

Characterizing Post-Myocardial Infarction Microvascular Obstruction by ECG: We Could Learn More From Cardiac Magnetic Resonance Imaging

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Despite successful restoration of blood flow of an infarct related coronary artery, a wealth of experimental and clinical data has confirmed the common existence of poor tissue perfusion.^{1,2} This no-reflow phenomenon due to microvascular obstruction (MVO) is known to have serious clinical consequences including significant ventricular arrhythmias, heart failure, adverse remodeling, and death.³⁻⁵ Impairment of microcirculatory flow after reperfusion remains complex spatially and temporally. Swelling of injured myocytes and endothelial cells, infiltration and activation of neutrophils and platelets, and deposition of fibrin cause capillary obstruction and eventually rupture, with resultant debris deposition and even hemorrhage. The mechanisms that lead to formation of MVO from prolonged ischemia followed by late reperfusion are rapid. It has been suggested that each 30-minute delay in reperfusion increases the risk of MVO by 20%.⁶ Challenging further understanding of the mechanistic basis of MVO, experimental setting of ischemia-reperfusion does not account for some of the clinical factors that contribute to MVO, such as distal microembolization of atherosclerotic or thrombotic debris commonly seen from percutaneous coronary intervention. All of these factors contribute to the currently incomplete understanding of the underlying pathophysiology of MVO. In addition, MVO is unfortunately common. The incidence of MVO varies widely in the literature but has been reported to exist in as high as 70% of patients presenting with an acute infarction.⁷ Therefore, a lack of optimal therapy against MVO remains an obstacle in achieving the next breakthrough in improving the mortality of patients post-myocardial infarction.

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The need to diagnose and quantify MVO has been well known for more than 3 decades. By coronary angiography, the corrected-TIMI frame count assesses tissue perfusion by counting the number of cine frames required for contrast to reach distal coronary landmarks in the culprit artery. A high corrected-TIMI frame count at 90 minutes after administration of a thrombolytic agent is associated with adverse cardiac outcomes despite achieving angiographic TIMI flow grade 3.⁸ Other angiographic parameters such as the semi-quantitative myocardial blush grade estimates tissue reperfusion by grading myocardial contrast density on the final angiogram. These semi-quantitative angiographic methods have demonstrated prognostic implication but are limited by their invasiveness and tissue perfusion can only be assessed immediately after achievement of epicardial patency, when microvascular flow is known to be hyperemic. It has been observed that there is a three-fold increase in perfusion in the first few hours after emergent primary coronary intervention of the infarct-related artery, stabilization between 48 hours and a few days and a reduction by six months in about 50%.⁹

Invasive angiographic techniques therefore cannot assess the final tissue perfusion or perform any monitoring in most patients. Timing to assess MVO and ability to assess the final tissue perfusion status are important. A recent report has noted that only MVO that is persistent beyond 1 week predicted adverse left ventricular remodeling.¹⁰ Myocardial contrast echocardiography has also been shown to detect MVO in a substantial fraction of patients despite achieving TIMI flow grade 3. However, its widespread use has been limited by its lack of complete left ventricular coverage especially in its suboptimal visualization of the lateral wall and poor tissue contrast. Tissue characterizing capability of cardiac magnetic resonance imaging (CMR) offers the best current tool in quantifying the presence and extent of MVO. CMR detects MVO using either one of the two techniques.^{11,12} The first approach detects delayed wash-in of gadolinium on first-pass perfusion, termed early hypoenhancement. Given epicardial patency, this hypoenhanced region represents no-reflow. The second detects regions of very low signal

intensity within the enhanced region of myocardial infarction on late gadolinium enhancement taken 10-15 minutes after gadolinium injection, termed late MVO. While MVO as measured by these 2 techniques are highly correlated, early first-pass perfusion technique appears to be slightly more sensitive.¹³ This difference in prevalence may be attributed to the ongoing slow diffusion of contrast into regions with less severe microvascular damage and smaller areas of reduced enhancement at late imaging and is likely to relate to a more extensive spectrum of obstruction MVO assessed by late gadolinium enhancement imaging. On the other hand, MVO assessed by late gadolinium enhancement imaging has the advantage of concurrent quantitation of total infarct size, volumetric left ventricular coverage, and substantially higher contrast-noise ratio. MVO by both techniques has been shown to predict adverse left ventricular remodeling and post-myocardial infarction cardiac events incremental to infarct size.^{14,15}

In this issue of *REVISTA ESPAÑOLA DE CARDIOLOGÍA*, Husser et al¹⁶ aimed to determine, using CMR as a reference, a simple ECG predictor of microvascular reperfusion. In this study, 85 consecutive patients presented with a first-time ST-segment elevation myocardial infarction achieved successful primary coronary intervention at a mean time of 3.5 hours since infarct onset. Patients then underwent serial ECGs (up to 96 hours) and a comprehensive CMR protocol at an average of 6 days post-infarct. Microvascular obstruction was defined as a lack of gadolinium retention (dark region) in the core of a segment surrounded by tissue showing late gadolinium enhancement, ie, late MVO. Using this definition, MVO was detected in 44% of selected patients. Patients with late MVO were more likely to have anterior infarction, be of younger age, have marginally lower systolic blood pressure and have a larger rise of serum creatine kinase-MB. By CMR, patients with MVO had larger infarct size, higher left ventricular volumes, and lower left ventricular ejection fraction. Several ECG parameters were tested; including the sum of ST-segment elevation (sumSTE) and the aggregate percent reduction of sumSTE (STR) over each chosen time point. The authors report that the sumSTE yielded a significantly larger area under the curve at every measurement point compared to the extent of STR. Adjusting for several variables chosen on the basis of a univariate *P* value of <.1, sumSTE at 90 minutes after coronary intervention and anterior MI were the only predictors of the presence of late MVO, thus proposing a simple ECG rule in predicting MVO after epicardial patency has been achieved.

The authors should be commended for their efforts in systematically assessing the serial changes in ECG

and their association with novel imaging marker of MVO by CMR late gadolinium enhancement imaging. The observed association of sumSTE and MVO is consistent with prior literature. Advancing bedside ECG methods in characterizing MVO, similar to the efforts made by Husser et al in the current study,¹⁶ can make significant impact to patient care. Prior reports have tested multiple ECG criteria in this regard. ECG ST resolution of >50% or >70% have been considered an established criteria of reperfusion in the thrombolytic era. However, method of coronary revascularization, ECG time-points, and definition of reperfusion vary between these studies in the literature. Such difference in study design can partially account for an observed concordance rate as low as 40% when myocardial blush and ECG were compared. The strengths of the study design in the current study include its prospective approach, serial ECG measurements at the most critical period of MVO formation after coronary intervention, and use of high quality late gadolinium enhancement imaging by CMR in characterizing MVO at a consistent and narrow interval of 6 (2) days after coronary intervention.

However, several major methodological issues of this paper remain questionable. The true prevalence of MVO in patients with acute ST elevation infarction has been underestimated due to sub-selection of patient with successful primary coronary intervention and achievement of TIMI 3 flow. MVO is hardly a dichotomous process. Despite the novelty in characterizing MVO using CMR late gadolinium enhancement imaging, the current paper did not consider the quantitative extent of MVO as a relevant parameter. It would have been valuable to know the number of patients who underwent aspiration thrombectomy and the influence this procedure had on the incidence of no-reflow. The multivariable logistic regression model appeared grossly overfitted in this pilot observational study of 85 patients where 37 (44%) demonstrated MVO on CMR. The argument that sumSTE >3 mm yielded a higher diagnostic accuracy than STR in detecting MVO seems circular, since this diagnostic threshold was derived from the optimal cut-off from the receiver operator curve of the training dataset. Finally, the authors provided little pathophysiologic rationale to explain the observed discrepancy between sumSTE and STR and the lack of diagnostic utility of STR within the first 24 hours.

There remains uncertainty how we can treat MVO. Various treatment options included aspiration thrombectomy, distal protection devices, intra-aortic balloon pump, glycoprotein IIb/IIIa receptor blockers, adenosine, sodium nitroprusside, verapamil, endothelin receptor antagonists, and nicorandil, have been studied, each with varying

level of evidence of success.⁷ Some of these novel therapies may prove to be efficacious against MVO. Noninvasive methods in identifying such patients at increased cardiac risk due to poor tissue reperfusion will provide the much-needed guidance to the proper delivery of such therapies that improve tissue perfusion, but only if high degree of diagnostic accuracy can be established.

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