Cardiac MR Imaging to Probe Tissue Composition of the Heart by Using T1 Mapping[1]

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Cardiac magnetic resonance (MR) imaging is well established as a standard of reference for evaluation of myocardial structure and function. A unique clinical role of cardiac MR is the use of late gadolinium–chelate enhancement (LGE) to define the presence of focal fibrosis or myocardial scar. Myocardial scar is most commonly observed as a result of myocardial infarction. However, nonischemic cardiomyopathies are also frequently associated with LGE. Cardiac MR can be used to classify patients with myocardial dysfunction as ischemic versus nonischemic etiology, based on LGE images. This distinction is meaningful for clinical treatment.

The LGE technique to detect myocardial scarring has a major advantage in that it is simple and robust: An inversion pulse is used to suppress normal myocardium, followed by a standard gated T1-weighted gradient echo acquisition. Recently, physicians who perform cardiac MR imaging recognized that the LGE method has a disadvantage in that the "normal" myocardium that is suppressed by the inversion pulse may actually be abnormal in many diseases. Diffuse myocardial fibrosis is a common endpoint of many disease processes, and gadolinium chelate–based contrast agents are retained in such tissues (1). Therefore, instead of nulling the myocardium by using the LGE technique, physicians who perform cardiac MR imaging also use T1 mapping to determine the actual T1 times of each element of myocardium on a pixel-by-pixel basis. Before administration of gadolinium chelate (ie, "native" T1 values), areas of diffuse myocardial fibrosis have greater T1 values than normal tissue. Ten to 20 minutes after administration of gadolinium chelate–based contrast agent, T1 values are lower than normal because of diffuse myocardial fibrosis. There is now a growing body of evidence that T1 mapping can detect early fibrosis that is not otherwise detected by the LGE method (2–5).

T1 mapping of the heart is technically demanding, and standardization of the methodologic analysis is required (6). In this month's issue of *Radiology*, Reiter et al (7) present advances in the methodologic analysis used for native T1 mapping of the heart. They studied 40 healthy volunteers (20 men, 20 women) using cardiac MR imaging. They found that left ventricular global and regional T1 times varied significantly between systole and diastole, which is in agreement with previous observations by Kawel et al (8). Diastolic values of T1 were slightly greater (by about 20 msec) than systolic T1 values; women had greater T1 values than men. The sex difference in T1 values was proportional to the T1 time of blood; on average, women have a lower hematocrit than do men, which results in higher T1 values of blood in women than in men, and theoretically results in higher myocardial T1 values. Together, these observations led the authors to conclude that the diastolic and systolic differences in T1 values may be because of greater blood volume within myocardial tissue during diastole.

A key element that is missing in this line of reasoning is that hematocrit values are not reported by Reiter et al (7). In theory, the difference in fluid fraction of the blood (quantified by the hematocrit) could be used to estimate the effect sizes that we might expect in T1 values between men and women, as well as for diastole versus systole. An alternate explanation for differences in T1 time between systole and diastole could be partial volume effects at the edge of the myocardium. Unless regions of interest are drawn several pixels away from the endocardium, noncompacted and trabecular myocardium will increase the T1 values because of partial

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Conflicts of interest are listed at the end of this article.

See also the articles by Reiter et al and Thuny et al in this issue.

volume averaging from the blood pool (9). Partial volume averaging is more likely for thinner myocardium during diastole versus during systole. The partial volume effect could be easily evaluated by careful definition of narrow regions of interest that are clearly within the myocardial borders.

Reiter et al (7) suggest that an approach to correction of this blood pool effect is to normalize the noncontrast T1 values to blood pool. The advantage of this approach is to eliminate the systolic and diastolic difference in T1 and much of the sex difference between men and women. Unfortunately, currently there are several disadvantages to taking this approach. Besides that there is no quantification of hematocrit effect, the data of Reiter et al (7) are based on 20 young men and women with an average age of 23 years. Patients with disease are frequently older and may have considerably different hematocrit, renal function, body composition, and heart rate, all of which are known to affect T1 measurements. Until the hypotheses of the authors for native T1 value correction can be established in several diseased populations, we suggest that the major value of this work is to highlight the need for sex-specific reference populations. T1 mapping data should be stratified by sex or by performing sex-age–adjusted analyses. In addition, this work of Reiter et al (7) emphasizes the need to standardize the reporting of T1 values obtained during diastole versus systole and the expected regional variation that can occur if global values are not reported.

The attraction of T1 mapping is the opportunity to identify early myocardial fibrosis that is not otherwise assessed by circulating biomarkers (10) at an early, treatable stage. Also in this issue of *Radiology*, Thuny et al (11) eloquently demonstrate that T1 mapping detects left ventricle involvement in early systemic sclerosis (SS). In late-stage SS, cardiac MR with LGE was previously known to be effective in identification of myocardial scar (12). Thuny et al quantified T1 values as a ratio of pre- and postgadolinium chelate–enhanced values of blood and myocardium, corrected for hematocrit (ie, extracellular volume fraction [ECV]). The authors evaluated ECV by using cardiac MR imaging for 33 consecutive SS patients who had normal echocardiographic images and no LGE in cardiac MR imaging. These patients were compared with 16 age-matched healthy control subjects. SS patients had significantly greater global ECV and greater regional ECV for all basal and midventricular left ventricle segments. ECV measures were related to subtle abnormalities of diastolic cardiac function, as measured with echocardiography. Global ECV significantly correlated with left atrial volume and grade of diastolic dysfunction. Early detection of presumed diffuse myocardial fibrosis (no biopsy was available in the study) may help guide therapy, especially because the majority of SS patients have clinically silent myocardial disease (13).

The study by Thuny et al (11) compared with that of Reiter et al (7) draws attention to current research focused on the optimal method to quantify T1 mapping results. The ECV expresses the proportion of the myocardium that represents interstitial space versus cellular space. With greater fibrosis, the interstitial component increases relatively to the cellular space. Gadolinium chelate distributes only to the extracellular space and appears to be retained preferentially in areas of collagen or scarring. Thus, in the presence of disease, native T1 is increased, T1 weighting after administration of gadolinium chelate is decreased, and ECV is increased. Published validation studies that use each of these variables (native T1, T1 weighting after enhancement with gadolinium chelate, and ECV) in relationship to histologic analysis and diseases are limited. ECV has been a particularly attractive variable to quantify myocardial fibrosis because it normalizes for blood pool and hematocrit. However, ECV incorporates five different variables into its computation, each with an associated measurement error. If the errors in these variables accumulate, ECV could be insensitive for disease detection.

An additional concern is that ECV has a wide range of normal values, from about 23% to 30% (14). This range may overlap with ECV values in early disease. Thuny et al (11) report very small differences of about 1% in ECV between, for example, women who are control subjects (29.2%) versus women who are patients (30.5%). This compares to the reproducibility for ECV of about 2%–3%. Thuny et al clearly show that the mean ECV values for SS patients are significantly different from those for normal control subjects. However, is the ECV value for an individual sensitive patient enough to identify early disease? Since myocardial biopsy is almost never performed in early disease, as was the case for the study by Thuny et al, the question of sensitivity of ECV must be resolved.

In conclusion, cardiac MR imaging methods to noninvasively identify diffuse myocardial fibrosis have great potential to characterize and quantify early disease. Myocardial fibrosis is a common endpoint of many chronic myocardial and systemic diseases (15), and it is not available by other noninvasive tests. T1 mapping methods have adequate power with relatively small sample sizes to determine change in T1 mapping parameters over time or as a response to therapy (14). Further work in the field is ongoing to determine which disease processes may benefit from T1 mapping and which parameter or parameters (eg, native T1, T1 after gadolinium chelate enhancement, ECV) are most sensitive and specific to identify the presence or absence of disease and its extent.

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