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EDITORIAL COMMENT

How to Mend a Broken Heart?*

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Despite improvements in early survival after an acute myocardial infarction (MI), the incidence of heart failure in the longer term remains persistently high (1,2). This conundrum is vexing. On the one hand, the epidemiology reflects the advances in acute cardiovascular care and secondary prevention (3,4), and perhaps generally increasing longevity. On the other hand, the pathophysiology of left ventricular (LV) remodeling and prognosis in acute MI survivors remains incompletely understood. This problem is further illustrated by the results of recent clinical trials in which novel therapies have not been associated with improvements in cardiac prognosis (5,6). Because of the public health burden of heart failure post-MI and mixed results with new therapies, do we need to rethink the approach to risk stratification for our post-MI patients?

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In this regard, the paper by Reinstadler et al. (7) in this issue of the *iJACC* is timely. They undertook a post hoc analysis of LV function and tissue characteristics in the infarct and remote zones revealed by multiparametric cardiac magnetic resonance (CMR) scans obtained within the first week of an acute ST-segment elevation myocardial infarction (STEMI) in a cohort of 255 patients. There were 2 main results. The first was the independent prognostic importance of the tissue changes in the myocardial remote zone, as revealed by native T1-mapping, for recurrent major adverse cardiac events (MACE). The second was the proposition of an integrative approach in which data on LV function and pathology within the infarct and remote zones could be assimilated within a prognostic model for individualized prediction of cardiac prognosis. Thus, rather than a focus on 1 parameter, the totality of parameters with distinct prognostic significance for MACE were statistically modeled to optimize risk prediction over and above the prognostic value of any 1 of the parameters in isolation.

Cardiac imaging of a post-MI patient is typically focused on LV function, infarct size, and complications (8). So why might the myocardial remote zone be worthy of focused attention in the clinical report? There is extensive literature on the pathophysiological significance of the myocardial remote zone post-MI (9–12). Acute MI triggers a systemic acute phase response, and neutrophils and monocyte and/or macrophages track to the infarct and remote myocardial tissues from reticuloendothelial stores (9,10). Macrophage cytokine production represents a stress response post-MI that leads to apoptosis, extracellular collagen degradation, and loss of microvessels (9). Potentially, inflammation may be the driver for maladaptive remodeling (11,12). The magnitude of systemic inflammation is prognostically important post-MI (12), and evidence-based therapies for MI may reduce inflammatory activation (13).

So what is native T1-mapping? Human tissue has fundamental magnetic properties, including the longitudinal (spin-lattice) proton relaxation time (native T1 in milliseconds). Native T1 is influenced by water content, which binds with macromolecules and cell composition (14). Myocardial water and inflammatory cell content increases as a result of injury (15), and longer T1 times are a biomarker of tissue injury (11,12).

In a recent natural history study, we enrolled 288 patients with acute reperfused STEMI who underwent CMR 2 days and 6 months post-MI and who had a follow-up for 3 years (Figures 1 and 2 in Carrick et al. [12]). Myocardial remote zone native T1 was approximately 10 ms higher, on average, in patients with

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electrocardiographic evidence of reperfusion injury, and increased by approximately 10 ms, on average, for every 1×10^9/l increase in peak monocyte count within 2 days of admission. Remote zone native T1 (milliseconds) was independently associated with LV remodeling, as revealed by CMR, the within-subject changes in N-terminal pro–brain natriuretic peptide concentration at 6 months, and MACEs and all-cause death or heart failure hospitalization in the longer term. The study by Reinstadler et al. (7) reported similar findings for MACE. Considering clinical translation, native T1-mapping could be considered as a surrogate biomarker in randomized controlled trials of interventions that are intended to prevent adverse remodeling.

The infarct zone hypothesis states that limiting infarct size early after acute MI by timely reperfusion increases myocardial salvage, prevents infarct complications (e.g., microvascular obstruction), and improves prognosis. However, in our experience, this infarct zone hypothesis is insufficient to fully account for adverse LV remodeling post-MI, and adaptive changes within the infarcted heart are multifactorial. Homeostatic changes within remote myocardial tissue seem to have a pivotal role in adaptive LV remodeling. An inadequate biomechanical response within the remote zone will result in pump failure and ventricular dilatation. Accordingly, the remote zone hypothesis identifies homeostatic changes within remote zone tissue as having a pivotal role in adaptive LV remodeling, and a unifying approach would integrate the imaging findings within the infarct and remote zones. Reinstadler et al. (7) integrated these parameters into 1 prognostic model that more fully exploits the unique biomarker parameters provided by a multiparametric CMR scan (8,12). There were also some limitations in this study. Their population was derived from a clinical trial (LIPSIA-CONDITIONING [Effect of Conditioning on Myocardial Damage in STEMI]; NCT02158468), the duration of follow-up was only 6 months, and the model included both infarct size and the myocardial salvage index, which are inextricably linked. Further research is warranted to assess the external validity of this CMR prognostic model.

So, how to mend a broken heart? Future prognostic studies should confirm the external validity of this (or any other) CMR model, and also confirm whether an integrative imaging model might have greater prognostic value for cardiac events post-MI than one that includes clinical parameters without CMR, or even, simply, N-terminal pro–brain natriuretic peptide. Because CMR early post-MI reveals myocardial function and pathology in a single scan, we hypothesize that an integrative CMR model will be more informative for prognostication than these other approaches. Should this be the case, then the CMR approach may have clinically useful applications for patient-specific risk assessment and stratification for more (or less) intensive therapy. Similarly, clinical trials of novel therapies could invoke a stratified approach to selectively enroll patients who are identified using a CMR model to be at higher risk of adverse cardiac outcome. In this sense, multiparametric CMR has an emerging role for personalized medicine of post-MI patients.

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