Microvascular Obstruction
The Final Frontier for a Complete Myocardial Reperfusion*

Carlos E. Rochitte, MD, PhD
São Paulo, Brazil

Microvascular obstruction (MO), or no-reflow phenomenon, defines an area within an acute myocardial infarction (MI) that had undergone not only myocyte necrosis but also severe and irreversible microcirculation damage (1). It has been shown that the presence of MO in humans after MI is associated with poorer prognosis and worse left ventricle (LV) remodeling (2).

Since the description of the no-reflow phenomenon in the myocardium by Kloner et al. (3) in 1974 as the absence of blood flow restoration to the myocardium after a temporary coronary occlusion, research in this field has progressed in 2 distinct directions.

One direction was the no-reflow definition in interventional cardiology based on angiographic aspects (4), which occurred with the advent of thrombolysis and primary percutaneous coronary angioplasty and the observation of slow antegrad e contrast filling in the infarct-related artery.

No-reflow definitions used Thrombolysis In Myocardial Infarction (TIMI) flow score, TIMI frame count (5), and, finally, intracoronary Doppler ultrasound with a typical Doppler pattern of angiographic no-reflow being a reduced or absent antegrade systolic flow followed by a retrograde systolic flow and rapid deceleration of diastolic flow (6). Prognostic information and effect of drugs on MO was derived from these measurements in several animal and clinical studies (7,8).

The other direction was the visualization of MO within the myocardium by contrast echocardiography (9), nuclear medicine (10), and cardiovascular magnetic resonance (CMR) (1–3,11,12). In both lines of studies, the term “no-reflow” was applied, referring to either angiographic no-reflow or MO, generating some confusion but reflecting 2 distinct facets of the same pathophysiology, which is the obstruction of microcirculation (3). Here, CMR took the lead owing to its higher spatial resolution, signal-to-noise, and contrast-to-noise ratio compared with the other modalities. In 1995, Lima et al. (12) were the first to detect areas of hypoenhanced myocardium by CMR in humans. Animal experiments by Judd et al. (11) and Rochitte et al. (1) confirmed the results and established a close correlation between hypoenhanced myocardial areas and blood flow at the microcirculation level by microspheres.

In this issue of the Journal, a convergence of these 2 factions of investigation happened with Hirsch et al. (13). The authors elegantly compared epicardial coronary blood flow characteristics by intracoronary Doppler with MO detected by CMR, the best techniques for angiographic and tissue no-reflow evaluation, respectively. Their data confirmed previous data from contrast-enhanced echocardiography (9) and demonstrated that the magnitude of MO by CMR was the independent force driving the behavior of coronary blood flow at the epicardial level. Despite investigating only patients with first anterior MI, this study provides a great step forward in MO pathophysiology in humans and in the definition of the best methodology to further this investigational field.

Cardiac magnetic resonance is very efficient for MO detection and more sensitive than the best invasive method of intracoronary Doppler. In the Hirsch et al. (13) study, all patients with early systolic retrograde flow (SRF) had MO by CMR, whereas none without SRF had MO. On the other side, only about one-half of patients with MO had SRF. The SRF may be detectable only in patients with a greater extent and severity of MO.

However, for the quantification of MO there is one critical point in using CMR with gadolinium contrasts. Gadolinium-based contrasts have an extracellular distribution in the myocardium and rapidly diffuse into the normal interstitial space as well as into areas of MO at a variable rate, thus changing its size over time after injection.

In the Hirsch et al. (13) study, late gadolinium enhancement (LGE) was performed 12 to 15 min after injection and might have underestimated the true extent and size of MO. Earlier studies using gradient-echo sequences (1), have investigated the time course of MO and demonstrated in canine models that at 3 min after contrast the area of MO correlated better with the size of the region with myocardial blood flow <50% than remote regions by radioactive microspheres (1,11,14). This might explain why the extent (number of segments) had a more powerful correlation than MO size itself, which was probably underestimated. Nonetheless, the time after gadolinium injection that best correlates with true size of MO in humans still remains to be determined, particularly with the additional role of thrombus and atherosclerotic material embolization present in the clinical situation of thrombolysis or PCI.

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From the Heart Institute (InCor), University of São Paulo Medical School, São Paulo, Brazil.
Another important aspect must be highlighted; MO is an extremely dynamic phenomenon, increasing progressively in the first 48 h after reperfused acute MI (1), as described by CMR and basic studies (1,14,15). Thus, choosing the time after reperfusion is also crucial to investigate the magnitude of MO.

Currently there is no consensus on which technique can perform the best MO quantification, with first-pass myocardial perfusion (16,17) competing with gradient-echo without (1,11) and with (13,17) inversion-recovery preparatory pulse or LGE technique. The latter 2 sequences can add infarct size information and have better spatial resolution, although the latter 1 has been best validated against microspheres (1). First-pass perfusion can present defects owing to chronic infarcts, artifacts, or other flow heterogeneities. Late gadolinium enhancement uses an inversion-recovery preparatory pulse that is adjusted to null the signal of normal myocardium. The effect of adjusting TI time on the MO size is not well understood. For instance, slight changes in TI might potentially cause a rim of bright signal on the border between the infarct and the MO area, causing an artificial reduction in MO size. Moreover, these current sequences are still techniques dependent on gadolinium dynamics.

Thus, we can still potentially benefit from even better CMR sequences not influenced by the gadolinium dynamics. Some future candidates may be T2 imaging, diffusion-weighted diffusion-tension imaging, and blood oxygenated level-dependent imaging.

But why should we define the anatomic area of MO so precisely? The no-reflow area can be closely related to a progressive hemorrhage of the myocardium, and if it grows over time after reperfusion it might be considered a reperfusion injury and, therefore, can be potentially avoided or treated. The precise definition of MO magnitude would open an opportunity to define influential factors on its course and to evaluate current and new therapy effects on MO and its clinical implications. In the future, with these developments, we will potentially be able to provide to acute MI patients the ultimate myocardial reperfusion, that is, not limited to the epicardial coronary artery, and likely an improved healing process.

REFERENCES


Reprint requests and correspondence: Dr. Carlos Rochitte, Setor de Ressonância e Tomografia Cardiovascular, Instituto do Coração—InCor, Av. Dr. Enéas de Carvalho Aguiar, 44—Andar AB, Cerqueira César, São Paulo—SP, Brazil—05403-000. E-mail: rochitte@incor.usp.br.