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EDITORIAL COMMENT

Myocardial Inflammation

An Important Pitfall During CMR T1 Mapping for the Quantification of Diffuse Fibrosis in Heart Failure*

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Heart failure is a global epidemic, affecting millions of adults worldwide. As a precondition for optimal treatment, a correct diagnosis of the underlying disease has to be made. In this respect, cardiac magnetic resonance imaging (CMR), and specifically quantification of myocardial extracellular volume (ECV) by T1 mapping, has recently attracted great interest (1). This novel technique has been developed as a tool for the quantification of diffuse myocardial fibrosis, a well-recognized hallmark in heart failure (2). ECV as measured by CMR has also been shown to provide additional mortality and morbidity information in heart failure populations with reduced (HFrEF) and those with preserved ejection fraction (HFpEF) (3,4). However, increases in myocardial free water, as occurs in acute myocardial edema and inflammation, also expand the interstitial space and hence ECV (1). T1 mapping and ECV have been shown to be sensitive to acute and chronic myocardial edema and inflammation (5). Particularly in patients with reduced ejection fraction, chronic inflammation after an episode of acute myocarditis may be present. Thus, such patients may be prone to both diffuse myocardial fibrosis and chronic inflammation. Chronic myocardial inflammation is frequently missed by clinical assessment and requires endomyocardial biopsy for definitive diagnosis. Such an invasive approach, however, is costly and carries significant risks; it will therefore not be carried out in every patient qualifying for it, even more so as therapeutic measures are limited (6). Therefore, it usually remains unknown whether chronic inflammation is present in a particular individual presenting with impaired left ventricular systolic function.

In this issue of *iJACC*, Lurz et al. (7) describe a prospective study of 107 patients with clinical suspicion of inflammatory cardiomyopathy who underwent left ventricular endomyocardial biopsy and ECV quantification by CMR. Myocardial inflammation was present in 62% of patients. Although the amount of ECV by histology was similar among patient groups with and without myocardial inflammation, ECV as estimated by CMR T1 mapping was significantly higher in patients with inflammation than in those without ($p = 0.02$). In addition, CMR T1 mapping showed a better diagnostic accuracy with regard to the amount of estimated ECV in patients without inflammation ($r = 0.72$; $p < 0.01$) than in those with inflammation ($r = 0.24$; $p = 0.06$).

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These findings add significantly to the field. They confirm the theoretical concept of ECV by CMR T1 mapping as an estimate of myocardial fibrosis but also demonstrate that the accuracy of such measurements is impaired in the presence of myocardial inflammation, which involves an expansion of the extracellular space. Assuming that various degrees of myocardial inflammation and fibrosis potentially coexist, the measured ECV will reflect a sum of these different pathologies but will not inform solely on the extent of myocardial fibrosis.

It now begs the question whether these new insights also explain discrepant findings concerning the prognostic power of CMR ECV and native T1 in heart failure patients. In patients with HFpEF, ECV but not native T1 was significantly associated with event-free survival in a recent prospective study (4). In contrast, a large-scale study of 637 patients with nonischemic dilated cardiomyopathy reported

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superiority of native T1 compared with ECV with respect to its association with outcome (8). Whether patients with unrecognized chronic myocardial inflammation were included in that study remains unknown. The Myo-Racer trial, however, reported a significant superiority of native T1 over ECV for the detection of acute myocardial inflammation in 129 patients who underwent endomyocardial biopsy in addition to CMR (5). There appear to be profound differences in the pathobiological substrates that determine event-free survival in HFpEF versus HFrEF, which may contribute to the observed discrepancies in prognostic power of ECV and native T1. Although prognosis in HFrEF is largely driven by pump failure of the left ventricle, the right ventricle is a major determinant of event-free survival in HFpEF (9,10). Right-sided heart failure in HFpEF is a consequence of altered hemodynamics due to myocardial stiffness and elevated filling pressures of the left ventricle, which are reflected by CMR ECV (4,11). In HFrEF patients, after exclusion of coronary artery disease and significant organic valve disease, both extracellular matrix accumulation and chronic inflammation may be important drivers of pump failure. Both pathologies are spotted by CMR T1 mapping but cannot be clearly distinguished from one another. Although ECV and native T1 times have been shown to be associated with prognosis in heart failure (3,8), definite cutoffs with regard to prognostic power and diagnostic accuracy are lacking.

Taken together, CMR T1 mapping is a hot topic in heart failure, with many questions still unanswered. A close cooperation of CMR imaging experts, heart failure specialists, and interventional cardiologists who take myocardial biopsy samples is needed to further define optimal clinical applications of CMR T1 mapping in heart failure patients.

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