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EDITORIAL COMMENT

Detecting Diffuse Myocardial Fibrosis With CMR

The Future Has Only Just Begun*

Theodoros D. Karamitsos, MD, PhD, Stefan Neubauer, MD
Oxford, United Kingdom

The development of late gadolinium enhancement imaging (LGE) in the late 1990s revolutionized the clinical application of cardiovascular magnetic resonance (CMR) in ischemic and nonischemic cardiomyopathies (1). Not only has the identification of even small subendocardial myocardial infarcts become possible due to the unsurpassed spatial resolution of the technique, but also specific patterns of fibrosis have enabled a detailed phenotypic characterization of many nonischemic cardiomyopathies (2). More recently, the prognostic capability of LGE-CMR to predict adverse outcomes has been demonstrated (3,4). However, as with every imaging technique, significant limitations of LGE soon became apparent. One inherent limitation is that LGE relies on the signal intensity difference between fibrotic and normal myocardial tissue, and hence a region of "normal" nulled myocardium is needed as a reference to detect abnormalities (5). This limits the ability of LGE to detect diffuse, homogeneously distributed fibrosis, which, according to histopathological studies, is a main feature in many forms of heart disease (6,7).

See page 672

An exciting recent development in CMR is the advent of techniques that provide quantitative information on diffuse myocardial fibrosis (8). These techniques measure the intrinsic magnetic resonance relaxation parameter T1 of the myocardium and map its spatial distribution (T1 mapping). The measured differences in R1 (= 1/T1) values pre- and post-gadolinium contrast allow quantification of the myocardial extracellular volume fraction (ECV), which is increased in the presence of diffuse fibrosis (9–13). Currently, there are 3 CMR techniques of ECV quantification, which differ in the way in which they account for the confounding effect of contrast kinetics (8). The first method, pioneered by Kellman and Arai (13), assumes that after sufficient time has lapsed, a dynamic equilibrium in contrast concentration between blood and myocardium is reached and therefore only 2 T1 measurements before and ~15 to 20 min after contrast are sufficient to measure ECV. The second technique, pioneered by Jerosch-Herold (9,12), requires multiple (typically 3 to 5) post-contrast T1 measurements spanning a 30-min period. The third technique, pioneered by Moon (10), uses a contrast bolus followed by a slow infusion for 30 to 60 min of the same contrast agent to induce contrast equilibrium between vascular and interstitial space. For all methods, a measurement of the blood volume of distribution (equal to 1-hematocrit) is needed to calculate ECV. Noninvasive calculation of ECV is an exciting new development in CMR, which opens new frontiers for research.

In this issue of *iJACC*, Neilan et al. (14) provide further insights into the distribution of ECV values in a healthy population, and they also provide histological validation of ECV measurements in mice. A multimeasurement post-contrast T1

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From the Oxford Centre for Clinical Magnetic Resonance Research, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford, United Kingdom. Financial support from the Oxford NIHR Biomedical Research Centre and from the British Heart Foundation Centre of Research Excellence was received. Dr. Neubauer is a consultant for Novartis. Dr. Karamitsos has reported that he has no relationships relevant to the contents of this paper to disclose.

mapping method was used in both humans and mice. The authors studied 32 well-defined healthy volunteers at 3-T and describe a relatively narrow range of ECV measurements (from 0.23 to 0.33, mean 0.28 ± 0.03). There was no difference in myocardial ECV between basal, mid, and apical left ventricular slices or between left ventricular segments (e.g., septum vs. anterior vs. inferior vs. lateral wall) within a slice. The interobserver and intraobserver variability and the test-retest difference of ECV measurements were small, which is important for the validity of follow-up studies. Furthermore, there was no sex-associated difference in myocardial ECV, but there was a significant positive correlation between myocardial ECV and age ($r = 0.74$, $p < 0.001$) in humans. In mice, there was a strong association between myocardial ECV and the histological extent of fibrosis ($r = 0.94$, $p < 0.001$). The authors concluded that ECV imaging is a useful index for noninvasively measuring myocardial fibrosis in vivo, thus demonstrating the promise of further application of the technique in patients with cardiovascular disease.

A major strength of this excellent study is the application of a robust T1 imaging protocol for ECV quantification, which extends a conventional CMR scan by only 5 to 10 min. Another strength is the histological validation of ECV measurements in mice, although, as the authors acknowledge, important biological differences may exist regarding the effect of aging in rodents compared with humans. The authors confirm recent data regarding the relationship between ECV and aging: Ugander et al. (13) studied 60 patients with known or suspected heart disease but no discernible LGE and measured ECV using a single pre- and post-contrast T1 protocol. They found a modest, although significant, relationship between ECV and age ($r = 0.28$, $p = 0.01$), which was, however, much weaker than that reported by Neilan et al. (14). A possible explanation for this discrepancy is that Ugander et al. (13) included patients with risk factors such as diabetes, hypertension, and hyperlipidemia, whereas Neilan et al. (14) only studied healthy volunteers. A limitation of the present study is the small sample size of the human cohort ($n = 32$), and further large-scale studies are needed to fully establish a database for age- and sex-specific normality of cardiac ECV measurements. Despite this limitation, the study by Neilan et al. (14) further expands our knowledge of ECV imaging in normal subjects and is an important contribution to this evolving field.

To date, T1 mapping/ECV results have been reported for small groups of selected patients with acute myocardial infarction (15,16), chronic myocardial infarction (16), acute myocarditis (17), aortic stenosis (18), hypertrophic cardiomyopathy (10), congenital heart disease (9), idiopathic dilated cardiomyopathy (11,12) and infiltrative heart disease (19,20). These studies have provided interesting preliminary insights into diffuse fibrosis detection with CMR, supported by histological validation in aortic stenosis, hypertrophic cardiomyopathy, and dilated cardiomyopathy. However, they have also highlighted several unresolved issues. First, and perhaps most important, the selection of T1 mapping sequence is crucial because different T1 mapping sequences have varying sensitivity to motion artifacts, heart rate, and native myocardial T1 value ranges. Newer fast T1 mapping sequences show improved clinical applicability (shorter breath-hold) and are robust even at high heart rates (21). Furthermore, with the use of rapid T1 mapping methods, current single-slice or 3-slice acquisition protocols will give way to whole-heart, multislice approaches. Most recently, non–breath-hold techniques with motion correction have also become available (22). Furthermore, T1 mapping without the use of gadolinium contrast can also detect diffuse fibrosis-associated changes (23), and this method could become particularly useful for patients with contraindications to gadolinium administration. As with every imaging method, widespread clinical applicability of ECV imaging will only become reality if current ECV acquisition methods are standardized and developed as a universally accepted rapid, robust protocol. As an imaging community, we have to embrace this challenge. Several important steps have already been made toward this goal, such as the demonstration that ECV estimation is gadolinium dose independent and that the infusion and bolus techniques yield similar ECV measurements (14,15). Post-processing, which is currently based on time-consuming manual contouring, should also improve and include contour detection algorithms. Last, ECV imaging should further expand to include hypertensive heart disease, diabetic cardiomyopathy, sarcoidosis, or other less common cardiomyopathies, bearing in mind that interstitial space expansion is not a specific response to fibrosis, but infiltration (e.g., due to amyloid deposition) or edema may also lead to ECV increases (19). Therefore, future clinical studies will need to be conducted in well-defined patient populations and provide histological validation whenever possible.

JACC: CARDIOVASCULAR IMAGING, VOL. 6, NO. 6, 2013
JUNE 2013:684–6

The future of diffuse fibrosis imaging is bright, and these exciting new developments underscore the main advantage that CMR has over other imaging modalities, namely, its ability to provide detailed in vivo myocardial tissue characterization. Diffuse fibrosis and ECV quantification may become powerful imaging biomarkers for the assessment of prognosis and for monitoring the effects of current (e.g., angiotensin-converting enzyme inhibitors, aldosterone receptor blockers) and novel antifibrotic therapies.

Reprint requests and correspondence: Dr. Stefan Neubauer, Division of Cardiovascular Medicine, Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Headley Way, OX3 9DU Oxford, United Kingdom. *E-mail: stefan.neubauer@cardiov.ox.ac.uk.*

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