Microvascular obstruction remains a portent of adverse remodelling in optimally-treated patients with left ventricular systolic dysfunction after acute myocardial infarction

Running Title: Weir: MO post-MI

Robin AP Weir, MBChB(Hons), BSc(Hons), MRCP, MD; Charles Aengus Murphy, MBChB, MRCP; Colin J Petrie, MBChB, BMedSci(Hons), MRCP; Thomas N Martin, MBChB, MRCP; Sean Balmain, MBChB, MD; Suzanne Clements, BN; Tracey Steedman, BSc; Galen S Wagner, MD; Henry J Dargie, MBChB, FRCP; John JV McMurray, MD, FRCP, FESC, FACC

1Cardiology Department, Western Infirmary, Glasgow G11 6NT, Scotland, UK
2Duke University Medical Center, Durham, North Carolina, USA

Address for correspondence:
Robin AP Weir
Cardiology Department
Western Infirmary
Glasgow G11 6NT, Scotland, UK
Email: robinweir75@hotmail.com
Tel: +441412118527
Fax: +441412111791

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Abstract

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

Methods and Results—100 patients (mean age 58.9±12 years, 77% male) underwent ceCMR at baseline (~4 days), 12 and 24 weeks. The effects on LV remodeling (i.e. 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 (69%) of patients and persisted, as late MO, in 56 (56%). Patients with late MO underwent significantly greater remodeling than those without MO (ΔLVESVi +4.1 [13.4] vs. -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 pre-discharge ceCMR remains an ominous predictor of adverse LV remodeling despite powerful anti-remodeling therapy, and may be useful in the risk-stratification of survivors of AMI.

Clinical Trial Registration Information—URL:www.clinicaltrials.gov. Unique Identifier: NCT00132093

Key words: microvascular obstruction; myocardial infarction; remodeling; magnetic resonance imaging
Background

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.\textsuperscript{1,2} Cardiac magnetic resonance imaging (CMR) facilitates examination of myocardial perfusion through early and delayed contrast-enhanced imaging sequences (ceCMR). Analysis of myocardial enhancement early (usually 2-5 minutes) after injection of a gadolinium-based contrast agent allows visualization of “early MO”, an area of hypoenhanced myocardium which bears a precise anatomical correlation with markedly reduced blood flow in animal studies, in addition to biopsy evidence of necrotic debris.\textsuperscript{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”.

Studies using myocardial contrast echocardiography to determine presence and extent of (early) MO have consistently shown strong correlations between its presence and adverse remodeling.\textsuperscript{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) post-infarct.\textsuperscript{9-13} Late MO is considered to be a stronger predictor of LV remodeling than early MO.\textsuperscript{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 anti-remodeling pharmacotherapy, the presence of late MO, while 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.\textsuperscript{15} We therefore examined the relationship between the presence of MO and a variety of infarct characteristics on LV outcomes following 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.\textsuperscript{16} Briefly, the patients were participants in a randomized, double-blinded, placebo-controlled clinical trial investigating the effects of eplerenone on LV remodeling following AMI in patients (n=100) with LV systolic dysfunction (LVSD). Eligible patients were $\geq$18 years of age and able to provide written, informed consent. All patients had an AMI in the 1-14 days prior to enrolment, and were required to have LV ejection fraction (LVEF) $<40\%$ on screening transthoracic echocardiography (TTE). Principal exclusion criteria were clinical or radiological heart failure (Killip score $>1$), established diabetes mellitus, serum creatinine $>220\mu$mol/l, serum potassium $>5$mmol/l, and conventional contraindications to MRI. ceCMR scanning was performed at baseline (prior to randomization 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 1.5T Siemens Sonata 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 8mm-thick slices with a 2mm inter-slice gap. After cine image acquisition, 0.1mmol/kg gadolinium diethylenetriaminepentaacetic acid (GE Healthcare) 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 non-selective inversion pulse without breath-hold. Typically 3-5 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 8mm and inter-slice gap 2mm; the time to inversion was varied within the range 200-300ms 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 one 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 1.05g/cm³).

Infarcted LV myocardium on ceCMR was defined as regional delayed
hyperenhancement following 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 one observer blinded
to treatment allocation and ECG data.

Early MO was defined as the appearance of at least one segment of hypoenhancement
surrounded by hyperenhancement on images acquired between 2 and 5 minutes post
contrast. 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 due to
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 hypoenhancement within a hyperenhanced region on the
delayed ceCMR images which persisted for ≥10 minutes after contrast injection. In
a similar fashion 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 anatomical location of the infarct was based on the AHA standardized 17-segment model. 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 – 1-25%, 2 – 26-50%, 3 – 51-75%, 4 – 76-100%) and calculating the mean. This produced a transmurality score. Endocardial infarct extent was calculated by measuring the circumferential extent of the infarct at each of the three short-axis slices used in the AHA segmentation model, and calculating the mean (Figure 2).

**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 ± 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 two 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 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 Chi-squared test for categorical variables. The relationships between infarct characteristics and ceCMR-measured LV volumes and function were assessed using Spearman’s correlation coefficients. All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA). A p-value less than 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 (ACE) inhibitor or angiotensin receptor blocker (ARB), 93 (93.0%) on a beta blocker and 50 (50.0%) additionally on eplerenone (by study design). The mean time from admission to screening TTE 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, while 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 vs. -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, p <0.001), LVEDVi (r=0.28, p=0.004) and LVEF (r=-0.55, p <0.001) at baseline, and with ΔLVESVi (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 three groups according to MO status: no MO (n = 31), early MO only (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 vs. -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] vs. 2.9 [0.6], $p <0.001$) as was endocardial extent (39.4° [11.1°] with MO vs. 33.5° [11.3°] without MO, $p = 0.010$).

Early MO was seen in 41/54 (75.9%) patients reperfused with thrombolytic in comparison to in 15/27 (55.5%) patients who underwent primary PCI ($p<0.001$); late MO was seen in 34/54 (63.0%) thrombolysed patients and in 12/27 (44.4%) of 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 48/56 (85.7%) patients with late MO on baseline ceCMR and in 37/44 (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%), while 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 CABG; smoker; hypertension; hypercholesterolaemia; thrombolysis; glycoprotein IIbIIIa inhibitor use; estimated glomerular filtration rate (eGFR); baseline aspirin and beta blocker therapy; 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).

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 following AMI. Unsurprisingly total infarct volume, endocardial extent and transmurality score were associated with adverse remodeling in keeping with previous studies, as all three 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 anatomical location. Importantly, the presence or absence of late MO divided patients into two distinct groups: those with late MO adverse remodeled while those without late MO reverse remodeled despite a high revascularization rate and very high prescription of evidence-based anti-remodeling medications across the cohort.
MO represents abnormal microvascular perfusion within an infarcted segment thus it is predictable that it is associated with deteriorating LV function. Several prior CMR studies have produced similar results, with incidences of MO of 45-55% amongst patients admitted with AMI, the majority of whom had low LVEF, and associations between MO and adverse remodeling. 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 between these two groups in LV remodeling over 4 months. 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 prescription of β blockers and ACE inhibitors/ARBs 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 anti-remodeling pharmacotherapy than in any other post-infarction remodeling trial to date.

Early MO predicts MACE following AMI, including cardiac death, nonfatal AMI, heart failure and stroke. We and others have shown that late MO is associated with adverse remodeling, which in turn portends progressive LV dilatation, dysfunction and premature death. Few studies, however, 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
due to diffusion of contrast into less dense areas of microvascular dysfunction;
although correlations were reported between MO and parameters of LV function,
neither study examined the influence of early and late MO on MACE.\textsuperscript{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 MACE were
provided.\textsuperscript{22} 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 \textit{likely} to be associated with adverse outcome although this
would have to be proven in an appropriately-designed trial.\textsuperscript{10,12,22}

A key aspect of post-MI care is the prediction of those patients in whom LV function
may progressively deteriorate, as 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 upon which such decisions are made. However,
early post-infarction LVEF measurement is not as powerful a predictor of adverse
remodeling and MACE as might be anticipated.\textsuperscript{5} Significant myocardial stunning may
lead to under-estimation of LVEF, while compensatory hyperkinesis of non-infarcted
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 post-infarction studies.\textsuperscript{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. While 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. Likewise, MO predicts development of a fibrous, transmural scar after AMI even when adjusted for infarct size. 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 following AMI, irrespective of the means of reperfusion. It is therefore of considerable interest that MO has been shown to be a stronger predictor of post-infarction death, re-infarction, CHF and stroke than patency of the IRA. 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 (i.e. 87.5%) ultimately had TIMI 3 flow within the IRA. This finding is of considerable significance, as TIMI flow was neither a uni- 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.\textsuperscript{9,22} We have, however, confirmed the relationship between MO and remodeling in a larger, more homogeneous patient group than those enrolled by Wu and colleagues, (n = 44, of whom 17 attended for follow-up CMR at 6 months) and by Nijveldt and colleagues (n = 60, all followed-up with CMR at 4 months), despite a higher prescription rate of anti-remodeling therapies.\textsuperscript{9,22} We also report for the first time on the inter-relationships between transmurality score, endocardial extent and MO, while the parent study design afforded the opportunity to examine whether there was any interaction between the presence of MO and the anti-remodeling efficacy of eplerenone. We found that MO was associated with significantly less remodeling in eplerenone- than in placebo-treated patients. This is of considerable interest, as the role of aldosterone antagonists on top of ACE inhibitors/ARBs and beta blockers in post-MI remodeling is still controversial. Our novel results support an anti-remodeling role for eplerenone in those at greatest risk of remodeling, i.e. those with MO.

\textbf{Limitations}

In comparison to previous studies examining infarct characteristics following AMI, there are a number of methodological issues that lead to marked inter-study 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.\textsuperscript{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 manuscript is, however, a limitation.

Finally, it must be acknowledged that the patients in this study were required to have LVSD, 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 upon from these data.

Conclusions
The findings of this study suggest that the presence or absence of late MO on pre-discharge ceCMR separates patients presenting with AMI into two groups with different remodeling outcomes regardless of powerful contemporary anti-remodeling 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-on 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.
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Disclosures: None.

References


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Table 1. Baseline characteristics of study patients. Unless otherwise stated, continuous data are expressed as mean (SD), while categorical data are expressed as percentages of the patient cohort. [eGFR = estimated glomerular filtration rate; PCI = percutaneous coronary intervention]

<table>
<thead>
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<th>Patient demographics</th>
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<td>Mean age (SD)</td>
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<td>Male/female</td>
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<td>Diastolic</td>
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<td>Aspirin</td>
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<td>Mean (SD) eGFR (ml/min)</td>
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<td>Mean (SD) creatinine (µmol/l)</td>
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<td>Eplerenone</td>
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Table 2. Mean (SD) values of CMR parameters of LV function and infarct volume at baseline (mean 93 hours) and 24 weeks after AMI.

Baseline data according to microvascular obstruction (MO) sub-groups (no MO, early MO, early + late MO) are also shown. [p* represents comparison of total population data at baseline and 24 weeks only]

<table>
<thead>
<tr>
<th>CMR parameter</th>
<th>No MO (n=31)</th>
<th>Early MO (n=69)</th>
<th>Early + late MO (n=56)</th>
<th>Total population (n=100)</th>
<th>24 weeks Total population (n=93)</th>
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<tbody>
<tr>
<td>LVESVi (mL/m²)</td>
<td>42.7 (18.8)</td>
<td>44.3 (13.4)</td>
<td>44.0 (12.7)</td>
<td>43.6 (15.2)</td>
<td>44.0 (20.7)</td>
<td>0.767</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>
<td>83.9 (18.0)</td>
<td>88.1 (23.0)</td>
<td>0.011</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>
<td>74.4 (15.3)</td>
<td>67.1 (14.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>50.5 (10.1)</td>
<td>48.3 (8.0)</td>
<td>48.4 (7.4)</td>
<td>48.9 (8.8)</td>
<td>53.0 (12.0)</td>
<td>&lt;0.001</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>
<td>34.0 (21.2)</td>
<td>20.9 (12.9)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Table 3. Baseline infarct characteristics. Infarcts classified according to the 17-segment AHA model. \(^\text{20}\) 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 number (%) for categorical variables unless otherwise stated. Two sample \(t\)-test used to compare continuous variables and chi-square test for categorical variables. †Comparison made between “anterior ± lateral” and “inferior±lateral” only as \(n=4\) in “lateral” group.

<table>
<thead>
<tr>
<th></th>
<th>Total ((n=100))</th>
<th>Anterior ± lateral ((n=55))</th>
<th>Inferior ± lateral ((n=41))</th>
<th>Lateral ((n=4))</th>
<th>(p^\dagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarct volume (ml/m(^2))</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>
<td>0.17</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>
<td>0.003</td>
</tr>
<tr>
<td>Transmural 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>
<td>0.031</td>
</tr>
<tr>
<td>Early MO (%</td>
<td>69 (69%)</td>
<td>35 (35%)</td>
<td>32 (32%)</td>
<td>2 (2%)</td>
<td>0.13</td>
</tr>
<tr>
<td>Late MO (%)</td>
<td>56 (56%)</td>
<td>29 (29%)</td>
<td>26 (26%)</td>
<td>1 (1%)</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Table 4. Change in each ceCMR-measured parameter between baseline and 24 weeks, according to microvascular obstruction (MO) status.

<table>
<thead>
<tr>
<th>ΔceCMR parameter</th>
<th>No MO (n=31)</th>
<th>Early MO only (n=13)</th>
<th>Early + late MO (n=56)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔLVESVi</td>
<td>-7.0 (12.7)</td>
<td>-4.9 (13.0)</td>
<td>4.1 (13.4)</td>
<td>0.001*</td>
</tr>
<tr>
<td>ΔLVEDVi</td>
<td>-2.5 (15.8)</td>
<td>-1.4 (9.5)</td>
<td>9.1 (15.5)</td>
<td>0.003*</td>
</tr>
<tr>
<td>ΔLVEF</td>
<td>8.5 (8.5)</td>
<td>3.9 (15.7)</td>
<td>1.7 (8.1)</td>
<td>0.010*</td>
</tr>
<tr>
<td>ΔLVMi</td>
<td>-6.0 (13.0)</td>
<td>-9.6 (7.6)</td>
<td>-7.5 (8.9)</td>
<td>ns</td>
</tr>
<tr>
<td>Δinfarct volume index</td>
<td>-6.4 (4.1)</td>
<td>-12.0 (7.6)</td>
<td>-16.8 (15.3)</td>
<td>&lt;0.001†</td>
</tr>
</tbody>
</table>

Key:

*  “early + late MO” group vs. “no MO” group only; no significant difference between “early MO only” and any other group.

† reduction in infarct volume index significantly greater in both “early and late MO” group (p<0.001) and “early MO only” group (p=0.002) than in “no MO” group.
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>ΔLVESVi (mL/m²)</th>
<th>ΔLVEDVi (mL/m²)</th>
<th>ΔLVEF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo Eplereone p</td>
<td>Placebo Eplereone p</td>
<td>Placebo Eplereone p</td>
</tr>
<tr>
<td>Early MO</td>
<td>4.0 (16.1) 0.6 (10.6) 0.003</td>
<td>10.2 (17.5) 3.7 (11.1) 0.007</td>
<td>2.4 (11.4) 1.7 (7.7) 0.068</td>
</tr>
<tr>
<td>Late MO</td>
<td>8.1 (15.2) 0.8 (11.0) &lt;0.001</td>
<td>15.9 (17.1) 3.4 (11.4) 0.001</td>
<td>2.0 (8.4) 1.4 (7.9) 0.081</td>
</tr>
</tbody>
</table>
**Figure legends**

**Figure 1**: Mid-ventricular short-axis CMR slices of a patient with an inferior myocardial infarction showing early MO (A; hypoenhanced region – arrow) but no late MO (B; no hypoenhancement within hyperenhanced region). In a separate patient with a posterolateral infarct both early MO (C; arrows) and late MO (D; arrows depicting hypoenhanced core within hyperenhanced region) are seen clearly.

**Figure 2**: Delayed-enhancement CMR of a mid-ventricular short-axis slice in a patient with full-thickness infarction of the inferior left ventricular wall. Radii were drawn to the medial and lateral extremities of the late gadolinium enhanced scar as shown, and the angle between the two radii calculated. This process was repeated at a basal and an apical short-axis slice, and the mean angle taken to represent the circumferential extent.

**Figure 3**: Boxplot displaying remodeling (ΔLVESVi between baseline and 24 weeks) according to MO status: no MO; early MO only; early and late MO. [Key: * p = 0.001 for “no MO” vs. “early+late MO” groups.]

**Figure 4**: Scatterplot displaying the inter-relationships between (baseline) infarct transmurality, endocardial extent and the presence or absence of (late) MO across the entire patient cohort. Correlation coefficient 0.26 (p=0.009) for transmurality score and endocardial extent.
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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