Editorial

Evaluation of Myocardial Iron Overload Using Cardiovascular Magnetic Resonance Imaging

Sophie Mavrogeni[1], Alessia Pepe[2], Massimo Lombardi[2]

[1]Onassis Cardiac Surgery Centre, Athens, Greece; [2]MRI Lab Fondazione "G. Monasterio", Regione Toscana-CNR, Pisa, Italy

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Address:
Sophie Mavrogeni

50 Esperou St.
175 61 P. Faliro
Athens, Greece
e-mail: soma13@otenet.gr

The thalassaemias are common genetic disorders worldwide and they constitute a major problem for patients, health providers and society. The term β-thalassaemia denotes a significant shortage or complete absence of beta globin chains as a result of decreased or absent function of one (heterozygous carrier) or both (homozygous form) β genes. The latter conditions result in an excess of a-chains, which continue to be normally synthesised, but cannot remain in solution; instead, they precipitate intracellularly, causing premature erythroid cell death (ineffective erythropoiesis in the marrow and severe haemolysis in the peripheral blood). The end result is severe anaemia (thalassaemia major or Cooley's anaemia) and the patients need to be transfused for life. The incidence of thalassaemia varies greatly across the world; it is higher in the Mediterranean countries, the Near-Middle East and expands into India, Thailand and Southern China, where thousands of patients survive.[1]

The disease, if left untreated, is fatal in childhood. Patients usually require regular blood transfusions to survive beyond the second decade of life. This intervention prolongs survival;[2] however, the chronic administration of large amounts of blood, combined with extravascular haemolysis and an increase in the intestinal absorption of iron, inevitably leads – despite chelation therapy – to significant haemosiderosis of all organs, including the heart. Cardiac complications such as heart failure and arrhythmias are the major causes of death in these patients.[3,4]

Although β-thalassaemia major is traditionally considered as an iron storage disease, it is not a simple haemochromatosis, but a combination of chronic haemolytic anaemia, iron storage disease and myopericarditis, probably related to a high incidence of infections due to abnormalities of the immune system.[5-8] Iron cardiomyopathy is reversible, if chelation starts in time, but the diagnosis is often delayed because of the late appearance of symptoms and echocardiographic abnormalities. Once heart failure develops, the prognosis is frequently poor, with precipitous deterioration and death despite intensive chelation. In patients with transfusion-dependent beta thalassaemia major, transfusions and iron chelation therapy with desferrioxamine have significantly improved survival, ameliorated clinical features and reduced morbidity.[2,9,10] However, cardiac complications are still responsible for significant morbidity and remain the leading cause of mortality.[2] In some cases, this is due to difficulty in tolerating the chelation treatment, but it may also occur even in some patients who tolerate the chelation therapy well.[11-13] The effectiveness of chelation has improved progressively, es-

pecially during the last decade with the introduction of two oral chelators, deferiprone and deferasirox. There are now more choices with respect to the provision of iron chelation therapy. Each chelator can be given as monotherapy and deferiprone and desferrioxamine have been administered widely in combination. Conventional chelation treatment with subcutaneous desferrioxamine does not prevent cardiac iron deposition in two thirds of patients, placing them at risk of heart failure.[14-16] Additionally, desferrioxamine may cause skin reactions at the injection site or neurological side effects, particularly visual and auditory. Oral deferiprone in monotherapy or in combination therapy with desferrioxamine is more effective than desferrioxamine as monotherapy in the removal of myocardial iron.[14-19] Some recent single-arm studies have suggested that oral deferasirox once daily is effective in increasing the heart T2* signal in thalassaemia major patients,[20,21] although the only retrospective comparative study available to date showed deferasirox to be less effective than deferiprone in removing or preventing cardiac iron.[22]

Bone-marrow transplantation offers the only complete cure for β-thalassemia, but can only be applied in selected patients. Although this carries some risk of death due to the procedure itself, and in some patients the thalassaemic cells re-grow, displacing the graft, it plays an important role in treatment. After successful bone-marrow transplantation, thalassaemic patients reach normal haemoglobin concentrations using the donor bone-marrow and require no more transfusions. However, if transplantation is performed in patients with advanced disease, the correction of the thalassaemic defect is not sufficient, because they still have a degree of organ iron overload and dysfunction, acquired during the pre-transplantation years. According to recent data, serum ferritin and unbound iron binding capacity were moderately abnormal in a moderate iron loaded group 7 years after transplantation, and highly abnormal in a high-loaded group.[23] These findings confirm the presence of iron overload at the time of transplantation and support the need for iron depletion treatment after bone-marrow transplantation. There is great concern about persistent long-term iron liver overload, because it increases the risk of fibrosis, cirrhosis and hepatoma in these patients.[24]

Therefore, it is imperative to document the myocardial iron deposition precisely in order to apply targeted treatment. Using clinical criteria, it is impossible 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 echocardiographic criteria, have already been proposed. The measurement of plasma ferritin provides an indirect index for estimating the total body iron stores, but the usefulness of this measurement is limited by many common clinical conditions, such as inflammation, fever, liver disease,[25] while in addition it does not reflect myocardial iron overload.[26,27]

Liver biopsy generally represents total body iron load and also does not reflect myocardial iron deposition, which usually takes place later and to a lesser degree compared to the liver.[26,27] Furthermore, it is an invasive procedure that cannot be repeated for routine follow up. A previous study suggested that maintenance of serum ferritin levels below 2500 μg/l decreased the risk for cardiac death in these patients,[28] but many others with ferritin below this level have died from heart failure. Echocardiography is a late indicator of heart involvement in β-thalassaemia, revealing the cases where impaired heart function is already present.[29] The addition of two-dimensional speckle tracking could be a promising indirect index of myocardial iron; however, further studies are needed for documentation.[30] Additionally, some recent publications[31] claimed that the hyper-density on a computed tomographic scan, though not specific for iron, was correlated strongly with heart T2*. However, more studies are needed before final conclusions can be drawn. The superconducting quantum interference device (SQUID), a non-invasive technique for the measurement of tissue iron stores, has been confined exclusively to liver evaluation in clinical studies. Furthermore, the lack of availability, cost, technical demands, unsatisfactory correlation with biopsy, lack of heart data and suboptimal reproducibility have restricted the clinical use of the method.[32]

In view of the above, it is clear that there is a need for a non-invasive, easily reproducible index, capable of accurate detection of iron in an individual organ and in an individual patient. Magnetic resonance imaging (MRI) uses the magnetic properties of the 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 are

placed in a horizontal cylinder and 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 normal. The strength of the signal varies, depending on the RF magnetic fields applied. A tissue that is 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 the 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 haemosiderin iron interacting with hydrogen nuclei. The presence of iron in the human body results in marked alterations of tissue relaxation times.[33-37] While T1 decreases only moderately, T2 demonstrates a substantial decrease.[38-40] Myocardial T2, a parameter measured by spin-echo techniques, has been shown in experimental animals to have an inverse correlation with myocardial iron content.[40] In a study by our group that compared myocardial T2 with iron content in heart biopsy, an agreement was found between myocardial biopsy and the MRI results.[41] Unfortunately, the MRI signal is affected by multiple acquisition variables. Although T2 is relatively independent of field strength, there is an exception in the case of iron overload. In these patients, there is the linear dependence of T2 relaxivity (1/T2) on field strength.[36,42] Most reports have measured T2 at relatively lower magnetic fields of 0.5 T, where the field effect is less.[42] Using 1.5 T, the T2 relaxation time was not measurable in heavily iron overloaded patients, because the signal intensity approximated to background noise.[43]

Anderson et al[43] reported for the first time a new reproducible, non-invasive method for measuring liver and cardiac iron deposition using a "T2-star" technique. The liver T2* was determined as follows: a single 10 mm slice through the centre of the liver was scanned at eight different echo times (TE 2.2-20.1 ms). The signal intensity of the liver parenchyma was measured in each of the eight images using in-house software and the net values were plotted against the echo time for each image. A trend line was fitted to the resulting exponential decay curve, using 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. For the measurement of myocardial T2*, a single short axis mid-ventricular slice was acquired at nine separate echo times (TE 5.6-17.6 ms) using a gradient-echo sequence. A full-thickness region of interest, located in the septum—distant from the cardiac veins to avoid susceptibility artefacts—was measured in the left ventricular myocardium, encompassing both epicardial and endocardial regions. The myocardial T2* was calculated in the same way as for the liver. A significant curvilinear, inverse correlation between iron concentration by biopsy and liver T2* was found.[44] In this study myocardial T2* measurement was performed using a single short axis mid-ventricular slice in a 1.5 T system (Figure 1). Myocardial iron deposition can be reproducibly quantified using T2*. This is the most significant variable for predicting a requirement for targeted treatment of myocardial iron overload and it

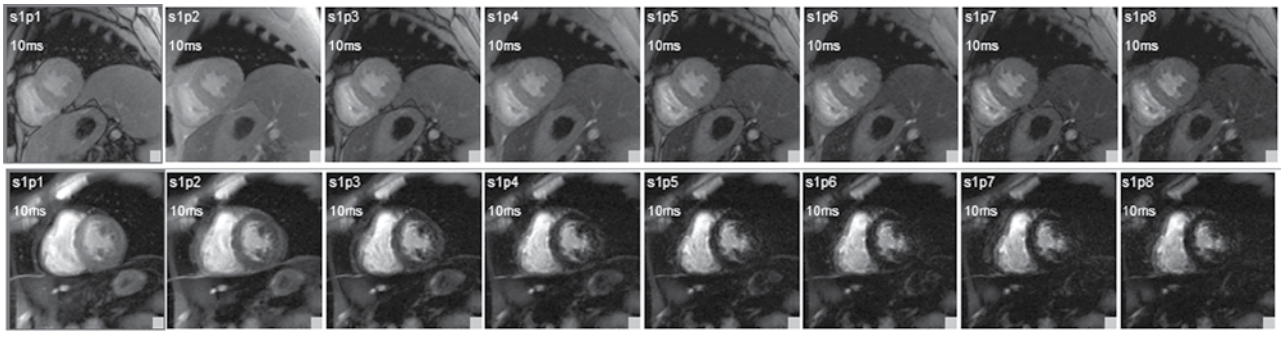

Figure 1. Left ventricular (LV) short axis using gradient-echo sequence with multiple echo times (TEs) for evaluation of T2*. It is clear that the signal intensity of the LV interventricular septum becomes darker at higher TEs due to iron deposition. The top row shows a patient with low heart iron (the heart is darker in the last images). The bottom row presents a patient with high heart iron (the heart becomes darker after the third image).

cannot be replaced by serum ferritin, liver iron or any other measurement.[15,44] Excellent T2* reproducibility among scanners from different manufacturers or different scanners from the same vendor supports the widespread implementation of the technique.[45-47] In a comparison of the single-breath-hold technique, used by Anderson, with the multi-echo technique for T2* measurement a close correlation was found.[46] Additionally, by using a multi-slice multi-echo T2* approach, it is possible to extend myocardial iron evaluation from the mid-ventricular septum to the entire left ventricle.[15,48] In fact, histological and MRI studies have previously demonstrated heterogeneous myocardial iron distribution. The application of one standardised T2* map of normal human hearts corrects for possible bias due to segmental T2* artefacts.[49] The global heart T2* value as an equivalent of heart iron showed better reproducibility than the measurement of the T2* in the mid ventricular septum[46,48] and good transferability among different scanners.[47]

The multi-slice multi-echo T2* approach, accounting for the heterogeneous myocardial iron distribution, has allowed the identification of 3 groups of patients (homogeneous, heterogeneous, and no myocardial iron overload) that are statistically different in terms of serum ferritin levels and liver iron concentration.[48] According to recently published papers, in patients with severe myocardial siderosis and impaired left ventricular function, combined chelation therapy with subcutaneous desferrioxamine and oral deferiprone reduces myocardial iron and improves cardiac function. Very prolonged tailored treatment with iron chelation is necessary to clear myocardial iron, and alterations in chelation must be guided by repeated myocardial T2* scans. Additionally, since 1999, there has been a marked improvement in survival in thalassaemia major patients in the UK, which has been driven mainly by a reduction in deaths due to cardiac iron overload. The most likely causes for this include the introduction of T2* cardiovascular magnetic resonance to identify myocardial siderosis and appropriate intensification of iron chelation treatment, alongside other improvements in clinical care. Furthermore, in comparison to the standard chelation monotherapy of desferrioxamine, combination treatment with additional deferiprone reduced myocardial iron and improved the ejection fraction and endothelial function in thalassaemia major patients with mild to moderate cardiac iron loading.[49-54] Thus, myocardial T2* has been proven to be the most sensitive and easily reproducible index of myocardial iron deposition available today. This explains why, in recent years, evidence-based medicine regarding the efficacy of chelation therapy has been viewed in terms of T2* MRI.[49-54]

Currently, cardiovascular magnetic resonance has been used for evaluation of myocarditis and other heart diseases.[55,56] Additionally, it provides the opportunity to quantify biventricular function parameters with excellent reproducibility.[57] Moreover, delayed enhancement cardiac MR is the sole non-invasive technique to detect myocardial fibrosis that has been demonstrated as present in thalassaemia major patients.[58]

In conclusion, MRI is the currently available technique of choice to measure the excess iron in the heart. It plays a significant role, both in the diagnosis of iron deposition in asymptomatic iron-overloaded patients, and in the evaluation of chelation therapy. Since MRI has the capability to perform, in parallel with iron quantification, evaluation of atrial and ventricular function, as well as myocardial fibrosis, thalassaemic patients can have, in the same examination, tissue characterisation, functional and morphological evaluation of the heart. Overall, MRI can play an important role in the treatment, follow up and understanding of the pathophysiology of iron cardiomyopathy.

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