Microvascular Obstruction Remains a Portent of Adverse Remodeling in Optimally Treated Patients With Left Ventricular Systolic Dysfunction After Acute Myocardial Infarction

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Background—Microvascular obstruction (MO) is associated with large acute myocardial infarction and lower left ventricular (LV) ejection fraction and predicts greater remodeling, but whether this effect is abolished by contemporary antiremodeling therapies is subject to debate. We examined the influence of several infarct characteristics, including MO, on LV remodeling in an optimally treated post–acute myocardial infarction cohort, using contrast-enhanced cardiac magnetic resonance.

Methods and Results—One hundred patients (mean age, 58.9±12 years, 77% men) underwent contrast-enhanced cardiac magnetic resonance at baseline (≈4 days) and at 12 and 24 weeks. The effects on LV remodeling (ie, change in LV end-systolic volume index [ΔLVESVi]) of infarct site, transmurality, endocardial extent, and the presence of early and late MO were analyzed. Mean baseline infarct volume index decreased from 34.0 (21.2) mL/m² to 20.9 (12.9) mL/m² at 24 weeks (P<0.001). Infarct site had no influence on remodeling, but greater baseline infarct transmurality (r=0.47, P<0.001) and endocardial extent (r=0.26, P<0.01) were associated with higher ΔLVESVi. Early MO was seen in 69 patients (69%) and persisted as late MO in 56 patients (56%). Patients with late MO underwent significantly greater remodeling than those without MO (ΔLVESVi, +4.1 [13.4] versus −7.0 [12.7] mL/m², respectively, P=0.001); those with early MO only displayed an intermediate ΔLVESVi (−4.9 [13.0] mL/m²). Importantly, late MO was seen frequently despite optimal coronary blood flow having been restored at angiography.

Conclusions—Late MO on predischarge contrast-enhanced cardiac magnetic resonance remains an ominous predictor of adverse LV remodeling despite powerful antiremodeling therapy and may be useful in the risk stratification of survivors of acute myocardial infarction.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00132093.

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Key Words: microvascular obstruction • myocardial infarction • remodeling • MRI

Relief of the occlusive obstruction within the infarct-related artery (IRA) is a key component in the management of acute myocardial infarction (AMI) and in the attenuation of left ventricular (LV) remodeling. Despite patency of the IRA, however, abnormal microvascular perfusion—termed microvascular obstruction (MO)—is related to worse outcome.1,2 Cardiac MRI (CMR) facilitates examination of myocardial perfusion through early and delayed contrast-enhanced imaging sequences (ccCMR). Analysis of myocardial enhancement early (usually 2 to 5 minutes) after injection of a gadolinium-based contrast agent allows visualization of “early MO,” an area of hypoenhanced myocardium that bears a precise anatomic correlation with markedly reduced blood flow in animal studies, in addition to biopsy evidence of necrotic debris.3–6 On delayed contrast-enhanced imaging sequences after large AMI, MO may persist as a central hypoenhanced core within the hyperenhanced infarct; this appearance has been termed “late MO.”

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Studies using myocardial contrast echocardiography to determine presence and extent of (early) MO have consis-
tentatively shown strong correlations between its presence and adverse remodeling.7,8 CMR studies have revealed strong correlations between both early and late MO and greater LV volumes at baseline, more significant remodeling, and increased risk of major adverse cardiovascular events (MACE) after infarction.9–11 Late MO is considered to be a stronger predictor of LV remodeling than early MO.13,14

Results of a recent study, however, showed that in patients with reperfused AMI, confirmed patency of the IRA, and a very high uptake of antiremodeling pharmacotherapy, the presence of late MO, though associated with greater infarct size, LV volumes, and lower LVEF at baseline, was not related to greater remodeling in comparison to patients without MO over a relatively short follow-up of 4 months.15 We therefore examined the relationship between the presence of MO and a variety of infarct characteristics on LV outcomes after AMI in a cohort of patients enrolled in a clinical trial with a very high prescription rate of evidence-based secondary preventive therapies.

Methods

Patients and Protocol

The design of the parent study, randomization process, inclusion/exclusion criteria, and primary results have been published in detail previously.16 Briefly, the patients were participants in a randomized, double-blinded, placebo-controlled clinical trial investigating the effects of eplerenone on LV remodeling after AMI in patients (n=100) with LV systolic dysfunction. Eligible patients were ≥18 years of age and able to provide written informed consent. All patients had an AMI in the 1 to 14 days before enrollment and were required to have LV ejection fraction (LVEF) <40% on screening transthoracic echocardiography. Principal exclusion criteria were clinical or radiological heart failure (Killip score >1), diabetes mellitus, serum creatinine >220 μmol/L, serum potassium >5 mmol/L, and conventional contraindications to MRI. ceCMR scanning was performed at baseline (before random assignment to placebo/eplerenone) and again at 12 and 24 weeks. The study complies with the Declaration of Helsinki and was approved by the local ethics committee.

ceCMR Protocol

ceCMR was performed using a 1.5-T Siemens Sonata (Erlangen, Germany) with a phased-array chest coil, during breath-hold, and gated to the ECG. A steady-state free-precession sequence was used to acquire a short-axis cine stack of the LV from base to apex, consisting of 8-mm-thick slices with a 2-mm interstice slice gap. After cine image acquisition, 0.1 mmol/kg gadolinium diethylenetriamine-pentaacetic acid (GE Healthcare, Waukesha, Wis) was administered as a rapid intravenous bolus during which first-pass perfusion imaging was performed. Two minutes after contrast injection, images were acquired for the determination of early MO. This required a single-shot steady-state free-precession sequence with a nonselective inversion pulse without breath-hold. Typically, 3 to 5 short-axis slices per heartbeat were acquired, copied from the short-axis cine stack. A single-shot sequence was acquired at 2, 3, 4, and 5 minutes after contrast injection. Fifteen minutes after contrast injection, a contrast-sensitive segmented inversion recovery sequence was used to acquire a second stack of short-axis images (positions copied from the cine stack), with slice thickness 8 mm and interstice gap 2 mm; the time to inversion was varied within the range 200 to 300 ms to obtain optimal nulling of the myocardium for the delayed enhancement sequences.

ceCMR Analysis

Postprocessing was performed using Argus software (Siemens, Erlangen). Manual planimetry, performed by 1 observer blinded to treatment allocation, was used to trace the epicardial and endocardial contours of each short-axis slice acquired in the cine stack, allowing calculation of LV volumes, LVEF, and LV mass (myocardial density, 1.05 g/cm3).

Infarcted LV myocardium on ceCMR was defined as regional delayed hyperenhancement after gadolinium injection involving at least the subendocardium. Applying standardized contrast settings during analysis, the infarcted volume of LV myocardium, defined as any region of signal intensity higher than normal (remote) myocardium, was delineated manually by 1 observer blinded to treatment allocation and ECG data.

Early MO was defined as the appearance of at least 1 segment of hyperenhancement surrounded by hyperenhancement on images acquired between 2 and 5 minutes after contrast.4 Quantitative analysis of the size and extent of both the first-pass defect and early MO tends to be imprecise as it requires multiple geometric assumptions because of the limited number of short-axis slices acquired during ultrafast imaging. Such quantitative analysis was not performed in this study. In purely qualitative terms, the presence or absence of early MO was recorded for each scan, but no further analysis of these images was performed.

Late MO was defined as hyperenhancement within a hyperenhanced region on the delayed ceCMR images that persisted for ≥10 minutes after contrast injection.13,14 In a fashion similar to the early MO images, the qualitative presence or absence of late MO was recorded for each patient. Representative examples of early MO and late MO are shown in Figure 1.

The anatomic location of the infarct was based on the American Heart Association (AHA) standardized 17-segment model.19 Infarct location was categorized as anterior, lateral, or inferior, defined as the location containing the highest percentage of infarcted myocardium. Infarct transmurality was calculated by visually deciding the transmural extent per segment in quarters (1 to 1% to 25%, 2 to 26% to 50%, 3 to 51% to 75%, and 4 to 76% to 100%) and calculating the mean. This produced a transmurality score.2,19 Endocardial infarct extent was calculated by measuring the circumferential extent of the infarct at each of the 3 short-axis slices used in the AHA segmentation model and calculating the mean (Figure 2).19

Invasive Studies

Decisions regarding diagnostic coronary angiography and/or percutaneous coronary intervention (PCI) were made by the attending consultant cardiologist and were independent of the trial protocol. The final Thrombolysis In Myocardial Infarction (TIMI) flow within the IRA was recorded for each patient who underwent angiography.

Statistics

ceCMR measurements were adjusted for total body surface area, creating the following indexed quantities: LVESV index (LVESVi), LV end-diastolic volume index (LVEDVi), LV mass index (LVMI), and LV infarct volume index. LV remodeling was defined as the change in LVESVi between baseline and 24 weeks. When change in each ceCMR parameter over time was examined, only patients with both a baseline and 24-week follow-up scan were analyzed. Paired t tests were used to detect changes in ceCMR measurements over the 24-week follow-up. Univariate ANOVA was used to assess the difference in mean ceCMR parameters according to presence or absence of early and/or late MO. Covariates predictive of remodeling were identified by stepwise selection of a model fitted with all baseline variables listed in Table 1. Variables thus selected (defined as those that were predictive of ΔLVESVi, with P<0.10 for both inclusion and exclusion) were included into a multivariable linear regression model, which included MO status and TIMI flow, to facilitate multivariate analysis of the predictive efficacy of these 2 parameters on remodeling. A separate multivariable analysis including study drug allocation was then performed to determine whether MO influenced the effects of eplerenone in comparison to placebo on LV remodeling outcomes.

All data are expressed as mean (SD) for continuous variables and number (%) for categorical variables unless otherwise stated. Comparisons between sites of infarction were made using paired sample t tests.
or Mann–Whitney U tests as appropriate for continuous variables and χ² test for categorical variables. The relationships between infarct characteristics and ceCMR-measured LV volumes and function were assessed using Spearman correlation coefficients. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, Ill). A probability value of <0.05 was considered significant.

Results

Study Population

The baseline characteristics of the study cohort are shown in Table 1. The uptake of contemporary secondary preventive therapies was high, with 94 (94.0%) discharged on an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, 93 (93.0%) on a β-blocker, and 50 (50.0%) additionally on eplerenone (by study design). The mean time from admission to screening transthoracic echocardiography was 30 hours and to the first ceCMR scan was 93 hours.

ceCMR Parameters

The change in ceCMR-measured parameters of LV function and infarct volume between baseline and 24 weeks is shown in Table 2.

Site of Infarction

The site of the acute infarct on baseline ceCMR was anterior in 53 (53.0%), inferior in 24 (24.0%), and lateral in 4 (4.0%). Infarcted myocardium was equally distributed between anterior and lateral segments in 2 (2.0%) and between inferior and lateral segments in 17 (17.0%)—such infarcts were classified as anterolateral and inferolateral, respectively. Baseline infarct characteristics according to site are shown in Table 3.

There was no significant difference in infarct volume between combined anterior/anterolateral, inferior/inferolateral and lateral infarct sites (Table 3). Anterior and anterolateral infarction was of greater mean endocardial extent than inferior and inferolateral infarction, whereas the latter group had mildly but significantly higher transmurality scores. Of note, there was no significant difference in the extent of LV remodeling between anterior/anterolateral and inferior/inferolateral infarcts (ΔLVESVi was +0.06 [15.4] mL/m² in anterior versus −0.9 [12.1] mL/m² in inferior AMI, P=0.76).

Transmurality Score and Endocardial Extent

Across the entire study cohort, there were significant correlations between transmurality score, endocardial extent, and LV volumes/LVEF at baseline and 24 weeks. Mean transmurality score correlated significantly with LVESVi (r=0.21, P=0.041) and LVEDVi (r=0.20, P=0.042) but not with LVEF (r=−0.15, P=0.12) at baseline and with ΔLVESVi (r=0.47, P<0.001), ΔLVEDVi (r=0.30, P=0.004), and ΔLVEF (r=−0.42, P<0.001) between baseline and 24 weeks. Endocardial extent correlated significantly with LVESVi (r=0.45,
Table 1. Baseline Characteristics of Study Patients

<table>
<thead>
<tr>
<th>Category</th>
<th>n=100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>58.9 (12.0)</td>
</tr>
<tr>
<td>Male/female</td>
<td>77%/34%</td>
</tr>
<tr>
<td><strong>Hemodynamics</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) blood pressure, mm Hg</td>
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</tr>
<tr>
<td>Systolic</td>
<td>113.0 (16.3)</td>
</tr>
<tr>
<td>Diastolic</td>
<td>69.9 (11.6)</td>
</tr>
<tr>
<td>Mean (SD) heart rate, bpm</td>
<td>65.8 (14.3)</td>
</tr>
<tr>
<td><strong>Medical history, %</strong></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>7.0</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>5.0</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>2.0</td>
</tr>
<tr>
<td>Angina</td>
<td>37.0</td>
</tr>
<tr>
<td>Current smoker</td>
<td>55.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>35.0</td>
</tr>
<tr>
<td>Hypercholesterolemia 25.0</td>
<td>94.0</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>6.0</td>
</tr>
<tr>
<td><strong>Admission medication, %</strong></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>23.0</td>
</tr>
<tr>
<td>β-blocker</td>
<td>18.0</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>12.0</td>
</tr>
<tr>
<td>Statin</td>
<td>15.0</td>
</tr>
<tr>
<td><strong>Treatment, %</strong></td>
<td></td>
</tr>
<tr>
<td>Thrombolysis</td>
<td>54.0</td>
</tr>
<tr>
<td>Primary PCI</td>
<td>27.0</td>
</tr>
<tr>
<td>Rescue PCI</td>
<td>6.0</td>
</tr>
<tr>
<td>Angiography performed</td>
<td>85.0</td>
</tr>
<tr>
<td>PCI performed</td>
<td>74.0</td>
</tr>
<tr>
<td><strong>Renal function</strong></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) eGFR, mL/min</td>
<td>70.2 (17.5)</td>
</tr>
<tr>
<td>Mean (SD) creatinine, μmol/L</td>
<td>100.1 (21.2)</td>
</tr>
<tr>
<td><strong>Discharge medication, %</strong></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>96.0</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>82.0</td>
</tr>
<tr>
<td>β-blocker</td>
<td>93.0</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>94.0</td>
</tr>
<tr>
<td>Statin</td>
<td>98.0</td>
</tr>
<tr>
<td>Frusemide</td>
<td>21.0</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>50.0</td>
</tr>
</tbody>
</table>

*CABG indicates coronary artery bypass grafting; TIA, transient ischemic attack; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate.*

Unless otherwise stated, continuous data are expressed as mean (SD); categorical data are expressed as percentages of the patient cohort.

P<0.001, LVEDVi (r=0.28, P=0.004), and LVEF (r=-0.55, P<0.001) at baseline and with ΔLVEF (r=0.26, P=0.013) and ΔLVEDVi (r=0.22, P=0.033) but not with ΔLVEF (r=−0.16, P=0.11).

**Microvascular Obstruction**

Early MO was present in 69% of the study cohort and persisted as late MO in 56%. Patients were divided into 3 groups according to MO status: no MO (n=31), early MO (n=13), and early and late MO (n=56); no patient had late but not early MO. Patients with both early and late MO underwent significantly greater increases in LVESVi and LVEDVi, significantly smaller improvements in LVEF, and significantly larger reductions in infarct volume index than patients with no MO (Table 4). Patients with early but not late MO displayed intermediate changes in each ceCMR-measured parameter over time (with the exception of LVMI). The presence of late MO was significantly correlated with adverse LV remodeling, whereas the absence of late MO was associated with reverse remodeling (ΔLVESVi, +4.1 [13.4] mL/m² in patients with late MO versus −6.4 [12.7] mL/m² without late MO, P<0.001); Figure 3.

The inter-relationships between infarct transmurality score, endocardial extent, and presence of (late) MO are shown in Figure 4. Transmurality score was significantly correlated with endocardial extent (r=0.26, P=0.009). Mean transmurality score was significantly higher in those with than in those without late MO (3.6 [0.4] versus 2.9 [0.6], P<0.001), as was endocardial extent (39.4° [11.1°] with MO versus 33.5° [11.3°] without MO, P=0.010).

Early MO was seen in 41 of 54 (75.9%) patients reperfused with thrombolytic agents in comparison to in 15 of 27 (55.5%) patients who underwent primary PCI (P=0.001); late MO was seen in 34 of 54 (63.0%) thrombolized patients and in 12 of 27 (44.4%) patients undergoing primary PCI (P<0.001).

**Eplerenone Therapy, MO Status, and Remodeling**

A comparison of remodeling parameters according to placebo/eplerenone randomization group and MO status is shown in Table 5.

**Invasive Studies**

Coronary angiography was performed in 48 of 56 (85.7%) patients with late MO on baseline ceCMR and in 37 of 44 (84.1%) without late MO. At the completion of angiography (with or without PCI), TIMI 3 flow within the IRA was present in 42 (87.5%) of those with late MO and similarly in 32 (86.5%) of those without late MO; TIMI 2 flow occurred in 2 (4.2%) and 3 (8.1%), whereas TIMI 0 flow occurred in 4 (8.3%) and 2 (5.4%), respectively; no patient had TIMI 1 flow.

**Predictors of Remodeling**

Baseline variables predictive of ΔLVESVi, selected as described in the statistical methods section, were age; previous coronary artery bypass grafting; smoker; hypertension; hypercholesterolemia; thrombolysis; glycoprotein IIbIIIa inhibitor use; estimated glomerular filtration rate; baseline aspirin and β-blocker therapy; and baseline LVESVi, LVEDVi, LVEF, LVMI, and infarct volume index. Both early MO (β-coefficient, 9.4; P=0.003) and late MO (β, 10.4; P<0.001) were associated with ΔLVESVi on univariate analysis, but TIMI flow was not (β, 2.6; P=0.46). Late MO remained significant on multivariate analysis (β, 6.1; P=0.036), but early MO fell out of the model (β, 2.5; P=0.24); TIMI flow was not related to remodeling (β, 3.4; P=0.20).
MO and adverse remodeling.9,18 One recent study in which
majority of whom had low LVEF, and associations between
of 45% to 55% among patients admitted with AMI, the
studies have produced similar results, with incidences of MO
associated with deteriorating LV function. Several prior CMR
an infarcted segment; thus, it is predictable that it is associ-
ated with evidence-based antiremodeling medications across the
cohort.

Discussion
Using ceCMR imaging, we analyzed the predictive value of a
number of characteristics of the acute infarct in remodeling in
an optimally treated cohort of patients with depressed LV
function after AMI. Unsurprisingly, total infarct volume,
endocardial extent, and transmurality score were associated
with adverse remodeling, in keeping with previous studies, as
all 3 quantities indicate more substantial infarction.9,21 We
demonstrated that late MO occurred in 56% of the population
and was evenly distributed between (predominantly) anterior
and (predominantly) inferior anatomic location. Importantly,
the presence or absence of late MO divided patients into 2
distinct groups: Those with late MO adverse-remodeled,
whereas those without late MO reverse-remodeled despite a
high revascularization rate and very high prescription of
evidence-based antiremodeling medications across the
cohort.

MO represents abnormal microvascular perfusion within
an infarcted segment; thus, it is predictable that it is associ-
ated with deteriorating LV function. Several prior CMR
studies have produced similar results, with incidences of MO
of 45% to 55% among patients admitted with AMI, the
majority of whom had low LVEF, and associations between
MO and adverse remodeling.3,18 One recent study in which
57.5% of infarcts displayed late MO reported that although
those with MO had larger infarct volumes, greater elevation in
cardiac biomarkers, and lower LVEF at baseline than their
counterparts without late MO, there was no difference be-
tween these 2 groups in LV remodeling over 4 months.15 This
appears counterintuitive, and although the authors argue that
the aggressive treatment of their patients abolished the
deleterious effect of late MO on serial LV function (all
patients underwent primary PCI, and the discharge prescrip-
tion of β-blockers and angiotensin-converting enzyme inhib-
itors/angiotensin receptor blockers was 100% and 80%,
respectively), their results are more likely to relate to the
small patient numbers involved (total population, n=40, of
whom 23 had late MO). In comparison, we have shown in a
larger cohort that not only is late MO common despite a very
high uptake of acute reperfusion therapies, but it also remains
ominous in terms of LV functional recovery despite a higher
uptake of contemporary antiremodeling pharmacotherapy
than in any other postinfarction remodeling trial to date.

Early MO predicts MACE after AMI, including cardiac
death, nonfatal AMI, heart failure, and stroke.9 We and others
have shown that late MO is associated with adverse remodel-
ing, which in turn portends progressive LV dilation, dys-
function, and premature death.10,12,22–23 Few studies, howev-
er, have directly compared early and late MO in relation to
remodeling and prognosis after AMI. Two small studies have,
similar to our study, shown a higher prevalence of early than
late MO, presumably because of diffusion of contrast into less
dense areas of microvascular dysfunction; although correla-
tions were reported between MO and parameters of LV
function, neither study examined the influence of early and
late MO on MACE.17,24 A recent small study (n=60) showed
that late MO was a stronger predictor of change in LV
volumes and LVEF than early MO, although again no data on

Table 2. Mean (SD) Values of CMR Parameters of LV Function and Infarct Volume at Baseline (Mean, 93
Hours) and 24 Weeks After AMI

<table>
<thead>
<tr>
<th>CMR Parameter</th>
<th>Baseline</th>
<th>24 Weeks</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No MO</td>
<td>Early MO</td>
<td>Total Population</td>
</tr>
<tr>
<td></td>
<td>(n=31)</td>
<td>(n=69)</td>
<td>(n=100)</td>
</tr>
<tr>
<td>LVESVi, mL/m²</td>
<td>42.7 (18.8)</td>
<td>44.3 (13.4)</td>
<td>44.0 (12.7)</td>
</tr>
<tr>
<td>LVEDVi, mL/m²</td>
<td>84.0 (21.0)</td>
<td>84.5 (16.7)</td>
<td>84.2 (16.7)</td>
</tr>
<tr>
<td>LVMi, g/m²</td>
<td>73.3 (15.0)</td>
<td>75.0 (15.0)</td>
<td>74.8 (14.3)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>50.5 (10.1)</td>
<td>48.3 (8.0)</td>
<td>48.4 (7.4)</td>
</tr>
<tr>
<td>Infarct volume, mL/m²</td>
<td>19.1 (11.7)</td>
<td>39.6 (20.8)</td>
<td>42.3 (21.3)</td>
</tr>
</tbody>
</table>

Baseline data according to MO subgroups (no MO, early MO, and early+late MO) are shown.

*Comparison of total population data at baseline and 24 weeks only.

Table 3. Baseline Infarct Characteristics

<table>
<thead>
<tr>
<th>Total</th>
<th>Anterior±Lateral (n=55)</th>
<th>Inferior±Lateral (n=41)</th>
<th>Lateral (n=4)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct volume, mL/m²</td>
<td>33.2 (20.7)</td>
<td>36.1 (22.1)</td>
<td>30.2 (18.8)</td>
<td>23.7 (16.2)</td>
</tr>
<tr>
<td>Endocardial extent, %</td>
<td>36.8 (11.5)</td>
<td>40.2 (11.0)</td>
<td>33.1 (11.1)</td>
<td>27.4 (5.8)</td>
</tr>
<tr>
<td>Transmurality score</td>
<td>3.3 (0.6)</td>
<td>3.2 (0.6)</td>
<td>3.5 (0.5)</td>
<td>3.1 (0.6)</td>
</tr>
<tr>
<td>Early MO</td>
<td>69 (69%)</td>
<td>35 (35%)</td>
<td>32 (32%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Late MO</td>
<td>56 (56%)</td>
<td>29 (29%)</td>
<td>26 (26%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Infarcts are classified according to the 17-segment AHA model.20 Four infarcts involved only lateral segments with
no anterior or inferior extension and are hence classified as lateral only. Data are presented as mean (SD) for
continuous variables and No. (%) for categorical variables unless otherwise stated. Two-sample t test was used to
compare continuous variables and χ² test for categorical variables.

*Comparison made between anterior±lateral and inferior±lateral only as n=4 in lateral group.
MACE were provided. In the absence of studies specifically powered to determine the predictive efficacy of early and late MO on MACE, we can only extrapolate from the relationships between MO and remodeling reported in this and previous studies that both early and late MO are likely to be associated with adverse outcome, although this would have to be proven in an appropriately designed trial.10,12,22

A key aspect of post-MI care is the prediction of those patients in whom LV function may progressively deteriorate because such patients warrant more stringent follow-up and may be candidates for specific pharmacotherapy (for example, aldosterone antagonists) or even implanted cardioverter-defibrillators. Many studies (and guidelines) use LVEF as the criterion on which such decisions are made. However, early postinfarction LVEF measurement is not as powerful a predictor of adverse remodeling, and MACE as might be anticipated.8 Significant myocardial stunning may lead to underestimation of LVEF, and compensatory hyperkinesis of noninfarced myocardium may “falsely” suggest a higher LVEF despite significant myocardial damage; variations in afterload may also influence LVEF acutely. It has been suggested that LVEF not be used as an end point in early postinfarction studies.25

The data provided in this study suggest that the presence or absence of MO may be of use in predicting remodeling outcomes. Previous criticisms of the use of MO as a predictor of adverse outcome were based on the theory that MO simply related to larger infarction and that it was infarct size that determined outcome rather than presence of MO. Although there is undoubtedly a relationship between MO and larger infarct size (as demonstrated in this and previous studies), presence of MO has been shown to remain an indicator of adverse prognosis even after controlling for infarct size.9 Likewise, MO predicts development of a fibrous transmural scar after AMI even when adjusted for infarct size.9 It therefore appears that although MO is related to infarct size, it also provides independent prognostic information rather than simply acting as a marker of the magnitude of infarcted myocardium.

A number of angiography-based trials have used patency of and TIMI flow rates within the IRA as end points. TIMI 3 flow is generally accepted as the optimal result after AMI irrespective of the means of reperfusion. It is therefore of considerable interest that MO has been shown to be a stronger predictor of postinfarction death, reinfarction, congestive heart failure, and stroke than patency of the IRA.9 Moreover, MO is frequently present despite TIMI 3 flow within the IRA; of the 48 patients with late MO in our study who underwent coronary angiography, 42 (ie, 87.5%) ultimately had TIMI 3 flow within the IRA. This finding is of considerable significance because TIMI flow was neither a univariable nor multivariable predictor of remodeling (unlike MO), implying that TIMI 3 flow alone does not equate to normal microcirculatory perfusion, and further suggesting that ceCMR-measured infarct characteristics, particularly MO, might be a more appropriate end point in clinical studies assessing the “success” of reperfusion therapies. MO may indeed be the missing pathophysiological link between reperfusion, remodeling, and cardiovascular outcome after AMI.

The results of this trial complement those of previous studies.9,22 We have, however, confirmed the relationship
between MO and remodeling in a larger, more homogeneous patient group than those enrolled by Wu et al9 (n=44, of whom 17 attended for follow-up CMR at 6 months) and by Nijveldt et al22 (n=60, all followed up with CMR at 4 months), despite a higher prescription rate of antiremodeling therapies. We also report for the first time on the interrelationships between transmurality score, endocardial extent, and MO, whereas the parent study design afforded the opportunity to examine whether there was any interaction between the presence of MO and the antiremodeling efficacy of eplerenone. We found that MO was associated with significantly less remodeling in eplerenone-treated than in placebo-treated patients. This is of considerable interest because the role of aldosterone antagonists on top of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers and β-blockers in post-MI remodeling is still controversial. Our novel results support an antiremodeling role for eplerenone in those at greatest risk of remodeling, for example, those with MO.

Limitations
In comparison with previous studies examining infarct characteristics after AMI, there are a number of methodological issues that lead to marked interstudy variability. These include partial volume effects, variability in gadolinium-DTPA dose and time to delayed enhancement imaging between studies, variations in the wash-in/wash-out profiles of different gadolinium-DTPA preparations, and in the definition of the boundary zones of the infarct.26–29 Such methodological issues provide compelling evidence for the need for a universal consensus on infarct size measurement on ceCMR.

The study was powered for CMR end points rather than MACE; the lack of clinical outcomes data in this report, however, is a limitation.

Finally, it must be acknowledged that the patients in this study were required to have LV systolic dysfunction, thus the findings cannot be applied to all AMI patients. MO is less likely to occur in association with smaller infarcts, and the predictive potential of MO in small-to-medium infarcts cannot be commented on from these data.

Conclusions
The findings of this study suggest that the presence or absence of late MO on predischarge ceCMR separates patients presenting with AMI into 2 groups with different remodeling outcomes regardless of powerful contemporary antiremodeling therapies and may assist in the risk stratification process. The detection of (late) MO, with its adverse effects on prognosis, in patients in whom angiography (with or without follow-up PCI) had ultimately confirmed TIMI 3 flow in the IRA, suggests that patency of and flow within the IRA are not necessarily markers of optimal outcome after AMI. Infarct characteristics on ceCMR, and in particular MO, may be more appropriate end points in future studies assessing the success of reperfusion therapies.

Sources of Funding
This study was supported by Pfizer UK Ltd, Surrey, United Kingdom.

Disclosures
None.

References

Table 5. Comparison of Change in LV Volumes and LVEF in the Presence of Early and Late MO According to Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Eplerenone</th>
<th>P</th>
<th>Placebo</th>
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<th>Placebo</th>
<th>Eplerenone</th>
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<tr>
<td>ΔLVEDVi, mL/m²</td>
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<tr>
<td>Early MO</td>
<td>4.0 (16.1)</td>
<td>0.6 (10.6)</td>
<td>0.003</td>
<td>10.2 (17.5)</td>
<td>3.7 (11.1)</td>
<td>0.007</td>
<td>2.4 (11.4)</td>
<td>1.7 (7.7)</td>
<td>0.068</td>
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<tr>
<td>Late MO</td>
<td>8.1 (15.2)</td>
<td>0.8 (11.0)</td>
<td>&lt;0.001</td>
<td>15.9 (17.1)</td>
<td>3.4 (11.4)</td>
<td>0.001</td>
<td>2.0 (8.4)</td>
<td>1.4 (7.9)</td>
<td>0.081</td>
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<td>ΔLVEF, %</td>
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<td>Early MO</td>
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<td>Late MO</td>
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Disclosures
None.

References
Adverse left ventricular remodeling after acute myocardial infarction (AMI) may be limited by early achievement of patency of the infarct-related artery. Despite this, microcirculatory dysfunction—observed on contrast-enhanced cardiac magnetic resonance imaging or microvascular obstruction (MO)—remains common. We have shown in a population of 100 survivors of AMI with resultant left ventricular systolic dysfunction that early MO on first-pass imaging occurred in 69% of patients and persisted as late MO on late postgadolinium imaging in 56%, despite restoring optimal angiographic coronary flow in the majority. Moreover, the presence of early and particularly late MO was strongly associated with persistent microvascular obstruction as assessed by contrast-enhanced cardiac magnetic resonance in reperfused acute myocardial infarction. Eur Radiol. 2009;19:2117–2126.


Weir et al MO After MI
Microvascular Obstruction Remains a Portent of Adverse Remodeling in Optimally Treated Patients With Left Ventricular Systolic Dysfunction After Acute Myocardial Infarction


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