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Effect of Microvascular Obstruction and Intramyocardial Hemorrhage by CMR on LV Remodeling and Outcomes After Myocardial Infarction

A Systematic Review and Meta-Analysis

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ABSTRACT

The goal of this systematic analysis is to provide a comprehensive review of the current cardiac magnetic resonance data on microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH). Data related to the association of MVO and IMH in patients with acute myocardial infarction (MI) with left ventricular (LV) function, volumes, adverse LV remodeling, and major adverse cardiac events (MACE) were critically analyzed. MVO is associated with a lower ejection fraction, increased ventricular volumes and infarct size, and a greater risk of MACE. Late MVO is shown to be a stronger prognostic marker for MACE and cardiac death, recurrent MI, congestive heart failure/heart failure hospitalization, and follow-up LV end-systolic volumes than early MVO. IMH is associated with LV remodeling and MACE on pooled analysis, but because of limited data and heterogeneity in study methodology, the effects of IMH on remodeling require further investigation. (J Am Coll Cardiol Img 2014;7:940–52) © 2014 by the American College of Cardiology Foundation.

In the setting of an acute myocardial infarction (MI), persistence of coronary artery occlusion for >40 min can lead to irreversible myocardial damage that spreads as a "wave front phenomenon" progressing from endocardium to epicardium (1,2). Although timely reperfusion is presently the best mechanism to salvage ischemic myocardium and limit myocardial necrosis, revascularization also can have detrimental effects by triggering ischemic reperfusion injury that results in microvascular damage and further myocyte necrosis (3). Ischemic reperfusion injury can account for up to one-half of the size of the final MI (4). Depending on the severity of the ischemic injury, microvascular injury can lead to: 1) microvascular obstruction (MVO) only; and 2) MVO with intramyocardial hemorrhage (IMH) (4). The National Heart, Lung, and Blood Institute has emphasized microvascular damage and reperfusion injury after MI as important targets to improve outcomes (5). Although left ventricular ejection fraction (LVEF) traditionally has been used as a predictor of major adverse cardiac events (MACE), its use as the sole predictor has come under question (6).

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Cardiac magnetic resonance (CMR) provides a comprehensive analysis of MI, including the assessment of myocardial scar, MVO, and IMH, and there is growing evidence that these parameters provide important information for predicting adverse left ventricular (LV) remodeling and MACE. This systematic state-of-the-art review will evaluate the literature examining the CMR parameters of MVO and IMH as biomarkers of adverse events after acute MI.

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MICROVASCULAR OBSTRUCTION. MVO or "no reflow" refers to the small vessel changes that prevent adequate tissue perfusion despite revascularization and an open epicardial coronary artery (2). MVO is thought to be caused by an abrupt release of cytotoxic factors (7) that promote vasoconstriction, myocardial cellular edema (2,8), capillary endothelial cells swelling, and distal microembolization of atherosclerotic debris leading to plugging of vascular lumen with neutrophils, red blood cells, and platelets. MVO begins in the infarcted core and can increase in size for up to 48 h (9). MVO is reported to be present in up to 84% of the patients after ST-segment elevation myocardial infarction (STEMI) (10–12). The diagnosis of MVO can be made using angiography (13,14), echocardiography (15), nuclear scintigraphy (16), myocardial contrast echocardiography (17), or CMR. On angiography, microvascular blood flow is assessed using Thrombolysis In Myocardial Infarction flow grades, myocardial blush grade, and/or corrected Thrombolysis In Myocardial Infarction frame count. The rate of myocardial uptake of microbubbles using contrast echocardiography has been used to assess MVO; however, this technique is limited by challenges of adequate acoustic windows, injection of microbubble contrast, and operator dependency (17). There are limited data using single photon emission computed tomography, and this has been used only in research applications (16). Of the available modalities, CMR provides the most comprehensive assessment of MVO.

MVO is detected on gadolinium-enhanced CMR as delayed or absent wash-in of contrast agent into the infarct zone. MVO as assessed by CMR is defined as "early" or "late" in reference to the timing of imaging relative to gadolinium administration (**Figure 1**). Early microvascular obstruction (EMVO) is identified by a prolonged perfusion defect on resting first-pass perfusion (FPP) imaging (18) or as a hypointense region in the core of the infarct on T1-weighted images obtained 2 to 5 min after contrast administration (19). Although FPP images have lower signal-to-noise ratio, spatial coverage, and ventricular coverage, a study comparing this technique with early T1-W imaging demonstrated concordance in 92% (20).

Depending on the severity of MVO, the absence of wash-in of gadolinium may persist for >10 min (21), resulting in a region of persistent hypoenhancement within the core of the infarct on conventional late gadolinium enhancement images, referred to as "late MVO" (LMVO). Late gadolinium enhancement imaging used for LMVO assessment has high spatial and contrast resolution (22) and enables full coverage of the LV myocardium. Because the wash-in of gadolinium into the infarct core is a dynamic process (23,24), it is presently unknown whether the rate of fill-in of the MVO area has prognostic importance and whether EMVO or LMVO is a better predictor of LV remodeling or MACE.

INTRAMYOCARDIAL HEMORRHAGE. IMH is considered a severe form of MVO and follows MVO development in the core of the infarct (25–27) with a tendency to expand for several hours after percutaneous coronary intervention (28,29). The cause includes vascular endothelial damage and accumulation of red blood cells in the myocardial extracellular space (30–34). It has been debated whether IMH is the cause or result of severe ischemic reperfusion injury (35). A high correlation between infarct size (IS) and IMH has been identified on histopathologic studies ($r = 0.90$); however, no correlation with the magnitude of early flow after revascularization (32,36,37) has been seen. Multiple factors contribute to the presence and severity of IMH, including the amount of collateral flow (25,38), ischemic preconditioning, extent of necrosis (25,33), distal coronary microembolization, and differences in individual risk factors, such as diabetes or smoking. IMH can be assessed with CMR using T2- or T2*-weighted imaging or parameter mapping sequences (**Figure 2**).

Most studies have used T2-weighted short-tau inversion recovery (STIR) or T2*-weighted gradient echo pulse sequences to assess for IMH. IMH appears as a hypointense region within the infarct on T2-weighted sequences because the hemoglobin breakdown products shorten the myocardial T2-relaxation time. Because the paramagnetic effects of hemoglobin breakdown products more strongly affect T2* relaxation, T2*-weighted imaging is thought to be more sensitive for the detection of IMH (39,40). However, T2*-weighted images have lower signal-to-noise compared with T2-weighted images and are more sensitive to off-resonance artifacts. T2* values are lowest acutely in the IMH core, but gradually normalize to that of the rest of the infarct at 4 weeks because of extensive collagen deposition and absence of iron with resolution of MVO and IMH (41). IMH detected by both T2 (41,42) and T2* images has been correlated with the presence of hemorrhage on histopathologic analysis (kappa 0.96, $p < 0.01$) (43–45) (**Figures 3 and 4**). A recent study (46) in

ABBREVIATIONS AND ACRONYMS

CHF = congestive heart failure
CI = confidence interval
CMR = cardiac magnetic resonance
EF = ejection fraction
EMVO = early microvascular obstruction
FPP = first-pass perfusion
IMH = intramyocardial hemorrhage
IS = infarct size
LMVO = late microvascular obstruction
LV = left ventricular
LVEF = left ventricular ejection fraction
MACE = major adverse cardiac events
MI = myocardial infarction
MVO = microvascular obstruction
PSIR = phase-sensitive inversion recovery
STEMI = ST-segment elevation myocardial infarction
STIR = short-tau inversion recovery