History and Current Impact of Cardiac Magnetic Resonance Imaging on the Management of Iron Overload

John C. Wood, MD, PhD

In this issue of Circulation, researchers from the Royal Brompton Hospital and University College London have published a long-anticipated report on the ability of magnetic resonance imaging (MRI) to predict cardiac dysfunction in transfusional siderosis.1

Briefly, they report that a cardiac T2* value <10 ms had a sensitivity of 98% and a specificity of 86% for prediction of symptomatic heart failure in 1 year. Risk was graded with respect to T2*, with 47% of patients having T2* <6 ms developing cardiac failure in the same interval. Similar, but less striking, risk stratification was also observed for prospective arrhythmia risk. Metrics of total body iron stores, liver iron concentration, and serum ferritin performed little better than chance in predicting heart failure.

To place these observations in context, it is important to review iron overload and its past and present management. Iron overload is a surprisingly common clinical problem, occurring through increased iron absorption (primary hemochromatosis) or through frequent blood transfusion therapy (secondary hemochromatosis).2 Primary hemochromatosis disorders, such as hfe mutations, are relatively common in white populations. However, variable hfe gene penetrance, increased genetic surveillance, and severity of noncardiac symptoms result in fewer hereditary hemochromatosis patients presenting with iron-mediated cardiac disease. By contrast, iron cardiomyopathy remains a major cause of death in secondary hemochromatosis disorders such as the thalassemia, Blackfan-Diamond anemia, and myelodysplastic syndromes because the iron-loading rates are many-fold greater than for primary hemochromatosis.3 The hemoglobinopathies are the most common genetic disorders in the world, particularly in regions where malaria is or was previously endemic, such as the Mediterranean, northern Africa, the Middle East, and Southeast Asia. Increasing economic and ethnic globalization has increased the importance of these disorders in the United States, and their impact is increasing. Iron overload is also becoming an increasingly critical problem in myelodysplasia syndromes because novel therapeutics have markedly increased life expectancy in low- and intermediate-risk patients.

Before the availability of deferoxamine iron chelation therapy, patients receiving long-term transfusions succumbed to arrhythmias and congestive heart failure once their transfusional burden exceeded approximately 200 U, usually in the second decade of life.4 Cardiac signs and symptoms were a late finding, usually heralding death within 6 months. Birth cohorts born after routine implementation of iron chelation demonstrate steadily improved survival.5 Classically, screening for iron cardiomyopathy consisted of serum ferritin or liver iron measurements combined with assessments of cardiac systolic function. This regimen was successful in reducing cardiac deaths in the second and third decade of life.6,7 Nonetheless, iron cardiomyopathy continues to be the leading cause of death in thalassemia patients, appearing even in patients with apparently good control of their somatic iron stores.8 Some postulated that such patients were succumbing to myocardiitis, not iron cardiomyopathy, but autopsies almost inevitably confirmed severe, previously silent, cardiac iron accumulation. Cardiac biopsy was performed in some patients having decreased ventricular function or arrhythmias, but its invasiveness and variability precluded use in routine screening.

In 2001, the Royal Brompton group published its first report of the use of cardiac T2* to detect preclinical cardiac iron in 103 patients with thalassemia major. Figure 1 demonstrates left ventricular ejection fraction as a function of cardiac T2*.9 The MRI relaxation time, T2*, is typically 37±5 ms in normal subjects but shortens in the presence of iron. A lower cutoff of 20 ms has generally been used to eliminate false-positive diagnosis from motion and magnetic susceptibility artifacts as well as possible contributions from fluctuations in deoxygenated hemoglobin concentration. The authors made 6 key observations in their seminal article: (1) All patients lacking detectable cardiac iron had normal cardiac function. Thus, a T2* >20 ms yields a high negative predictive value. (2) Thalassemia patients lacking cardiac iron appeared to have higher ejection fractions than population norms. This was confirmed in a subsequent study and likely reflects lower cardiac afterload and greater cardiac preload associated with chronic anemia.10 (3) There was a graded negative relationship between cardiac T2* and cardiac ejection fraction as T2* decreased below 20 ms, indicating an association between increased cardiac iron and cardiac dysfunction. (4) Many patients with detectable cardiac iron exhibited normal cardiac function, which suggested that T2* was identifying preclinical iron deposition. (5) Iron appeared to clear more quickly from the liver than from the heart. In a subsequent study, the effective half-life of cardiac iron clearance in response to continuous deferoxamine therapy was found to be 13.5 months compared with 1.4 months for liver iron reduction.11 (6) Lastly, no statistical association was observed between cardiac and liver iron concentration or serum ferritin.

This final observation was particularly challenging to the thalassemia community, and the authors faced severe criticism when they used T2* methods to compare chelator efficacy (see letters to the editor that follow their 2002 case–control study.12
In response to challenges raised, the authors demonstrated that T2* measurements were reproducible over time, across different T2* methods, and across different MRI platforms. Subsequently, our laboratory demonstrated that cardiac T2* is inversely proportional to cardiac iron in gerbils and in humans, as predicted by MRI relaxivity relationships. As an indirect validation, we superimposed a crude T2*–cardiac iron calibration curve against the original 2001 data points (Figure 1). Predicted cardiac iron concentration (right axis) rose sharply for T2* values <10 ms, coinciding with declining left ventricular ejection fraction. Furthermore, the predicted cardiac iron concentrations in this range matched directly measured cardiac iron concentrations in autopsy specimens. These data, combined with extensive MRI validations in liver, demonstrated that cardiac T2* reflected cardiac iron and was a robust measurement tool.

However, several puzzles remained relative to the new method. Why did cardiac and liver iron levels appear to be unrelated, when clinical studies suggested prospective cardiac risk for increased liver iron and serum ferritin? Why did some patients have high cardiac iron but low liver iron? Longitudinal comparisons of heart and liver iron are beginning to clarify these observations. One explanation is slow kinetics of cardiac iron clearance. Intensive chelation can rapidly and completely remove liver iron in 6 months, but clearance of cardiac iron may take several years, leaving patients with high cardiac iron and low liver iron. The converse situation is also common; the heart is initially spared in patients as their liver iron rises. Over time, however, patients with high liver iron concentrations are at risk for precipitous cardiac iron deposition. Figure 2 demonstrates the temporal evolution of de novo cardiac siderosis in 5 patients; cardiac R2*, the reciprocal of T2*, is a linear surrogate for cardiac iron. Each line represents 3 to 7 consecutive heart and liver iron measurements collected 6 to 18 months apart. Two patients with severe hepatic siderosis rapidly developed profound cardiac siderosis, as might be expected from survival data. Although high liver iron predisposes to cardiac iron accumulation, two patients prospectively developed cardiac siderosis despite excellent control of liver iron. Cardiac and endocrine tissues are known to have different iron uptake mechanisms and kinetics compared with the liver. Extrahepatic organs develop iron overload only when circulating transferrin becomes saturated and labile-free iron species appear in the blood. This represents a steeply thresholded process and is modulated by transfusion rate, liver iron concentration, and systemic inflammation, as well as the type and pattern of chelator usage. As a result, one can deliver iron chelation therapy sufficient to maintain overall iron balance but inadequate to suppress circulating labile iron, leading to slowly progressive cardiac iron deposition. Such patients, who accumulate cardiac iron despite neutral or negative liver iron balance, require either higher drug dosages, longer drug exposure, or addition of a second chelating agent. Thus, while controlling total body iron stores remains an important goal of iron chelation therapy, MRI surveillance of extrahepatic tissues remains essential to exclude maldistribution of iron to sensitive target organs.

A second puzzle was the observation that some patients with low T2* were asymptomatic whereas others were in heart failure. The key was recognizing which iron species MRI...
detected. We demonstrated that dispersed iron-loaded ferritin molecules produce little MRI relaxation; free inorganic iron molecules have even lower influence. However, attaching the same amount of ferritin to 800-nm synthetic liposomes increased the relativity (lowered the T2*) 6-fold. Thus, MRI T2 and T2* measurements primarily detect lysosomally stored iron in the form of hemosiderin, not ferritin or free iron. Cardiac arrhythmias and dysfunction are caused by labile inorganic iron, not ferritin or hemosiderin. As a result, some patients with heavy cardiac iron burden may be initially asymptomatic. However, labile iron stores are in equilibrium with short-term (ferritin) and long-term (hemosiderin) buffering mechanisms. Consequently, cardiac T2* conveys high relative risk for prospective development of iron cardiomyopathy.

The third, and related, puzzle was how a clinician should respond to T2* measurements that were highly abnormal (<10 ms) when patients were asymptomatic and had normal cardiac testing. Did low T2* convey prospective risk of heart failure? Should one stay the course unless cardiac dysfunction appeared? Intuitively, this latter approach was unappealing. Although cardiac dysfunction may be entirely reversible when detected on routine screening, rescue chelation therapy requires 2 to 5 years of strict and arduous compliance with continuous deferoxamine infusion. Mortality was universal in patients unable or unwilling to maintain intensified chelation (21% of all patients with asymptomatic dysfunction). The present work strongly suggests that patients with cardiac T2* <10 ms should preemptively undergo chelation intensification regardless of ejection fraction. Although controlled studies are lacking, early recognition of cardiac iron appears to be translating into improved survival.

Taken together, all evidence indicates that cardiac T2* measurements are reproducible, transferable, and strong predictors of clinical outcome. They represent robust and sensitive metrics for clinical trials of iron chelation therapy and should become the standard of care for all patients receiving long-term transfusions. Unfortunately, technical barriers to widespread implementation still exist. Although all major MRI vendors have pulse sequences capable of generating T2* images on their newest software releases, the cost is prohibitive for many centers, and the software is incompatible with older hardware. Commercial postprocessing software approved by the US Food and Drug Administration is available (CMR Tools, London, UK), but annual licensing fees may be prohibitive for some institutions. Offline analysis packages are also offered by some vendors, but these have not been extensively validated to date. Nonetheless, increasing awareness of the prevalence and clinical consequences of iron overload in hemoglobinopathies, myelodysplasia, cancer, and hemochromatosis has increased market pressure for “push-button” T2* measurements. As these techniques permeate regional hospitals over the next 5 years we will witness the translation of a novel research idea to the clinical standard of care.

In summary, the authors should be commended not only for an excellent article but for changing the management and outlook of an important international disease. The present article culminates almost a decade of creative and systematic exploration of the role of cardiovascular MRI in the management of transfusional siderosis.

Disclosures
Dr Wood’s work is supported by the General Clinical Research Center at CHLA-USC (NIH #RR00043–43), NHLBI (1 R01 HL075592–01A1), and the Centers for Disease Control (Thalassemia Center Grant U27/CCU922106). Dr Wood receives research funding from Novartis.

References
History and Current Impact of Cardiac Magnetic Resonance Imaging on the Management of Iron Overload
John C. Wood

Circulation. 2009;120:1937-1939; originally published online November 2, 2009;
doi: 10.1161/CIRCULATIONAHA.109.907196
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/120/20/1937

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/