

Role of Magnetic Resonance Imaging in Myocardial Iron Assessment

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Abstract: Myocardial iron overload is a common finding in iron storage diseases like β -thalassemia. It is due to frequent transfusions and occurs despite chelation therapy. Cardiac complications (heart failure and arrhythmias) lead to early death. MRI can offer a noninvasive index for heart iron deposition, before overt clinical and echocardiographic picture of heart failure takes place. Tissue iron is detected indirectly by the effects on relaxation times of ferritin and hemosiderin iron, interacting with hydrogen nuclei. Paramagnetic ferritin and hemosiderin iron shorten proton relaxation times, particularly T2 and T2*. Conventional MRI measurements are affected by iron excess, the instrumentation used, the applied field strength, the repetition time used in the imaging sequence, and other technical aspects. Myocardial T2* seems to be the most sensitive and easily reproducible index of myocardial iron deposition. However multicenter trials are needed for further evaluation of this technique.

Keywords: MRI, myocardial iron, thalassemia.

Myocardial iron overload is a common finding in many diseases, including hereditary hemochromatosis, sickle cell disease, aplastic anemia, myelodysplasia and β -thalassemia. The gene frequency of β -thalassemia is 0.1 in several countries, including Italy and Greece. The disease is also prevalent in India, Africa (and African Americans) and certain parts of Asia and the south Pacific [1]. The homozygous form of β -thalassemia (Cooley's anemia) is the most severe form of congenital hemolytic anemia and it is the first cause of cardiac death in people under 35 years in the above mentioned areas [2]. Patients usually require regular transfusions to survive beyond the second decade of life. Although this intervention prolongs survival [2], the chronic administration of large amounts of blood combined with extravascular hemolysis and an increase in the intestinal absorption of iron inevitably leads -despite chelation therapy - to significant hemosiderosis, which can affect cardiac function. In fact, cardiac complications, such as heart failure and arrhythmias are the major cause of death in patients with thalassemia [3,4].

Although β -thalassemia major is traditionally considered as an iron storage disease, it is not a simple haemochromatosis, but a combination of chronic hemolytic anemia, iron storage disease and myopericarditis, which is possibly related to high incidence of infections due to abnormalities of the immune system [5]. The role of myocarditis has been reported as an important factor in the development of heart failure in these patients [6].

Therefore, it is imperative to document precisely the myocardial iron deposition in order to understand the role it plays in the pathogenesis of heart dysfunction. Clinically it is difficult to predict at an early stage, which patients are at high risk of dying from iron related heart failure. Many indirect indices such as serum ferritin, liver biopsy, ECG and

echocardiograms have been proposed (Table 1). The measurement of plasma ferritin provides an indirect index to estimate the body iron stores, but the usefulness of this measurement is limited by many common clinical conditions in which plasma ferritin is not a reliable index of body iron. Serum ferritin is influenced by many factors like inflammation, fever, liver disease, infections, hemolysis, ineffective erythropoiesis, and ascorbic deficiency [7]. Although liver biopsy generally represents total body iron load, it does not reflect myocardial iron deposition, which usually takes place later and in a lesser degree compared to liver [8]. Additionally it is an invasive procedure, which can not be repeated for routine follow-up. Some studies suggest that maintenance of serum ferritin below 2500 mcg/l is satisfactory [9], but many patients with ferritin below this level have died from heart failure. Echocardiography does not detect iron deposition and it is a late indicator of heart involvement in β -thalassemia, revealing the cases where impaired heart function is already present [10]. Furthermore hyper-density on CT scan is not specific for iron [11].

The magnetic dipole moment is the main concept underlying in both MRI and magnetic susceptometry performed by superconducting quantum interference device (SQUID). In an applied magnetic field, all magnetic dipole tend to align their axes. The magnetic susceptibility of a tissue is determined by the strength of the magnetic response evoked in this tissue by an applied magnetic field [12]. This property is much simpler than the resonance behavior in MRI. In a steady applied magnetic field, all materials respond with an induced magnetic field on their own. This response can be used diagnostically, because the magnitude of the induced magnetic field varies greatly in different materials. In a measurement of hepatic magnetic susceptibility *in vivo*, the opposing diamagnetic (tissue) and augmenting paramagnetic (ferritin and hemosiderin iron) responses are superimposed. The diamagnetic effect of liver tissue is small and constant. Consequently, the observed resultant magnetic susceptibility may be used to count the iron storage present. Using this technique, the determination

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Table 1. Comparison of Various Approaches to Heart Iron Overload Evaluation

Method	Advantages	Disadvantages
Serum ferritin	-available -easy -cheap	-non-specific for heart -influenced by other conditions
Liver biopsy	-total body iron estimation	-invasive -not related with heart iron
ECG	-available -easy -cheap	-late index of cardiac dysfunction -not related with heart iron
ECHO	-available -easy -cheap	-late index of cardiac dysfunction -not related with heart iron
CT scan	-available	-not related with heart iron
SQUID	-best standardized non-invasive index for liver iron	-limited availability -application for the study of heart iron pending
MRI-T2	-non-invasive -available	-field effect in higher fields -cost
MRI-T2*	-non-invasive -available -applicable also in higher fields -high sensitivity	-lack of a universal standardized protocol -cost

of the magnetic susceptibility of the liver provide a direct measurement of hepatic iron. SQUID is at present the only noninvasive technique for measurement of tissue iron stores that has been calibrated, validated and used in clinical studies, but the complexity, cost and technical demands of the liquid-helium-cooled superconducting instruments required, have restricted clinical access to the method. Additional research is needed to develop biomagnetic susceptometry to measure iron concentration in the heart, that is not applicable at the moment [12]. It is clear from the above that there is a need for a noninvasive, easily reproducible index, capable of accurately, detecting the iron stores of an individual organ and the total iron burden in an individual patient. That would provide a means to relate iron deposition to the other clinical findings and to evaluate the effectiveness of chelation therapy regimens.

Magnetic resonance imaging (MRI) uses the magnetic properties of human body to provide pictures of any tissue. Hydrogen nuclei are a principal constituent of body tissues in water and lipid molecules. A hydrogen nucleus produces a dipole moment (magnetic field) that can interact with an external magnetic field. MRI machines generate a strong, homogeneous magnetic field by using a large magnet made by passing an electric field through super-conducting coils of wire. Patients placed in a horizontal cylinder are exposed to the magnetic field. Hydrogen nuclei in the body, which normally have randomly oriented spins, align in a direction parallel to the magnetic field. The MRI machine applies short electromagnetic pulses at a specific radio frequency (RF). The hydrogen nuclei absorb the RF energy and precess

away from equilibrium. When the RF pulse is turned off, the precessing nuclei release the absorbed energy and return to the normal. The strength of the signal varies, depending on the applied RF magnetic fields. A tissue examined returns to normal in the longitudinal plane over a characteristic interval called the T1 relaxation time. In the transverse plane, the return to normal occurs over a characteristic interval called T2 relaxation time. These values may also be expressed as relaxation rates, R1 (1/T1) and R2 (1/T2).

Using MRI, tissue iron is detected indirectly by the effects on relaxation times of ferritin and hemosiderin iron interacting with hydrogen nuclei. The precise detection of iron deposition is difficult. Hemosiderin and ferritin, the iron storage proteins, are mainly intracellular. Both ferritin and hemosiderin have about 2000 Fe³⁺ ions per molecule and each ion has five unpaired electrons. Because both are super-paramagnetic, all electrons of each particle are parallel to each other. However, their common direction fluctuates rapidly, and only the average magnetization can be observed. Due to this property of iron storage proteins, magnetic resonance imaging (MRI), a noninvasive technique, has been applied to detect iron deposition in liver and brain [13, 14]. The presence of iron in the human body results in marked alterations of magnetic resonance observed tissue relaxation times [15, 16]. Decreases observed in T1 relaxation times have been attributed either to paramagnetic enhancement [13] or to alterations of hydrated tissue proteins [17]. Decrease in T2 relaxation times is caused by dephasing of water protons as they diffuse through field inhomogeneities created by magnetic bodies –in this case ferritin molecules

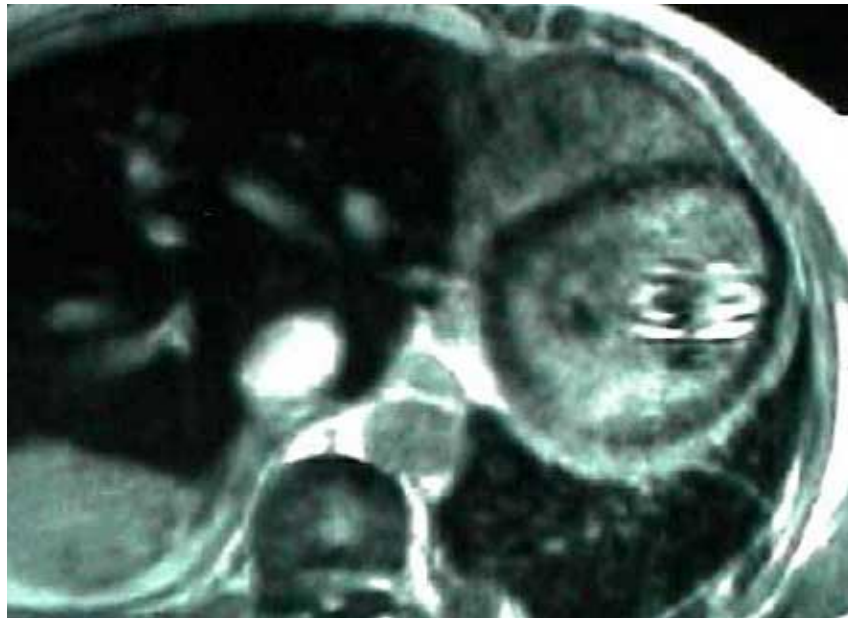


Fig. (1). A spin-echo T2 image of a patient with heavy heart iron overload examined in 1.5T system, using commercially available echo times. Signal of myocardium is equal to liver and to background noise.

[18]. While T1 decreases only moderately, T2 demonstrates a substantial decrease [19]. Myocardial T2 in experimental animals has been shown to have an inverse correlation with myocardial iron content [20]. Such observations have not yet been made in humans. In a preliminary study from our group that compared myocardial T2 with iron content in heart biopsy, an agreement was found between biopsy and MRI especially in patients with higher levels of myocardial iron [21]. Unfortunately, magnetic resonance signal is affected by multiple acquisition variables (instrumentation used, applied field strength, imaging protocol, method used to analyze relaxation curves, etc) and cannot be directly correlated to myocardial iron concentration. Thus, comparative quantitative data need to be extracted in order to determine absolute T2.

Although T2 is relatively independent of field strength, there is an exception in case of iron overload. In these patients, there is a linear dependence of T2 relaxivity ($1/T2$) on field strength [18]. Most reports have measured T2 at relatively lower magnetic fields of 0.5T, where the field effect is less [22]. Using 1.5T in another study from our group the T2 relaxation time was not measurable in the more heavily iron overloaded patients, since signal intensity approximated to background noise [23] (Fig. 1). Such T2 measurements are of limited value in 1.5T systems using commercially available software (i.e. echo times or TEs). New pulse sequences using very short TEs in 1.5T are currently under evaluation, but not yet available for widespread clinical use.

In a recent study, Anderson et al report on a new reproducible, noninvasive method for measuring liver and cardiac iron deposition, using a "T2-star" technique. A significant curvilinear, inverse correlation between iron concentration by biopsy and liver T2* was found [24]. In this study myocardial T2* measurement was performed using a single short axis mid-ventricular slice acquired at nine echo

times (TE 5.6-17.6) in a 1.5T system. A gradient-echo sequence was used and the repetition time was adjusted to the patients' heart rate. A gating delay time of 0 msec after the R wave was chosen in order to obtain myocardial images in a consistent position in the cardiac cycle, because T2* varies by small but measurable amount during myocardial contraction. Signal intensity of the heart was measured in each image and was plotted against the echo time of each image. A trendline was fitted to the resulting exponential decay curve, with an equation of the form $y=Ke^{-TE/T2^*}$ where K represents a constant, TE represents the echo time and y represents the image signal intensity.

Using a 1.5T system, spin-echo techniques suffer from motion artifacts and poor signal-to-background noise ratios. Gradient-recalled-echo (GRE) techniques have been suggested as an accurate technique to quantify heart iron overload. Although these images ("T2-star") are noisier, they are more sensitive to field inhomogeneities than spin-echo images and are useful for measuring iron concentration at lower field strengths or for measuring extremely low iron concentration at higher field strengths [25]. Myocardial iron deposition can be reproducibly quantified using T2* and this is the most significant variable for predicting a requirement for treatment of ventricular dysfunction. Heart iron deposition cannot be predicted from serum ferritin or liver iron [24]. Excellent T2* reproducibility between two manufacturers scanners supports the widespread implementation of the technique [26]. Comparing the single-breath-hold technique, used by Anderson, with the multi-echo technique for T2* measurement a close correlation was found [27]. This index has been successfully used for evaluation of patients taking oral deferiprone, which seems more effective than the conventional desferrioxamine in removal of myocardial iron [28]. Myocardial T2* seems to be the most sensitive and easily reproducible index of myocardial iron deposition available today. However, this

type of sequence is not implemented on all magnetic resonance devices. Additionally T2* measurements in more than one slice of the heart and a consensus in the T2* imaging protocol by all involved centers will increase the clinical value of the technique.

In conclusion, at present MRI provides a simple way to measure the excess iron in the body, but further efforts are needed to make this technique a clinically useful diagnostic tool. Priorities in MRI should include: a) improvement in understanding of contribution of ferritin and hemosiderin iron to magnetic resonance effects b) development of optimal methods for measuring relaxation times (best techniques for data acquisition, choice of field strength, selection of timing parameters, reduction of noise, identification of region of interest and selection analysis c) phantom studies for calibration and validation of iron concentration detected by MRI d) standardization between different laboratories e) a widely acceptable imaging protocol for iron overload evaluation. MRI can play a significant role both in the diagnosis of iron deposition in asymptomatic thalassemic patients and in the evaluation of chelation therapy. Provided the ability of MRI to perform at the same time right and left ventricular function evaluation and tissue characterization, such patients would benefit from this accurate, easily reproducible, non-invasive technique.

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