JACC: CARDIOVASCULAR IMAGING
VOL. 7, NO. 10, 2014

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2014.05.012

EDITORIAL COMMENT

Seeing the Unseen Fibrosis in Heart Failure With Preserved Ejection Fraction*

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Heart failure (HF) is a major cause of morbidity and mortality and is a leading reason for hospitalization in older patients. The economic impact of HF is astronomical, exceeding $37 billion in the United States alone (1). Heart failure with preserved ejection fraction (HFpEF) accounts for nearly one-half of all cases of HF with a similar mortality to that of systolic heart failure (SHF) (2). Although the mortality rate for SHF has steadily declined over the past few decades with improved medical therapy, the mortality rate for HFpEF has remained high; in addition, despite numerous therapeutic trials, there are no proven therapies for HFpEF. The diagnosis of HFpEF is often clinically challenging, relying on a combination of clinical symptoms, echocardiographic criteria, and biomarkers such as brain natriuretic peptide, which all have potential limitations (3).

Cardiac magnetic resonance (CMR) is well established for the evaluation of focal myocardial fibrosis using the late gadolinium enhancement technique but cannot detect diffuse myocardial fibrosis. There has been growing interest in using T_1 mapping techniques to assess diffuse myocardial fibrosis (4). Multiple studies in patients with HF undergoing myocardial biopsy have shown an inverse correlation between the degree of histological fibrosis and the T1 relaxation time measured 10 min after gadolinium contrast injection (5,6). However, the T1 of the myocardium is a function not only of the amount of fibrosis but also of contrast dose, clearance rate, and time after injection (4). Gadolinium contrast agents, which act by shortening the T1 relaxation time of water, are confined to the extracellular space. Thus, T1 mapping techniques can be used to quantify the extracellular volume (ECV). By measuring T1 before and after either a bolus or equilibrium infusion of gadolinium, the partition coefficient and ECV can be measured (7,8). Validation of the correlation between ECV and histological evidence of myocardial fibrosis has been assessed in aortic stenosis, hypertrophic cardiomyopathy, dilated cardiomyopathy, and congenital heart disease (7,8). Increased ECV has been shown to be associated with adverse cardiovascular events (9). However, to date, there has been limited application of ECV assessment to patients with HFpEF.

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In this issue of *iJACC*, Su et al. (10) evaluated the relationship between ECV measured by T1 mapping to diastolic dysfunction as assessed by cine CMR in control subjects, patients with SHF, and patients with HFpEF (10). The authors used a variant of the modified Look-Locker inversion recovery (MOLLI) pulse sequence, which should be robust to variations in heart rate. Imaging was performed before and 10 min after gadolinium injection using the bolus method. ECV was quantified with care taken to exclude areas of focal myocardial fibrosis.

The main finding of the study was that patients with heart failure, both those with SHF and those with HFpEF, had increased ECV as compared with control subjects with the highest ECV in the cohort with SHF. Similarly, peak filling rates were significantly reduced in patients with SHF and reduced to a lesser extent in patients with HFpEF. Interestingly, ECV was correlated with peak filling rate in the HFpEF group but not in the control subjects or those with SHF. The precontrast T1 time (native T1) was not significantly different between the groups. This is not entirely unexpected because native T1 is sensitive to water in both the intracellular and extracellular compartments of the myocardium. Post-contrast T1 times were

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

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shortest in the SHF group followed by the HFpEF group and longest in healthy subjects, which is explained by the accumulation of the gadolinium contrast agent in the extracellular space. A reduction in post-contrast T1 times has also been shown in patients with HFpEF and was associated with either hospitalization for HF or cardiac death (11). Increasing ECV was associated with reduction in ejection fraction and a decrease in the peak filling rate. This suggests that ECV is sensitive to subtle changes in systolic and diastolic function, because fibrosis likely contributes to both of these components of cardiac function in patients with HFpEF.

Overall, this study was well conducted; however, there are a few limitations. The authors only used volume-time curve analysis to assess diastolic function. This concept has been validated in nuclear studies and duplicated with CMR, but these techniques are much less frequently used than established echocardiographic parameters (12). Furthermore, CMR has multiple other techniques for evaluation of diastolic function that were not studied. It would have been interesting to see if measures of diastolic functional grade by echocardiography or E/e′ measurements correlated with ECV in patients with HFpEF or SHF. Second, post-contrast imaging was only performed at 10 min post-contrast. The bolus technique requires an assumption of "equilibrium" of contrast concentrations in the myocardium and blood pool and this may take longer than 10 min, particularly in patients with increased ECV. Furthermore, the use of only a single post-contrast time precludes assessment of the validity of this assumption (13). Also, although the diastolic functional parameters correlated with ECV in HFpEF, it is somewhat surprising to see a lack of correlation among patients with SHF because these patients also have diastolic dysfunction. It is possible that this could be due to both the presence and effects of both diffuse and focal fibrosis in patients with SHF.

ECV mapping to detect diffuse fibrosis and infiltration has been a topic of intense research; however, there are multiple important issues that still need to be addressed by the field for widespread application. Although the field appears to be converging on a few acquisition strategies, there is still a lack of consensus about the optimal technique. Small biases in T1 caused by T2, off-resonance, and magnetization transfer effects limit direct comparison between different techniques and field strengths. ECV is also influenced by contrast agent concentration and the type of gadolinium contrast agent, because ECV measured by CMR is the effective volume of distribution of the contrast agent. Thus, care should be taken when comparing ECV measurements using different techniques. ECV relies on multiple T1 measurements, so inaccuracies in the quantification of T1 can propagate into the determination of ECV. Additionally, greater study will be required to determine if ECV can be used as a diagnostic tool in the management of individual patients. Further standardization and study will be required to prove diagnostic and prognostic utility, and the first consensus document on this topic was recently published (14).

The measurement of ECV could have important implications in patients with HFpEF. Elevation of ECV in patients with shortness of breath could provide additional evidence of HFpEF in patients with borderline echocardiography or biomarker findings. ECV could better define a phenotype of patients with HFpEF who may benefit from novel antifibrotic therapies. Finally, ECV could be used to track the therapeutic response of a drug or potentially serve as a surrogate marker for clinical trials. ECV mapping will likely be an important tool for helping us see previously unseen aspects of the clinically challenging pathology of HFpEF.

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KEY WORDS cardiac magnetic resonance imaging, extracellular volume fraction, heart failure with preserved ejection fraction