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Population-Associated Variance in Native Myocardial T1:

Value Added or Is There More to Come?*

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Abnormal left ventricular (LV) function is an important consequence of many forms of cardiovascular (CV) disease. Noninvasively acquired images via transthoracic echocardiography, radioisotope imaging, computed tomography, or magnetic resonance may identify abnormalities of LV systolic and diastolic function that forecast adverse CV events.[1] Somewhat uniquely, clinically available cardiac magnetic resonance (CMR) myocardial perfusion techniques, late gadolinium enhancement methods, and more recently the implementation of scanning processes that measure LV myocardial T1, T2, and T2* relaxation can be implemented during the same exam used to acquire CMR measures of LV function for the purpose of characterizing the LV myocardial tissue. In so doing, one has the capability to obtain clues to help determine why or what is responsible for the LV systolic or diastolic LV dysfunction.

Each CMR measure of LV myocardial T1, T2, or T2* signifies a different characteristic of the LV myocardium.[2] Left ventricular T2* reflects LV myocardial iron (useful for iron overload states, such as thalassemia), and LV myocardial T2 reflects LV myocardial water (often increased in acute inflammation [eg, myocarditis] or acute injury, such as seen in myocardial infarction). Elevations of LV myocardial T1 is somewhat nonspecific as it can reflect increases in LV myocardial water, fibrosis (reactive, replacement, or interstitial), or an infiltrative process, as seen in cardiac amyloidosis. Increasingly, in small- to moderate-size studies, measures of both T1 and T2 relaxation have been found helpful to diagnose a variety of conditions affecting the LV myocardium and are associated with adverse CV

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prognosis.[3] In addition, in a large cohort, LV myocardial T1 has been found to be elevated in women compared with men.[4]

To this end, in this issue of *JACC: Cardiovascular Imaging*, Raisi-Estabragh et al,[5] acquired LV myocardial T1 values obtained on widely available 1.5-T CMR scanners in 42,894 participants from the UK Biobank study. The authors examined the relationship between LV myocardial T1, traditional CV risk factors such as hypertension and diabetes, and future cardiac events. Over 3 years of follow-up, there were 402 deaths, 76 of which were attributable to CV disease and 44 to ischemic heart disease. In addition, incident diseases included 649 cases of ischemic heart disease, 243 cases of heart failure, 241 incident myocardial infarctions, and 215 cases of atrial fibrillation and stroke.

The authors noted associations between higher levels of LV myocardial T1 and the presence of heart failure, nonischemic cardiomyopathy, incident atrial fibrillation, all-cause mortality, and CV disease—and ischemic heart disease–related mortality (all ORs of 1.24 to 1.47). Also of note, overall, women exhibited higher LV myocardial T1 values than men (confirming previous results at 3.0-T from Cavus et al[4]), which tended to decline with advancing age, whereas men exhibited LV myocardial T1 values that increased over time with age. In addition, within the entire cohort, increasing LV myocardial T1 values were not associated with hypertension. This finding is somewhat unexpected given that hypertension, particularly when LV hypertrophy is present, often promotes LV myocardial interstitial fibrosis which in turn would elevate LV myocardial T1.

Although the results of this study provide a glimpse into the potential utility of CMR LV myocardial measures of T1 relaxation for identifying those at risk of future CV events, there are issues to consider if one tries to apply them for the management of individual patients. First, due to the very large sample size, there were statistically significant differences in LV myocardial T1. For example in men, the LV myocardial T1 averages ranged from 913 to 926 ms over 4 decades of life. Importantly, however, on an individual basis, one might consider these 2 average values only 13 ms apart to be nearly indistinguishable. As such, when examining an individual patient, the clinical relevance of these differences is lacking. Second, the authors did not include other information from the CMR exam. As noted, LV myocardial T1 values are often interpreted in the context of measures of LV volumes, mass, ejection fraction, and strain, measures of LV myocardial T2, perfusion or late gadolinium enhancement, and valvular function. Without that information, the clinical context is not provided for using these values to effectively diagnose a condition for which management can be appropriately directed. Third, the values were obtained on 1.5-T scanners of a specific vendor. It is known that T1 values can differ with scanner field strength, vendor, or coil and configurations. It is not clear from the data presented how the values represented here would have prognostic utility if the data were gathered in another location with a scanner from a different vendor. Importantly, the LV myocardial T1 values obtained in this study would not be applicable to those obtained at 3.0-T, for which normative ranges of LV myocardial T1 are higher.[4] Fourth, we really do not have much information pertaining to race, ethnicity, acute status of the patients (ie, the presence of heart failure), nor increasingly recognized nontraditional risk factors such as social determinants of health or chronic

psychosocial stress that are associated with systemic and perhaps cardiac inflammation. Variation of LV myocardial T1 may occur in these situations.

Fifth, statistical considerations could possibly account for the findings related to the associations observed between LV myocardial T1 and hypertension as well as serum cholesterol. Men (n = 7,818 with lower LV myocardial T1 values) were outnumbered by women (n = 11,479 with higher LV myocardial T1 values), and men exhibited much higher rates of hypertension and high cholesterol in this study than women. Therefore, when trying to examine the relationship between hypertension or cholesterol with T1 values, these observed sex-related effects may in fact be too large to simply "adjust" for by including age and sex in a logistic regression model. If the results had been stratified by sex, then one could see whether in fact within each sex the relationships between LV myocardial T1 and hypertension (or serum cholesterol levels) would have been maintained.

Also, the authors examined the prevalence of a dichotomous variable in blood pressure or high cholesterol. One challenge with modeling the prevalence of a risk factor or outcome is that it is difficult to determine the actual timing of the event. Essentially, one knows that at a particular point in time that the event (eg, hypertension) is present; however, it is not clear when this event first occurred. Therefore, it is challenging to determine a causal link between such measures (ie, T1 and hypertension) in this context. If incident hypertension (or high cholesterol) could be examined, then one could understand that a person was free of the outcome at the beginning of the study and then could determine in a longitudinal fashion whether the T1 measures were in fact associated with the eventual development of hypertension or high cholesterol. Both of these statistical challenges provide reasonable possible explanations for the counterintuitive findings concerning the relationship between T1 and hypertension and high cholesterol.

In summary, the authors are to be congratulated for performing a large study involving characterization of the LV myocardium using CMR-derived measures of LV myocardial T1. As noted, there are clearly associations with several adverse cardiac events. While some of these associations are somewhat expected, others are puzzling. Clinically, it is important to note that LV myocardial T1 values are nearly always obtained contextually with assessments of LV systolic and diastolic performance and other LV myocardial tissue characterization measures. Further research is necessary to understand the importance of LV myocardial T1 in the context of these additional measures in patients with and without known CV disease. As the use of CMR continues, more is yet to come.

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