

Editorial

Cardiac Magnetic Resonance Imaging and Endothelin-1: A Step Forward in the Detection of Microvascular Obstruction

Resonancia magnética cardíaca y endotelina-1: un nuevo paso en la detección de la obstrucción microvascular

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In recent years, cardiac magnetic resonance has become an indispensable clinical and research tool widely used for the assessment of cardiac function and infarct size in patients following an acute myocardial infarction (MI)¹. Left ventricular size and function are well known and important predictors of adverse remodeling and cardiac death after an ischemic event. However, the presence of myocardial stunning and/or hibernation in patients following MI has demonstrated that left ventricular function may provide a poor estimation of the severity and the extent of myocardial damage². The development of contrast-enhanced cardiac magnetic resonance imaging (ce-CMR) to highlight differences in tissue characteristics has played a decisive role in the expansion of this non-invasive technique in cardiology. In particular, late gadolinium contrast enhancement allows easy differentiation between areas of infarction and scar from normal myocardium and blood pool. This technique has been shown to have high spatial resolution, great reproducibility and good correlation with the histopathological infarcted areas³. Moreover by delineating the transmural extent of irreversibly infarcted myocardium, potentially salvageable myocardium can be evaluated. This distinction of dysfunctional yet viable myocardium is of crucial importance for the management of cardiac patients in predicting functional recovery following acute reperfusion to improve patient outcomes and long-term prognosis⁴.

In spite of the monumental achievements in improving patient prognosis following an acute MI, the integrity and maintenance of microvascular perfusion during acute myocardial reperfusion remains an important target. Even with successful restoration of epicardial coronary patency after MI, adequate reperfusion is not always achieved at the microvascular level. Microvascular obstruction (MO) can be assessed using different methods as summarized in Table 1. However, ce-CMR provides a direct assessment of myocardial perfusion and is widely considered the reference technique for MO identification and direct quantification.

MO can be diagnosed as: a) a lack of gadolinium contrast wash-in after the peak signal intensity in normal myocardium during first pass perfusion or early imaging^{5,6}, and b) a persistent absence of gadolinium enhancement signified by the appearance of a hypoenhanced core region surrounded by infarcted contrast hyperenhancement during late gadolinium enhancement^{7,8}. Either finding of delayed (during first pass) or absent (on late imaging) wash-in of gadolinium contrast within the infarct zone indicates capillary occlusion at the microcirculatory level that is typical of the pathophysiology behind MO.

This absent contrast enhancement has been found to be a strong prognostic marker of adverse outcomes that is associated with larger infarct size, lower left ventricular ejection fraction, worse functional recovery and greater risk of postinfarction complications. In a previous single study investigation by Hombach et al in 110 acute MI patients, the incidence of MO was 46%. MO was a more powerful predictor of major adverse events and survival⁷. These results correlate with the studies of other authors such as Wu et al⁵, who showed that the presence of MO remained a stronger prognostic marker than infarct size, or Nijveldt et al⁸, who found that MO was the best predictor of global and regional left ventricular remodeling after acute MI.

Potentially, the identification of patients at high risk to develop MO is necessary in order to implement a more aggressive or novel approach to alter this negative remodeling process and prognosis. Likewise, the use of adjunctive therapy aimed at improving microvascular reperfusion might also be potentially beneficial even prior to primary percutaneous coronary intervention or thrombolysis. Unfortunately, clinical predictors for the occurrence of MO are not yet well established. Therefore, development of a measurable factor or biomarker that is highly suggestive for absent microvascular reperfusion would be of great utility in the management of these patients.

Current serum biomarkers that are routinely measured, such as troponin, creatine kinase or brain natriuretic peptide, facilitate the clinical management of patients with ischemic heart disease to help improve prognosis. However, there is a paucity of studies and data about biomarkers to predict the development of MO or myocardial salvage. Recently, Verouden et al⁹ found an association between NT-pro-BNP levels assessed on arrival before

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Table 1
Different Methods to Evaluate the Microvascular Obstruction.

Diagnostic Method	Presence of MO
TIMI flow grade	Score 0-1: absent or faint antegrade coronary arterial flow beyond the occlusion with incomplete filling of the distal coronary bed
TIMI myocardial blush grade	Score 0-1: failure of dye to enter or exit the microvasculature
Electrocardiogram	Lack of resolution of ST-segment elevation >50–70% 1 h after reperfusion
Myocardial contrast echocardiography	Lack of intramyocardial contrast opacification after injection of microbubbles
Positron emission tomography	Increased regional FDG uptake in the acute infarct area
CMR first pass perfusion	Persistence of hypoenhanced areas after the peak of signal intensity in normal myocardium within 3 min after contrast
CMR late gadolinium enhancement	Hypoenhanced regions surrounded by hyperenhancement infarction greater than 10 min after contrast

CMR, cardiac magnetic resonance; MO, microvascular obstruction; TIMI, Thrombolysis in Myocardial Infarction.

revascularization and ST-segment recovery in patients with ST-segment elevation as a reflection of the state of microvascular perfusion. Likewise, Neizel et al¹⁰ concluded that a higher concentration of cardiac troponin T at 24 hours was an independent predictor for MO. The current study by Freixa et al¹¹, published in *Revista Española de Cardiología*, discusses the usefulness of endothelin-1 (ET-1) assessment in acute MI and the reperfusion injury after percutaneous coronary intervention related to ce-CMR findings.

ET-1 is a peptide that possesses potent vasoconstrictor and mitogenic properties that is produced primarily in the endothelium and plays a key role in vascular homeostasis. It is involved in salt and water homeostasis and furthermore stimulates the sympathetic nervous system and renin-angiotensin system. These actions make endothelin an important mediator in many cardiovascular complications including coronary artery disease. High levels of this biomarker are very frequently associated with worse prognosis after MI¹².

The current investigators similarly found elevated levels of ET-1 to be associated with two important measurable parameters by ce-CMR: the presence of MO and reduced myocardial salvage. There are broad mechanisms that could potentially obstruct the distal microvasculature bed resulting in an overall impairment of myocardial tissue perfusion. The exact pathogenesis for the development of MO is unknown, but it seems to have a multifactorial etiology¹³. Besides the potential of distal thrombus embolization from an interventional procedure, the clinical cause of angiographic «no-reflow» relates to a combination of reperfusion injury from proinflammatory mediators, oxygen free radicals, and proteolytic enzymes causing myocardial cell swelling, endothelial protrusions, and endothelial damage. The resultant endothelial damage leads to further platelet aggregation and stimulation of microthrombi formation causing MO. Therefore, it can be reasonably hypothesized that patients with elevated ET-1 secondary to acute MI would lead to localized vasoconstriction within the risk region and allow preferential blood flow to be shunted to other areas of the heart.

Two implications of the authors' findings are remarkable. First, ET-1 levels could be useful as biomarkers identifying patients who may develop MO. Clearly, patients with preserved systolic function following acute MI have an excellent prognosis and need not be evaluated by ce-CMR. However, using elevated ET-1 levels as an indicator of a potentially pathogenic process could prompt an evaluation by ce-CMR to confirm the presence of MO and degree of myocardial salvage. Identifying at-risk patients early can also potentially risk-stratify patients who will particularly benefit from early adjunctive therapy and close clinical follow-up.

Second, the pathophysiological perspective provided in this research identifies a new therapeutic target. Anti-endothelin therapy in the treatment of ischemic heart disease might offer

additional benefits and favorably alter the progression to heart failure. ET-1 blockade during myocardial ischemia/reperfusion injury has been demonstrated to be reduced in experimental animal models, in terms of both reduction in final infarct size and improved recovery of myocardial performance and coronary flow^{14,15}. However, caution must be raised as the presence of elevated ET-1 levels could also be a beneficial mechanism to prevent arrhythmias, increase inotropy and preferentially shunt blood away from the necrotic myocardium. Further inhibition of ET-1 may have a deleterious effect and careful detailed research in this line of inquiry is paramount.

For all these reasons, the results from the present study show promise of monitoring ET-1 levels in patients with ischemic heart disease. Further studies are warranted as the major question remains whether elevated circulating levels of ET-1 lead to the development of microvascular perfusion or is only a secondary byproduct that arises from profound myocardial damage.

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