Risk-stratification by cardiovascular magnetic resonance following reperfused ST-segment elevation myocardial infarction: Ready for prime time?

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Despite successful restoration of epicardial coronary artery blood flow by primary percutaneous coronary intervention (PPCI), microvascular obstruction (MVO) occurs in about 50% of reperfused ST-segment elevation myocardial infarction (STEMI) patients.(1) MVO is caused by a complex interplay of factors including distal coronary embolization of plaque debris and thrombi; external compression of capillaries by edema; release of thrombogenic and vasoactive particles; neutrophil plugging; and extravasation of blood.(2) It is closely linked with the development of intramyocardial hemorrhage (IMH),(3) a complication of severe microvascular injury.(4)

Cardiovascular magnetic resonance (CMR) is considered to be the most reliable imaging modality for detecting MVO and IMH following STEMI.(5) Late MVO occurs in around 50-55%, and IMH in about 35-40% of reperfused STEMI patients.(1,6) Late MVO is more prognostic than early MVO,(6) and patients with late MVO persisting until 7 days post-PPCI have a worse prognosis.(7) Late MVO and IMH are both dynamic and follow distinct time courses within the first few days of STEMI.(8) Both late MVO and IMH are associated with larger MI sizes, adverse LV remodeling, and worse short- and medium-term clinical outcomes, and both predict outcomes independent of myocardial infarct (MI) size (1,6). Whether the presence of late MVO can predict long-term clinical outcomes beyond 2 years following STEMI was not previously known.

In this issue of *JACC: Cardiovascular Imaging*, Symons et al (9) investigated the long-term incremental prognostic value of CMR over clinical predictors in STEMI patients treated by PPCI. They prospectively recruited 810 STEMI patients from 6 European centers over a period of 12 years, and CMR was performed at a median of 4 days following PPCI. After a median follow-up of 5.5 years, late MVO, both as a

continuous variable and as a binary measure, was demonstrated to be an independent predictor of the composite endpoint of all-cause death and decompensated heart failure. The authors found that the extent of late MVO of ≥2.6% of the left ventricle (LV) on the acute CMR scan, provided incremental prognostic value over clinical score and LV systolic function. This study extends the findings from previous studies that showed late MVO to be a strong independent prognostic marker following STEMI (1). The authors should be commended for completing a CMR study of this size in the acute STEMI setting, and for reporting the longest follow-up so far following PPCI. The particular strengths of this study include its multi-center design, centralized analysis of all CMR images, and manual quantification of MVO by experienced operators. There are, however, a few limitations to the study to be discussed, which serve to highlight the challenges of undertaking multi-center CMR studies of this magnitude in acute STEMI patients.

There was likely a strong selection bias with the STEMI patient cohort investigated in this study, and the findings may not be representative of the real-world setting. STEMI patients selected for CMR evaluation are usually less sick, a reflected by the relatively low numbers of STEMI patients recruited over the 12 years (approximately 12 patients on average per center each year), the relatively small MI size observed in this study (15% versus 21% in a series of randomised controlled trials [RCTs])(10), and the lower incidence of late MVO in this patient cohort (44% versus over 50% in other published studies).(1)

Although the CMR protocol was supposed to be standardized across the 6 centers in this study, there were some differences in slice thickness and slice gap of the late gadolinium enhancement (LGE) sequences, and the choice of contrast agent and dose. A cut-off value of 2.6% of the LV for the extent of MVO was used in many

of their analyses and interpretations. However, it is well recognized that late MVO is dynamic, and its incidence and extent can be influenced by the timing of the acute CMR scan post-PPCI, the dosage and contrast agent used, and the timing of acquisition of the LGE images post-contrast injection.(7,8,11)

Finally, it may have been more relevant to have determined the prognostic impact of late MVO on *cardiac death* and decompensated heart failure, instead of all-cause death and decompensated heart failure, given the high incidence of non-cardiac deaths (41% of all death) due to the extended follow-up.

The study findings also raise an interesting and thought-provoking question for the field. *Is CMR ready for risk-stratification of STEMI patients in the clinical setting to guide management and improve outcomes?* CMR in the acute STEMI patient has emerged as an important tool for assessing surrogate endpoints in RCTs,(10), for providing mechanistic insights into acute ischemia/reperfusion injury,(12,13) and for predicting clinical outcomes.(1,6) However, there is a lack of standardization in CMR protocols used in STEMI patients with respect to a number of factors including the timing of the CMR scan, the type and dose of contrast used, the timing of post-contrast LGE images, and the method used for MI size quantification.(10) Furthermore, performing a CMR study can be time-consuming, and requires numerous breath-holds, thereby precluding sicker patients from CMR studies. Crucially, once late MVO and/or IMH have been detected on the acute CMR scan, there is currently no established therapy for targeting these complications to improve clinical outcomes, although promising pre-clinical work is ongoing.(14) Therefore, as it stands, acute CMR in STEMI patients may not yet be ready for clinical application to guide management and improve clinical outcomes.

There is, therefore, a need to standardize CMR protocols for acute scans performed in reperfused STEMI patients.(10) Furthermore, there is a requirement to shorten CMR scanning time using non breath-hold protocols, and a need to reduce costs, in order to make this imaging modality more accessible to a wider range of STEMI patients, and available in more centers. Only then can CMR, in combination with clinical prognostic factors such as late MVO demonstrated by Symons et al in their study,(9) be used as an important tool for risk-stratifying STEMI patients to guide management and improve clinical outcomes.

In summary, although CMR has greatly improved our understanding of the pathophysiological sequelae of reperfusion on the ischemic myocardium in STEMI patients treated by PPCI, and it has highlighted the key factors contributing to morbidity and mortality in the current era of PPCI, more work is needed before CMR can be used to risk-stratify reperfused STEMI patients in the clinical setting.

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References

1. van Kranenburg M, Magro M, Thiele H et al. Prognostic value of microvascular obstruction and infarct size, as measured by CMR in STEMI patients. JACC Cardiovascular imaging 2014;7:930-9.
2. Bulluck H, Foin N, Tan JW, Low AF, Sezer M, Hausenloy DJ. Invasive Assessment of the Coronary Microcirculation in Reperfused ST-Segment-Elevation Myocardial Infarction Patients: Where Do We Stand? Circulation Cardiovascular interventions 2017;10:e004373.
3. Driesen RB, Zalewski J, Vanden Driessche N et al. Histological correlate of a cardiac magnetic resonance imaged microvascular obstruction in a porcine model of ischemia-reperfusion. Cardiovasc Pathol 2012;21:129-31.
4. Zia MI, Ghugre NR, Connelly KA et al. Characterizing myocardial edema and hemorrhage using quantitative T2 and T2* mapping at multiple time intervals post ST-segment elevation myocardial infarction. Circulation Cardiovascular imaging 2012;5:566-72.
5. Lund GK, Stork A, Muellerleile K et al. Prediction of left ventricular remodeling and analysis of infarct resorption in patients with reperfused myocardial infarcts by using contrast-enhanced MR imaging. Radiology 2007;245:95-102.
6. Hamirani YS, Wong A, Kramer CM, Salerno M. Effect of microvascular obstruction and intramyocardial hemorrhage by CMR on LV remodeling and outcomes after myocardial infarction: a systematic review and meta-analysis. JACC Cardiovascular imaging 2014;7:940-52.
7. Orn S, Manhenke C, Greve OJ et al. Microvascular obstruction is a major determinant of infarct healing and subsequent left ventricular remodelling following primary percutaneous coronary intervention. European heart journal 2009;30:1978-85.
8. Carrick D, Haig C, Ahmed N et al. Myocardial Hemorrhage After Acute Reperfused ST-Segment-Elevation Myocardial Infarction: Relation to Microvascular Obstruction and Prognostic Significance. Circulation Cardiovascular imaging 2016;9:e004148.
9. Symons R, Pontone G, Schwitter J et al. Long-Term Incremental Prognostic Value of Cardiovascular Magnetic Resonance after ST-segment Elevation Myocardial Infarction. JACC Cardiovascular imaging 2017.
10. Bulluck H, Hammond-Haley M, Weinmann S, Martinez-Macias R, Hausenloy DJ. Myocardial Infarct Size by CMR in Clinical Cardioprotection Studies: Insights From Randomized Controlled Trials. JACC Cardiovascular imaging 2017;10:230-240.
11. Rodriguez-Palomares JF, Ortiz-Perez JT, Lee DC et al. Time elapsed after contrast injection is crucial to determine infarct transmurality and myocardial functional recovery after an acute myocardial infarction. Journal of cardiovascular magnetic resonance : official journal of the Society for Cardiovascular Magnetic Resonance 2015;17:43.

12. Bulluck H, Rosmini S, Abdel-Gadir A et al. Residual Myocardial Iron Following Intramyocardial Hemorrhage During the Convalescent Phase of Reperfused ST-Segment-Elevation Myocardial Infarction and Adverse Left Ventricular Remodeling. Circulation Cardiovascular imaging 2016;9.
13. Bulluck H, Rosmini S, Abdel-Gadir A et al. Automated Extracellular Volume Fraction Mapping Provides Insights Into the Pathophysiology of Left Ventricular Remodeling Post-Reperfused ST-Elevation Myocardial Infarction. Journal of the American Heart Association 2016;5.
14. Betgem RP, de Waard GA, Nijveldt R, Beek AM, Escaned J, van Royen N. Intramyocardial haemorrhage after acute myocardial infarction. Nature reviews Cardiology 2015;12:156-67.