Future challenges in the use of magnetic resonance imaging for the diagnosis of iron overload

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Dear Editor,

the review by Mavrogeni on the evaluation of myocardial iron overload using magnetic resonance imaging (MRI) provides important information on recent developments in this area both with respect to diagnosis of cardiac iron overload and the effect of chelation therapy[1].

The evaluation of cardiac iron overload using the MRI T2* and T2 relaxation time measurements appears to be the only reliable method for the diagnosis of the iron-overloaded heart. Patients with excess cardiac iron load are thought to be in danger of congestive cardiac failure, which until recently was the main cause of mortality of patients with thalassaemia major[1,2]. No other invasive or non-invasive methods, including the superconducting quantum interference device (SQUID) or serum ferritin, can be used for determining excess cardiac iron deposition[2,3].

It is now clear from MRI T2* and T2 relaxation time estimates and recent studies that, in contrast to previously accepted theories, cardiac iron load is not related to serum ferritin levels or liver iron concentration and that the latter two parameters are unreliable for estimating excess cardiac iron concentration[2,3]. This explains why in the past many thalassaemia patients suffered congestive cardiac failure and some died despite having a low serum ferritin (<1,000 μg/L), while other patients with much higher serum ferritin levels had no cardiac iron toxicity[2,3]. It is also apparent that with early diagnosis of excess cardiac iron load using MRI T2* and T2 and the prophylactic use of deferiprone (> 80 mg/kg/day) as monotherapy or in combination with deferoxamine, excess iron in the heart can be removed and the incidence of iron-induced congestive cardiac failure diminished or abolished[1-4].

New physiological mechanisms of iron deposition and removal have been identified following the introduction of MRI T2* and T2 for the diagnosis of iron overload. For example, it was found that the organ distribution of excess iron load differs between the heart and the liver of iron-loaded thalassaemia patients. Furthermore, the distribution within each organ also differs and in some cases focal points of excess iron deposition could be identified in the heart or mosaic iron distribution in the liver[1,3,5]. The heterogeneity of iron distribution within each organ suggests that liver biopsies and other techniques monitoring sections of organs, may not provide accurate estimates of excess iron load and new diagnostic criteria may be needed for more accurate iron load estimations[3]. Moreover, the heterogeneity in the deposition of excess iron in various parts of the heart, liver and other organs may be relevant to the degree of iron toxicity and the level of malfunction of each of these organs. A determination of total excess iron load by using, for example, multislice, multiecho T2* techniques could minimise errors in the estimation of excess iron load deposition caused by heterogeneous iron distribution in the various organs[1,3,5]. In this context further studies are needed to clarify the physiological and pharmacological mechanisms involved in iron deposition, organ distribution and removal, as well as the toxicological mechanisms of iron overload affecting organ function[4,5].

Despite the fact that any form of excess iron is potentially toxic, it is now apparent that not all the patients with excess iron are in danger of congestive cardiac failure and that only those patients with deposits of iron of about T2* < 9 ms are likely to be at higher risk[4]. Ultrastructural pathology studies using electron microscopy of cardiac biopsy samples from patients with congestive heart failure indicated extensive iron deposition and damage in myocytes, including disruption of lysosomes, damage to other intracellular components and loss of myofibres[4]. This

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potential mechanism of iron overload toxicity in congestive heart failure could lead to death but may also be reversible, especially if effective dose protocols of deferiprone and deferiprone/deferoxamine combination therapies are used[4]. In the latter cases excess cardiac iron load would be cleared and the patient would become asymptomatic with no further need for anti-arrhythmic and other drugs previously used for the treatment of the cardiomyopathy[4].

Although the diagnosis of iron overload of the heart and other organs by MRI T2* is generally very reliable, further standardisation is required for the methodology, techniques and the equipment to be used worldwide[3,5]. In recent studies some variability between MRI T2* and T2 in cardiac iron load estimation has been identified, suggesting that, ideally, both techniques should be used for the most accurate estimation of iron overload[3]. It has also been suggested that the factors contributing to the differences in iron load estimation between MRI T2* and T2 include the ferritin and haemosiderin composition of the excess deposited iron, which lead to signal variation between the two methods[1,3]. In general, T2* relaxation time is preferred over T2 for estimating iron overload in the heart and other organs because of the former's shorter monitoring time, ease of scanning on many scanners, lower cost and better validation of the results[3].

The high cost of the use of MRI T2* and T2 for monitoring excess iron load precludes its widespread application for the vast majority of thalassaemia and other transfusion iron-loaded patients, most of whom live in the developing countries. In developed countries, MRI for monitoring excess iron load is usually carried out once a year. The intervals of monitoring can be extended to 2 or 3 years for patients who have achieved and maintained normal range serum ferritin, as well as normal cardiac and liver MRI T2* and T2 relaxation times following the effective use of the deferiprone/deferoxamine combination or deferiprone monotherapy[4].

Future challenges in the use of MRI are the diagnosis and standardisation of iron overload in other organs such as the pancreas and pituitary gland, affecting the production of insulin and other hormones. Similarly, iron deposition in the knees, which may be related to the arthropathy observed in iron-loaded patients, and localised excess toxic iron in the brain, kidneys or other organs, which affects many other important physiological functions, may also be considered for future investigations.

Overall, MRI T2* and T2 relaxation times could be used as a diagnostic method for monitoring excess iron load in the heart and other organs in regularly transfused and other iron-loaded patients[3,5]. These techniques could also be used for monitoring the ferrokinetic profile of iron deposition and iron removal during chelation therapy. This approach could help in the adjustment of dose protocols and the selection of appropriate chelation regimens for the optimisation of chelation therapy and the reduction of iron overload toxicity as well as the associated morbidity and mortality observed in thalassaemics and other transfused patients.

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