Cardiovascular disease is the leading cause of morbidity and mortality in the United States. Although clinical assessment is the cornerstone of patient management, clinicians often demand additional laboratory or imaging studies to help formulate a management plan.1 There are growing, consistent data supporting an important role for noninvasive cardiac imaging studies as clinically and cost-effective tools in the diagnosis and risk stratification of patients with known or suspected cardiovascular disease. The past decade has witnessed an accelerated evolution of cardiovascular imaging, not only in its growing body of evidence to support its use, but also the development of novel technologies (eg, cardiac magnetic resonance, multidetector computed tomography, positron emission tomography) that will likely expand our ability to see more (eg, atherosclerosis, plaque morphology, myocardial tissue characterization) and possibly extend our treatment options.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Editorial

Insights Into Left Ventricular Remodeling Through Noninvasive Measures of Myocardial Matrix Expansion With Cardiovascular Magnetic Resonance

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Cardiovascular disease is the leading cause of morbidity and mortality in the United States. Although clinical assessment is the cornerstone of patient management, clinicians often demand additional laboratory or imaging studies (disease markers or biomarkers) to assess differential diagnosis and to help formulate a management plan.1 There are growing, consistent data supporting an important role for noninvasive cardiac imaging studies as clinically and cost-effective tools in the diagnosis and risk stratification of patients with known or suspected cardiovascular disease. The past decade has witnessed an accelerated evolution of cardiovascular imaging, not only in its growing body of evidence to support its use, but also the development of novel technologies (eg, cardiac magnetic resonance, multidetector computed tomography, positron emission tomography) that will likely expand our ability to see more (eg, atherosclerosis, plaque morphology, myocardial tissue characterization) and possibly extend our treatment options.

Cardiac magnetic resonance (CMR) imaging has emerged as a powerful imaging technique that allows precise tissue characterization in a wide range of myocardial disorders. Several CMR techniques have been described and used for diagnosis, risk stratification, and to guide patient management. One of the most widely used and validated approaches is the detection and quantification of late gadolinium enhancement (LGE) in myocardial tissue. Myocardial tissue characterization with LGE is one of the unique biomarkers of CMR, which reflects the relative differences in the volume of distribution of the gadolinium contrast between normal and abnormal myocardium. Gadolinium is normally confined to the extracellular space leading to a relatively large accumulation of gadolinium contrast. Recently, novel CMR T1 techniques have been described for the quantitative assessment of the full range of extracellular matrix expansion beyond what is visually evident on LGE CMR (so-called T1 mapping).2–4 The measurements derived from the pre- and postcontrast T1 measurements represent the partition coefficient for gadolinium contrast, which, in conjunction with the blood hematocrit, allows an estimate of the extracellular volume fraction (ECV). This quantitative measurement of ECV correlates modestly with histological markers of collagen volume fraction (reflecting diffuse fibrosis) in experimental animals subjected to angiotensin-2 infusions,5 as well as in humans with aortic stenosis and hypertrophic cardiomyopathy.6 It is noteworthy that under normal conditions, CMR measures of extracellular volume fraction appear to significantly overestimate collagen volume fraction. For example, in a carefully performed experimental study, Messroghli and colleagues5 showed significantly higher mean values of extracellular volume fraction by T1 mapping as compared with collagen volume fraction by pathology in control animals (17.2±4.3% versus 3.5±0.8%, respectively). Likewise, mean ECV estimates in healthy volunteers with structurally normal hearts are also reported to be elevated (≈25%).7 This suggests that ECV measures derived from T1 mapping only partially reflect diffuse interstitial fibrosis, and that they may be affected by an expansion of other components of the extracellular matrix. Indeed, the extracellular matrix is a dynamic collection of collagen and noncollagenous proteins organized in a delicate balance to provide a scaffold for myocytes, fibroblasts, endothelial cells, and vessels and facilitate proper mechanical, chemical, and electric signaling between cells.8 Furthermore, T1 measures can also be affected by an expansion of the extracellular matrix resulting from infiltrative processes (eg, cardiac amyloidosis)9–11 or myocardial edema.12 In this issue of Circulation, Wong and colleagues13 provide new information regarding an association between ECV measurements and clinical outcomes. This analysis included 793 consecutive patients undergoing CMR based on clinical grounds for the evaluation of known or suspected coronary artery disease, cardiomyopathy, or arrhythmias. They excluded patients with cardiac amyloidosis and other forms of infiltrative disease, as well as those with hypertrophic cardio-

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myocardial function. Overall, patients in this analysis had normal left ventricular function. Extracellular volume fraction was derived from pre- and postcontrast T1 measurements using an ECG-gated single shot modified look locker inversion recovery (MOLLI) technique, which has been shown to have very good reproducibility. Quantitative ECV estimates were derived from mid and basal short axis images and excluded areas of LGE consistent with classic pattern of myocardial infarction. In patients with previous myocardial infarction, however, the computation of ECV did include remote (non-infarcted) myocardial areas showing patchy, presumably non-coronary artery disease related LGE. Compared with some of the previous reports, the technique used by Wong et al accounted for the myocardial change in T1 relative to blood and the effects from patient hematocrit, thereby reducing the measurement errors introduced from contrast dosing, renal function, and anemia. Like in prior reports, the quantitative estimate of ECV ranged from 22% to 26% in healthy volunteers, whereas it ranged from 21% to 46% in the study patients. Over a median follow-up period of 6 months, 39 patients died, and 43 experienced a major adverse event (composite of death/cardiac transplant/left ventricular assist device implantation). In multivariable modeling, ECV was associated with adverse cardiac events, after adjusting for age, left ventricular ejection fraction, and infarct size. For every 3% increase in ECV, there was a 50% increased probability of an adverse cardiac event.

This is the first study describing an association between measurements of ECV and clinical outcomes in a relatively large patient cohort undergoing CMR imaging. This is an important first step in demonstrating a prognostic association of this novel CMR marker with cardiac events. However, it should be noted that the follow-up period was short and the number of adverse cardiac events was relatively limited. Compared with patients without events, those with events were older, more likely diabetics and inpatients at the time of CMR (likely reflecting a sicker group), and had lower left ventricular ejection fraction and more advanced left ventricular remodeling. Consequently, the study appears underpowered to fully adjust the multivariable models, and there is likely residual confounding in the association between ECV and adverse events. Larger studies with longer follow-up are needed to further explore the strength of the association between ECV and clinical outcomes. Such studies should be able to provide information regarding the incremental prognostic value of ECV measurements and define ECV thresholds to optimize risk prediction. This level of evidence will need to be defined in each of the common cardiac conditions included in the study by Wong et al.

Another question is whether and how the proposed measures of ECV would be able to contribute to differential diagnosis of cardiomyopathy beyond the conventional LGE technique. There is emerging evidence that ECV measures are elevated in a wide variety of cardiomyopathies, suggesting a high sensitivity to uncover structural abnormalities before LGE becomes evident. However, specificity is likely to be a challenge because, as shown in the study by Wong et al, significant overlap exists between normal and disease states, and even between different forms of cardiomyopa-

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