‘No-reflow’ after acute myocardial infarction: direct visualisation of microvascular obstruction by gadolinium-enhanced CMR

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Cardiovascular magnetic resonance is considered the standard imaging modality in clinical trials to monitor patients after acute myocardial infarction. However, limited data are available with respect to infarct size, presence and extent of microvascular injury (MVO) and changes over time, in relation to cardiac function in optimally treated patients. In the current study we prospectively investigate the change of infarct size over time, and the incidence and significance of MVO in a uniform, optimally treated patient group after AMI. (*Neth Heart J* 2008;16:179-81.)

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Survival and prognosis of patients with an acute myocardial infarction (AMI) have improved substantially using therapies aiming at early restoration of myocardial blood flow.¹ Despite successful recanalisation of the infarct-related artery by percutaneous coronary intervention (PCI), perfusion of the ischaemic myocardium is not or incompletely restored in up to 30% of patients due to microvascular obstruction (MVO), angiographically referred to as the no-reflow phenomenon.² The presence of angiographically assessed no-reflow in these patients has been found to be a predictor of adverse events, with higher incidence of left ventricular remodelling, congestive heart failure and death. The diagnosis of no-reflow is clinically most often made using angiographic (TIMI flow grade, myocardial blush grade)^{3,4} or electrocardiographic (ST-segment resolution)⁵ criteria of reperfusion. However, these criteria are indirect reflections of MVO and do not allow visualisation of the actual size and extent of the injury.

Cardiovascular magnetic resonance (CMR) allows a complete and accurate assessment of left ventricular status in patients after AMI. Functional CMR allows highly reproducible quantification of left ventricular function, and gadolinium-enhanced CMR visualises total infarct size and MVO in vivo. Hypoenhancement 1-2 minutes after injection of a gadolinium chelate is assumed to represent zones of MVO, which has been validated against histological microvascular injury assessed by injection of thioflavin S.⁶ Occlusion of the microvasculature with erythrocytes, neutrophils and cellular debris causes a lack of gadolinium enhancement in the endocardial core, which can still be depicted on late gadolinium-enhanced images, depending on the degree of

microvascular injury and the rate of gadolinium diffusion.⁷ In earlier reports of patients predominantly treated by thrombolysis, MVO detected by CMR has been shown to predict LV remodelling and outcome, even after statistical correction for the predictive value of infarct size.⁸ However, limited data are available on presence and significance of CMR MVO in patients after AMI receiving current state-of-the-art treatment.

Because of its capability to assess global and regional ventricular function, size and transmural extent of infarction, and microvascular injury in one single examination, CMR is expected to become a powerful noninvasive technique for the determination of MVO, and evaluation of its clinical significance.

To investigate the prevalence and significance of MVO detected by CMR, we studied 50 consecutive patients who participated in a larger project evaluating the current role of gadolinium-enhanced CMR in ischaemic heart disease. Patients were eligible for the study if they were admitted with a first ST-segment elevation AMI and had undergone angiographically successful (no residual stenosis) primary PCI with stent implantation of the infarct-related artery. All patients were treated with aspirin, heparin, abciximab, clopidogrel, statins, β -blocking agents and ACE inhibitors, according to ACC/AHA practice guidelines. Fifty patients underwent cine and gadolinium-enhanced CMR within nine days and at four months after primary stenting (figure 1).

Figure 1. CMR images of a patient with anterior wall myocardial infarction. The left images were acquired at baseline and the right images during follow-up. The top images are cine images in systole, with an akinetic area (black arrows), and at the bottom the corresponding gadolinium-enhanced images with hyperenhancement of the infarct region (white arrows). At follow-up, left ventricular volumes have increased, infarct size has decreased, and the myocardial wall of the infarcted region has become thinner.

Global left ventricular volumes, left ventricular ejection fraction, and infarct size were calculated, and the presence of MVO was assessed.

The mechanism of gadolinium enhancement is a complex process. After injection, gadolinium rapidly extravasates from the blood pool into the interstitium and diffuses into the infarct area. The infarct area will appear as hyperenhanced (bright) myocardium on images acquired late after gadolinium administration, leading to the aphorism 'bright is dead'.⁹ Areas with microvascular injury will demonstrate a lack of contrast wash-in due to impaired perfusion and a slow process of diffusion, and will therefore appear as hypoenhanced, dark areas (figure 2).

Consequently, the presence and size of MVO will not only depend on the degree of microvascular damage and gadolinium wash-in, but also on the time point of scanning. To evaluate the significance of MVO on left ventricular volumes, function and infarct size in our study population, we therefore used a standardised image acquisition and analysis protocol.¹⁰

Our results indicate that in the majority of patients after PCI, despite early and optimal revascularisation, MVO can be demonstrated on gadolinium-enhanced CMR images. In a group of 50 patients, 27 patients (54%) had evidence of MVO at baseline CMR scan.

Patients with MVO had larger enzyme rise, larger left ventricular volumes, worse ejection fraction, and larger gadolinium-enhanced infarct size at baseline. At follow-up,

Figure 2. Gadolinium-enhanced CMR image during baseline (left panel) and follow-up (right panel), of a patient with posterolateral wall myocardial infarction. At baseline, a region with microvascular obstruction (white arrows) can be seen within the infarcted, hyperenhanced (bright) area. At follow-up, the region with microvascular obstruction has disappeared, and infarct size has decreased.

patients with adequate reflow of the infarcted myocardium showed a decrease in left ventricular volumes with concomitant improvement of ejection fraction, whereas left ventricular volumes worsened and ejection fraction did not significantly improve in patients with MVO. In addition to the larger infarct size at baseline, patients with MVO also showed a greater infarct size reduction at follow-up ($p=0.001$), suggesting a higher degree of infarct involution and myocyte loss. In the group of patients with MVO, no relation was found between the size of MVO, and change in left ventricular volumes and function.

Interestingly, in contrast to previous studies, patients with evidence of MVO had symptom-to-balloon times comparable with patients who had successfully reperfused infarcts (3.8 ± 4.2 hours versus 3.5 ± 2.7 hours respectively, $p=0.78$).

These data demonstrate that, using gadolinium-enhanced CMR, microvascular obstruction is present in the majority of patients despite optimal reperfusion therapy for AMI. The presence of MVO was associated with worse functional outcome, larger infarcts and greater reduction in infarct size at follow-up. To further explore the diagnostic value of MVO as detected by CMR, we have recently investigated the significance of the size of microvascular injury on functional recovery.¹¹ Intriguingly, we found no significant differences in left ventricular volumes, function and infarct size when the 23 patients with MVO were stratified to infarcts with large or small areas of MVO. This suggests that presence of MVO on CMR imaging may be more important for functional outcome than the total volume of microvascular injury. One explanation may be that the drastic change in infarct treatment has resulted in an increase in myocardial salvage, and subsequent limited extent of microvascular damage. The variation of the total volume of MVO in optimally treated patients is therefore small, and differences in functional outcome may possibly be found in larger study populations.

To ultimately address the clinical significance of CMR MVO, we will directly compare angiographic, electro-

cardiographic and gadolinium-enhanced CMR characteristics of microvascular injury in patients with AMI, and study their predictive value on functional outcome. ■

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