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], and perhaps generally increasing longevity. Alternatively, the pathophysiology of left ventricular 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]. Given 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?

In this regard, the article by Reinstadler et al. [7] is timely. They undertook a post-hoc analysis of left ventricular function and tissue characteristics in the infarct and remote zones revealed by multi-parametric cardiac magnetic resonance (CMR) scans obtained within the first week of an acute STEMI in a cohort of 255 patients. There are two main results. The first is 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 is the proposition of an integrative approach in which data on left ventricular function and pathology within infarct and remote zones can be assimilated within a prognostic model for individualized prediction of cardiac prognosis. Thus, rather than a focus on one parameter, the totality of parameters with distinct prognostic significance for MACE are statistically modeled to optimize risk prediction over and above the prognostic value of any one of the parameters in isolation.

Cardiac imaging of a post-MI patient is typically focused on left ventricular function, infarct size and complications [8]. So why might the myocardial remote zone be worthy of focused attention in the clinical report? There is an 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 / macrophages track to infarct and remote myocardial tissues from reticuloendothelial stores [9,10]. Macrophage cytokine production represents a stress response post-MI leading 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, binding 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 follow-up to 3 years (see Figures 1 & 2 from [12]). Myocardial remote zone native T1 was approximately 10 ms higher on average in patients with ECG evidence of reperfusion injury and increased by approximately 10 ms, on average, for every $1x10^9$/L increase in peak monocyte count within 2 days of admission. Remote zone native T1 (ms) was independently associated with LV remodeling, as revealed by CMR, the within-subject changes in NT-proBNP concentration at 6 months, and MACE 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, such as microvascular obstruction, and improves prognosis. However, in our experience, this infarct zone hypothesis is insufficient to fully account for adverse left ventricular 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. integrated these parameters into one prognostic model that more fully exploits the unique biomarker parameters provided by a multi-parametric CMR scan [7,8,12]. There were also some limitations in this study. Their population was derived from a clinical trial (LIPSIA-CONDITIONING, NCT02158468), the duration of follow-up was only 6 months, and the model included both infarct size and 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 or not 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, NT-proBNP. Since CMR early post-MI reveals myocardial function and pathology in a single scan, we hypothesise that an integrative CMR model will be more informative for prognostication than those 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 identified using a CMR model to be at higher risk of adverse cardiac outcome. In this sense, multi-parametric CMR has an emerging role for personalized medicine of post-MI patients.

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