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EDITORIAL COMMENT

T2* Magnetic Resonance: Iron and Gold†

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As a clinician, it is important to never underestimate the power of basic science to deliver new answers to old questions. At the outset of the development of magnetic resonance (MR), scientists demonstrated differences in magnetic relaxation between normal and malignant tissues that were of significant interest, although only clinically exploited later through MR spectroscopy. Some 30 years on, the fundamental magnetic properties of tissues are once again becoming more interesting in a range of diseases. The most relevant relaxation parameter is T2* (pronounced T2 star), which has the valuable property of being shortened in tissues containing particulate iron, which disturbs the local magnetic microenvironment. Although T1 and T2

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are also shortened by particulate iron, the relaxation effects are less marked. T2* is not significantly affected by elemental iron in solution, such as nontransferrin-bound iron. Conditions in which this T2* is relevant include reversible neurological dysfunction in Freidreich's ataxia (1), hemorrhage into atherosclerotic plaque (2), hemorrhage into myocardium during infarction (3), and myocardial siderosis. In these conditions, the abnormal distribution of iron is a measurement and treatment target. Most importantly, currently T2* can be used to investigate a wide range of conditions of abnormal cardiac iron deposition, including the obligatory transfusion-dependent hemoglobinopathies such as beta-thalassemia major, the less frequently transfusion-dependent sickle cell disease, and rarer hematological conditions that cause myocardial siderosis such as sideroblastic anemia and Blackfan-Diamond syndrome. Thalassemia patients are the most common group, and the best studied. These patients are typically transfused 2 U of blood/month, which leads to a 5 to 6 g iron load/year, which humans (unlike some animals) are unable to excrete. The iron is therefore deposited throughout the body and is compartmentalized intracellularly in siderosomes as iron particles.

These conditions (and others) may cause cardiac siderosis, but only in the long term, as the liver usually stores the overwhelming majority of excess iron. The reasons for the development of cardiac iron loading in only some patients are not yet fully clear, but probably relate to chronic chelator usage with loading and unloading kinetics that vary between tissues, and genetic factors. Cardiac siderosis manifests itself as a toxic cardiomyopathy, which is the cause of death in 50% to 70% of beta-thalassemia major patients. The onset of cardiomyopathy is insidious, and unfortunately, the diagnosis is usually masked by left ventricular ejection fractions (EF), which are in the normal range for nonanemic people. Measurement by cardiovascular magnetic resonance (CMR) in thalassemia patients, in whom cardiac siderosis has been excluded by demonstration of normal myocardial T2* values, has shown that thalassemia patients run a high EF and cardiac output at rest (4), which is attributable to the chronic anemia as thalassemia patients are typically maintained with a pre-transfusion hemoglobin in the region of 10 g/dl, which suppresses extramedullary hematopoiesis but minimizes the iron-loading transfusions. The unexpected consequence of this is that asymptomatic left ventricular

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dysfunction may be advanced before being recognized. The clinical course of progression to decompensated heart failure may be catastrophic, with patients entering a vicious cycle of rapidly deteriorating cardiac function that is assumed to be the result of massive release of toxic elemental iron wreaking intracellular havoc, and sometimes myocarditis. The trigger for decompensation often appears to be relatively trivial, including infection. Historical records suggest that quite recent cohorts of patients had up to a 50% death rate before age 35. Thus relative to patients dying from heart failure due to coronary disease in their mid-70s, we could state that such patients are losing up to 40 years of life by comparison. The tragedy of this situation is that aggressive iron chelation treatments can reverse early and even advanced myocardial siderosis (5). Therefore, what has been urgently needed is a means to identify myocardial siderosis as a much earlier stage and to do so reliably.

The assessment of myocardial iron using T2* was first proposed in 1991, and has proved useful because of its simplicity (6). Myocardial T2* is easy to measure using gradient echo imaging, which is commonly used for CMR, and can be performed in a single breath-hold of about 10 s (7). Analysis is equally fast and can be completed in 1 min. Interstudy reproducibility is excellent at 4% (8), and roll-out across the world has proved successful (9,10). Calibration of iron levels against T2* has been shown in animals and is awaited in humans (11). The normal myocardial T2* is 40 ms and has a nonparametric distribution such that normal subjects do not have values below 20 ms. Therefore, iron overload in the heart is "defined" as a T2* <20 ms, and there is a clear relation between T2* values below 20 ms and falling EF (2). In patients presenting in heart failure, 89% have a myocardial T2* <10 ms (12). Therefore, myocardial T2* values <10 ms are considered severe and an indication for increased iron chelation.

Since the introduction of this new gold standard for evaluating myocardial siderosis, there has been considerable interest in comparing T2* with more conventional measurement techniques to assess whether something more widely available, such as echo, might be useful as an alternative. The paper by Leonardi et al. (13) in this issue of *iJACC* (*JACC: Cardiovascular Imaging*) assessed the role of echo diastolic function measurement in patients with thalassemia (13). There are obvious reasons for examining this because diastolic dysfunction is considered an early marker of left ventricular impairment and is potentially more sensitive than EF. Leonardi et al. (13) found that all patients had a restrictive filling pattern and normal relaxation. There was no significant correlation between EF and E/E′ or the Tei index, and only weak correlations were found with E/A and E′. There was no significant correlation between myocardial T2* and any of the diastolic parameters measured. The work of Leonardi et al. (13) accords with and builds on previous data examining diastolic function in thalassemia. Westwood et al. (14) showed disappointingly weak relations between cardiac T2* and CMR measures of diastolic dysfunction (14), and Vogel et al. (15) found that tissue Doppler imaging showed more abnormalities in cardiac siderosis using parameters reflecting systolic contraction than diastolic relaxation.

Therefore, these data suggest that echo-based diastolic parameters should not be used to assess myocardial iron loading. The T2* CMR remains the gold standard for assessing myocardial siderosis and needs to be made available to all patients with thalassemia. This is a challenging, but not impossible, task. Validated centers now stretch from California eastward through the Mediterranean, Middle East, South Asia, Far East, and Australia. Product CMR sequences are available for 1.5-T scanners from Siemens (Erlangen, Germany), GE Healthcare (Milwaukee, Wisconsin), and Philips Healthcare (Best, the Netherlands), and European Union/U.S. Food and Drug Administration–approved T2* analysis software (CMRtools, Cardiovascular Imaging Solutions, London, United Kingdom) is available. Once early myocardial siderosis is identified, randomized controlled trials indicate that deferiprone is superior for myocardial iron removal in comparison with standard treatment with deferoxamine (16,17), and deferiprone use is linked with improved survival (18,19). Deferiprone is available worldwide, and although it is not currently licensed in the U.S., it is available within a compassionate use program. Additional randomized controlled data on cardiac efficacy using the new iron chelator deferasirox compared with deferoxamine are awaited with considerable interest, and these should be available in 2011.

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