applicability should not be assumed beyond that established empirically. In particular, the accuracy of MRI iron quantification methods may depend sensitively on such things as the main magnetic field strength, the tissue type, and the details of the sequence (e.g., echo times). Nonetheless, impressive correlations between MR parameters and tissue iron concentrations have been demonstrated by a number of studies [5-8].

Below we summarize several of the MR methods that have been used for iron detection and quantification. Each has its own advantages and disadvantages, which should be carefully considered when selecting one for a particular application. When feasible, the use of more than one approach may be helpful.

Gradient Echo Sequences

Gradient echo sequences (GES) are simple, fast, and universally available. Iron concentration quantification has been performed using signal intensity ratios between target and control regions [9], but recent work is mostly based on the R2* relaxation rate calculated from monoexponential fits to the GES signal decay [10]. The use of a relaxation rate eliminates the need for a control region, which is a potential source of error due to signal intensity variations caused by flip angle errors and other non-iron-related mechanisms. Both single echo and multiple echo GES can be used for R2* estimation, with the multiple echo approach usually being more efficient and accurate. For iron quantification, R2* is normally taken to be linearly related to the iron concentration, an assumption supported by several studies [6,8,11].

An important issue with GES is that the signal decay is altered by macroscopic field gradients due to interfaces between tissue and air [10]. This effect depends on the dimensions of the imaging voxel, increasing with voxel size. Thus, small voxels are preferred, although these can cause signal-to-noise problems especially for highly iron loaded tissues. Macroscopic gradients can also lead to non-monoexponential signal decay, rendering the calculated R2* dependent on the details of the selected echo times and fitting procedure.

Since the GES phase is very sensitive to iron, it can be exploited to enhance the detection of iron, as is done in susceptibility-weighted imaging [12]. Although technically challenging, GES phase maps can also be used to calculate the full magnetic susceptibly distribution, which provides another approach to iron quantification [13].

Spin Echo Sequences

Spin echo sequences (SES) have the important advantage of being insensitive to macroscopic gradients, thus overcoming a principal disadvantage of GES. However, the image acquisition times may be substantially longer. Iron quantification is normally achieved by calculating the relaxation rate R2, and utilizing a mathematical relationship between R2 and iron concentration [5,6,8,10]. This relationship has often been assumed to be linear [8], although careful studies have shown that this is not true for iron overloaded liver [5,6]. R2 can be obtained from either single echo SES or multiple echo SES. The former approach is more robust with respect to radiofrequency (RF) pulse imperfections, but the latter is much more time efficient and convenient. When using multiple echo SES, care should be taken to minimize flip angle errors by, for example, increasing the refocusing slice thickness to about three times that of the selection slice thickness [14].

The simplest approach for calculating R2 is with a standard monoexponential fit. However, SES signal decay can deviate noticeably from a monoexponential form, particularly in iron overloaded tissues, and more complicated fitting models have also been employed [4,5,15]. It is also important to bear in mind that R2 estimates may be influenced by the choice of echo times and the water diffusion coefficient of the tissue [3]. This is because the degree to which spin dephasing caused by microscopic field inhomogeneities is refocused depends on the ratio of the diffusion length between RF pulses and the characteristic length scale of the inhomogeneities.

One recently proposed approach exploits the differing effects of ferritin and hemosiderin iron on multiple echo SES signal decay to separately quantify ferritin and hemosiderin iron in liver and heart [15,16].

Asymmetric Spin Echoes

In brain, asymmetric spin echo sequences (ASES) have been also used for iron quantification. With a fixed refocusing pulse time but multiple signal readout times, both R2* and R2 can be estimated with a single sequence [17]. This permits the relaxation rate $R2' \equiv R2^* - R2$ to also be calculated. An advantage of R2' is that it is less sensitive to dipolar interactions than either R2* or R2 and therefore potentially more specific to tissue iron. However, R2' is affected by macroscopic gradients in the same way as R2*.

Another approach for using ASES is to fix the readout time and vary the timing of the refocusing pulse. This allows for the determination of a quantity referred to as the magnetic field correlation (MFC) [18,19]. The MFC is the average temporal correlation between the magnetic fields experienced by a water proton at two different times. Since this correlation is believed to be determined mainly by iron-generated

magnetic field inhomogeneities, the MFC provides another metric for characterizing tissue iron. Advantages of the MFC are that it is independent of dipolar interactions and that the contributions due macroscopic and microscopic inhomogeneities may be conveniently distinguished.

Noise

Because tissues with high iron concentrations have rapid signal decay, an important practical issue for all MRI iron quantification methods is proper consideration of the effect of noise on parameter estimates. In order to minimize noise related errors, either low signal-to-noise ratio data points should be systemically eliminated from the data fits or an appropriate noise model should be used. If one of these procedures is not employed, then large errors in iron estimates may result.

Summary

MR signal decay is very sensitive to tissue iron and a variety of MR methods for detecting and quantifying iron have been developed. Some of these have demonstrated a high correlation with tissue iron under specific experimental conditions. However in general, the relationship between the MR signal and quantitative aspects of tissue iron is complicated. As a consequence, most techniques have a limited domain of validity, depending on the details of the MRI sequence, and they rely on tissue specific empirical calibration parameters. Judgment should therefore be exercised when selecting any particular approach and interpreting its results. The simultaneous application of two or more independent MR iron quantification methods may improve both the sensitivity and specificity to tissue iron alterations associated with pathology.

References

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