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Mapping myocardial salvage index by extracellular volume fraction: Are we there yet?

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In ST-segment elevation myocardial infarction (STEMI) patients treated by primary percutaneous coronary intervention (PPCI), the myocardial salvage index (MSI) provides a more sensitive measure for assessing the efficacy of novel cardioprotective therapies, than an absolute reduction in myocardial infarct (MI) size. Knowledge of the MI size and the size of the area-at-risk (AAR) are pre-requisites for measuring the MSI, and both may be obtained by cardiovascular magnetic resonance (CMR) in reperfused STEMI patients, with the MSI shown to predict clinical outcomes following PPCI. CMR is considered the gold standard imaging modality for quantifying MI size, and it can also delineate the edema-based AAR, with T2 and T1-mapping CMR emerging as the most robust techniques, although no consensus has yet been reached.

In this issue of Circulation: Cardiovascular Imaging, Garg et al report on a potentially novel approach for quantifying the AAR, chronic MI size, and MSI in a study of 50 STEMI patients reperfused by PPCI, based on extracellular volume fraction (ECV) maps from an acute CMR scan. The study derived specific ECV cut-off values on an acute CMR scan (performed at a median of 48 hours post-PPCI) in a subset of 10 patients, to delineate the AAR (when compared to T2-STIR imaging), and chronic MI size (when compared late gadolinium enhancement [LGE]) on a follow-up scan performed at 3 months post-PPCI). Using acute ECV cut-off values of >33% to delineate the AAR and >46% to delineate chronic MI size, they concluded that acute ECV maps could be used to reliably quantify AAR, chronic MI size, and MSI. Being able to accurately quantify MI size using a pixel-wise acute ECV map would be appealing, and could be potentially easily implemented in clinical practice with the wider availability of in-line, automated ECV map generation from the scanner, to improve workflow. However, there are several potential limitations to
consider concerning the use of acute ECV maps to detect the AAR, chronic MI size and MSI in reperfused STEMI patients.

Firstly, the study did not specifically compare the performance of ECV-derived MSI with conventional MSI (from LGE and T2-STIR), and whether acute ECV maps can be used to estimate the MSI remains to be demonstrated. The authors could have considered using the reference standard of manual delineation of AAR and MI size by experienced operators, rather than semi-automated thresholding methods, which are known to have their limitations \(^5,^6\). The presence of microvascular obstruction (MVO) on the acute CMR scan is known to pseudo-normalize the ECV \(^5,^7\), due to failure of the gadolinium chelate to penetrate areas of MVO, which could have affected MI size regression, thereby making it challenging to estimate chronic MI size from the acute ECV in patients with MVO. Finally, the study used \(\leq 75\%\) transmural MI on the follow-up CMR scan to define viable myocardium, and an increase of \(\geq 15\%\) in left ventricular (LV) end-systolic volume to define adverse LV remodeling, instead of the conventionally accepted definitions of \(\leq 50\%\) for viability on CMR \(^8\), and \(\geq 20\%\) increase in LV end-diastolic volume for adverse LV remodeling on echocardiography \(^9\). In this regard, we have recently proposed CMR-based definitions for assessing adverse LV remodeling following STEMI, which may be helpful for future CMR studies \(^10\). The study findings are also thought-provoking, and raise some interesting questions for the field.

*Can acute ECV maps be used to accurately delineate the chronic MI size given the pathological differences that exist between acute and chronic MI?*

It is well-recognized that acute MI size is dynamic, and acutely reduces in size within the first week \(^11,^12\), and more chronically reduces over the first few months \(^5,^11\). The regression in MI size represents the gradual resolution of myocardial edema,
intramyocardial hemorrhage (IMH) and MVO, and the gradual replacement of necrotic tissue with fibrosis in the chronic infarct. Furthermore, LV remodeling leads to thinning of the infarcted territory, and compensatory LV hypertrophy of the adjacent and remote myocardium, resulting in the overall reduction in LGE mass observed in the chronic phase. The over-estimation of acute MI size by LGE on the acute CMR scan can be minimized by acquiring LGE images at least 15 minutes after contrast injection and undertaking the acute CMR scan at day 7. In addition, acute MI size has recently been shown to be prognostic, and may help to reduce sample size in clinical cardioprotection studies in reperfused STEMI patients, thereby obviating the need to measure chronic MI size, which can be challenging to perform in clinical cardioprotection studies. Therefore, the differences between the pathologies underlying acute and chronic MI, may in part, have impacted on the study findings, and may have contributed to the substantial variability observed between acute MI size by ECV and chronic MI size by LGE, with the Bland-Altman analysis showing a bias of 1.9% and wide limits of agreement of ±10.5%. This suggests that acute ECV maps may not yet be ready to measure chronic MI size following STEMI.

*Can acute ECV maps be used to accurately delineate the AAR given that edema in salvaged myocardium can be both intracellular and interstitial following STEMI?*

During acute myocardial ischemia, interruption of the blood supply to the myocardium disrupts cardiomyocyte Na⁺/K⁺ channel function, leading to increased trans-membrane Na⁺ gradients and intracellular edema. Prolonged periods of ischemia can result in cardiomyocyte cell membrane rupture, thereby adding to the intracellular edema. Alterations in capillary permeability can promote interstitial edema, resulting in both intracellular and interstitial edema during acute myocardial ischemia.
Furthermore, reperfusion can exacerbate both interstitial and intracellular edema, and may also lead to extravasation of red blood cells\textsuperscript{15}. Native T1-mapping, T2-mapping or T2-STIR CMR imaging detect both intracellular and interstitial edema, whereas acute ECV can only detect edema in the latter compartment\textsuperscript{16}, and therefore areas of intracellular edema in the salvaged myocardium may be overlooked by acute ECV.

It may also be challenging for acute ECV maps to reliably differentiate salvaged myocardium within the AAR from remote myocardium outside the AAR, given that there can be overlap in acute ECV values between the salvaged and remote myocardium following STEMI. In this regard, Hammer-Hansen et al\textsuperscript{17} have recently reported an overlap in acute ECV values between salvaged versus remote myocardium (95% of the acute ECV values were 18 - 30% in the remote, and 28 - 51% in the salvaged myocardium) following STEMI. An overlap in acute ECV values between the salvaged and remote myocardium may also have affected the study by Garg et al\textsuperscript{3}, with areas of acute ECV >33% observed in the remote myocardium (see figure 3, case 1). Furthermore, a previous study by the same research group had reported an acute ECV of 29±6% in the remote myocardium\textsuperscript{18}, confirming the potential for overlap in acute ECV values between salvaged and remote myocardium.

Again, this may explain, in part, the wide limits of agreement (±10.4%) observed in the current study, indicating a large variability in the observed values between acute ECV AAR and T2-STIR AAR\textsuperscript{3}. In a previous study, we had observed limits of agreement of ±5.1% when comparing T1 and T2-mapping to detect the AAR in reperfused STEMI patients\textsuperscript{2}, and limits of agreement of ±10.4% observed with acute ECV maps for delineating T2-weighted AAR may be too wide for clinical application. This suggests that acute ECV maps may not yet be ready to measure AAR following STEMI.
In summary, performing a comprehensive CMR study in acutely reperfused STEMI patients can be very challenging, and Garg et al.\(^3\) should be congratulated on their study investigating the potential role of acute ECV mapping for assessing AAR, chronic MI size and MSI. Although, multi-parametric CMR mapping has the real potential to provide valuable insights into the changes occurring in areas of MI, MVO, IMH, salvaged and remote myocardium in the setting of STEMI\(^7,19,20\), more validation work is needed before acute ECV mapping, can be used to reliably assess AAR, MI size, and MSI in reperfused STEMI patients.

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**Disclosures**

The authors declare no disclosures
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