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CARDIOVASCULAR IMAGING

ORIGINAL ARTICLE

Temporal course of microvascular obstruction after myocardial infarction assessed by MRI

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PURPOSE
We aimed to analyze the extent of microvascular obstruction (MO) after the index event compared with the follow-up at a median of three months.

METHODS
We identified 31 patients with MO after primary percutaneous coronary intervention of acute myocardial infarction by cardiac magnetic resonance imaging. The initial examination was performed after the index event, and 27 patients had the follow-up exam after a median of three months (interquartile range, 2–4 months). In addition, we examined 10 patients without MO after transmural myocardial infarction, as a control group.

RESULTS
MO disappeared in 23 of 27 patients (85%) in the follow-up and transformed into transmural late gadolinium enhancement. In patients with persistent MO, mean MO size decreased from 2.25% to 1.25%. In patients with MO, mean infarct size decreased significantly from 20.8% to 14.7% ($P < 0.001$). In the control group, mean infarct size decreased from 12.7% to 10.5% in the follow-up scan ($P = 0.137$).

CONCLUSION
MO is significantly reduced during the follow-up after acute myocardial infarction.

Microvascular obstruction (MO) appears as a no-reflow area due to reperfusion after a prolonged myocardial ischemia. MO can be directly visualized by cardiac magnetic resonance imaging (MRI) (1–4). The exact pathophysiology of MO remains unclear; however, a no-reflow area as a result of capillary obstruction due to myocardial necrosis or distal embolization after primary percutaneous coronary intervention (PCI) is being discussed (5). MO is observed in patients with ST-elevated myocardial infarction (STEMI) and non ST-elevated myocardial infarction (NSTEMI). The fact that MO is observed in both successfully and unsuccessfully reperfused myocardium underlines the hypothesis of myocardial tissue hypoperfusion despite a patent culprit lesion (5, 6). The presence of MO has been associated with an increased risk for left ventricular remodeling, rehospitalization, reinfarction, and death and is therefore a strong prognostic marker (3, 7–10).

Some authors distinguished between early and late MO, differentiated by the period between gadolinium injection and image acquisition (9, 11). These studies identified late or persistent MO after 15 minutes as a stronger prognostic factor after acute myocardial infarction (9).

There are only a few studies on time-dependent changes of MO, predominantly with animal data. Most of these studies analyzed the extent of MO after reperfusion in the acute phase of myocardial ischemia (2, 11, 12). Data on long-term course of MO are lacking, so far.

The objective of this study was to assess the follow-up of MO in patients after acute myocardial infarction.

Methods

Study population

We identified 31 patients with MO after acute myocardial infarction and primary PCI by cardiac MRI. Patients were eligible if they had ST-segment elevation of at least 0.1 mV in

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≥2 extremity leads or at least 0.2 mV in ≥2 precordial leads; or if plasma levels for creatine-kinase (CK), creatine kinase myocardial band (CK-MB), or high-sensitive troponin I were pathologically elevated.

All patients underwent the initial scan at a median of three days (range, 1–14 days) after the index event. Of these, 27 patients underwent a follow-up cardiac MRI after a median of three months (interquartile range, 2–4 months). In addition, 10 patients with acute myocardial infarction matched for age and gender without MO served as a control group. Postinterventional reperfusion success of the infarct artery was evaluated using the thrombolysis in myocardial infarction (TIMI) criteria classifying TIMI-flow (0, lack of procedural success; I-II, incomplete reperfusion; III, reperfusion success) (18). Two independent observers blinded to clinical events and cardiac MRI results analyzed the postinterventional TIMI-flow.

The study was approved by the local ethics committee. All patients gave written informed consent.

Baseline characteristics, cardiovascular risk factors and postinterventional results for all patients are displayed in Table 1.

Main points

- Microvascular obstruction is an area of no reflow on myocardial tissue level due to myocardial necrosis, which can be visualized by delayed contrast-enhanced cardiac MRI. Its occurrence is associated with a poor prognosis in acute myocardial infarction.
- Less is known about the temporal course of microvascular obstruction and morphologic presentation at the chronic stage. In our study, we observed significant decline of microvascular obstruction after three months of acute myocardial infarction.
- The majority of patients with initial microvascular obstruction presented with transmural late gadolinium enhancement after three months. Simultaneously, infarct-size decreased in the follow-up.
- Microvascular obstruction was associated with larger infarct-size and lower left ventricular ejection fraction.
- It is important to understand the morphologic and temporal course of microvascular obstruction since prevalence of microvascular obstruction may be underestimated depending on the timing of image acquisition.

Table 1. Baseline characteristics and cardiovascular risk factors of microvascular obstruction and control groups

	Patients with MO (n=31)	Control group (n=10)
Gender (male/female), n	20/11	6/4
Age (years), median (range)	63 (32–78)	63 (38–86)
BMI >31 kg/m^2	13 (41.9)	3 (30)
Current smoker	14 (45.1)	6 (60)
Hypertension	19 (61.3)	5 (50)
Family history	9 (28.9)	3 (30)
Diabetes mellitus	8 (25.8)	1 (10)
TIMI-III flow after PCI	23 (74)	10 (100)

Data are presented as n (%), unless otherwise noted.
MO, microvascular obstruction; BMI, body mass index; TIMI, thrombolysis in myocardial infarction; PCI, percutaneous coronary intervention.

Cardiovascular MRI

Cardiac MRI was performed on a 1.5 Tesla scanner (Intera Achieva, Philips Healthcare). Independent observers blinded to clinical events and angiographic results evaluated left ventricular function, wall motion analysis and late gadolinium enhancement (LGE) images. Left ventricular function was assessed by a standard steady-state free precession technique with 2D turbo gradient echo sequence. LGE images of the left and right ventricles were acquired 10 min after injection of 0.2 mmol/kg bodyweight of gadoteridol (Prohance®, Bracco-Imaging; Konstanz, Germany). A 3D inversion-recovery turbo gradient echo sequence was used for image acquisition.

Image analysis was performed by a dedicated software (Extended MR Workspace 2.6.3.4, Philips Medical Systems and CMR 42, Version 4.0, Circle Cardiovascular Imaging Inc.). Left ventricular ejection fraction (LVEF) was calculated by assessment of the volumes of the endocardial contours in diastole and systole of the four- and two-chamber slices. Total left ventricular mass was calculated from endocardial and epicardial contours of the short-axis view.

Infarct size was defined as a combination of LGE and MO according to the suggested analyses by Mahrholdt et al. (13). Quantification of the LGE extent was performed by semi-automatic detection with a signal intensity threshold of five standard deviations above a noninfarcted remote region. MO was defined as a dark area in the center of the hyperintense LGE area (Fig. 1). Furthermore, MO size was assessed separately. Percent extent of LGE and MO in relation to the total left ventricular-mass was compared between initial and follow-up scans.

Statistical analysis

Clinical and MRI parameters were analyzed using the Wilcoxon rank-sum-test for continuous variables. Age is presented as median values with range. Each categorical variable is expressed as number and percentage of patient. *P* values less than 0.05 were considered to indicate significant difference. All statistical analysis was performed using STATA/IC 13.1 software (Stat Corp.).

Results

The distribution of age, sex, and cardiovascular risk factors were similar in both examined groups (Table 1).

MO disappeared in 23 of 27 patients (85%) in the follow-up examination and transformed into a transmural LGE pattern (Fig. 2). Four patients had a persistent MO in the follow-up scan. Two patients with persistent MO showed a reduced MO size and the other two patients showed constant MO size in the follow-up scan. Correspondingly, in patients with persistent MO, median MO size decreased from 2% (range, 1%–16%) in the initial scan to 0% (range, 0%–2%) in the follow-up (Table 2).

The median infarct size decreased significantly between the initial and follow-up scans (19% vs. 12%, $P < 0.001$) and the median LVEF showed a slight improvement from 44% to 48% ($P = 0.036$) for patients with MO in the initial scan (Table 2).

In the control group, comparison of median infarct size (11% vs. 9.5%, $P = 0.137$)

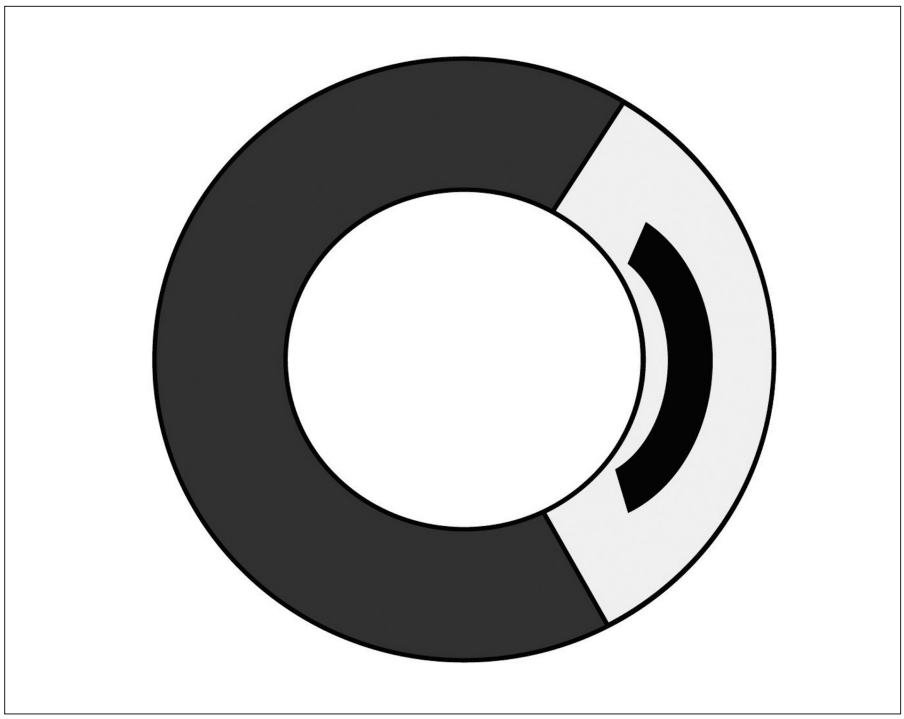

Figure 1. Schematic short axis view of the heart with an example of microvascular obstruction *(dark area)* within late gadolinium enhancement *(white area)* in the lateral segment.

Table 2. Characteristics of microvascular obstruction size, infarct size, and LVEF

	Initial cardiac MRI	Follow-up cardiac MRI	*P*
Patients with MO* (n=27)			
Relative infarct size, %	19 (7–46)	12 (5–31)	<0.001
Relative MO size (%) in patients with remaining MO (n=4)	2 (1–16)	0 (0–2)	
LVEF, %	44 (27–66)	48 (23–65)	0.036
Control group (n=10)			
Relative infarct size, %	11 (4–31)	9.5 (3–24)	0.137
LVEF, %	46 (33–70)	57.5 (33–75)	0.153

Data are presented as median and range.
*Patients with MO include 27 of 31 patients who underwent initial and follow-up scans.
MO, microvascular obstruction; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging.

and median LVEF (46% vs. 57.5%, $P = 0.153$) showed no statistically significant difference.

In the MO group, 23 patients (74%) had a postinterventional TIMI-III-flow, while all patients of the control-group had a postinterventional TIMI-III flow. Among four patients with persistent MO, two patients had a postinterventional TIMI-III-flow, and two patients had a TIMI-II-flow.

Discussion

MO after acute myocardial infarction evolved to a transmural LGE pattern after a median follow-up of three months in 85% of our patients. The massive reduction of MO might be due to an organization of the necrotic no-reflow area after myocardial infarction. So far, most observations on the time course of MO are available from short-term animal studies. Consistent with our data, Ghurge et al. (14) found a resolution of MO and T2* abnormality after six weeks in a porcine model of myocardial infarction. Rochitte et al. (2) found an increasing extent of MO and infarct size within the first 48 hours after ischemia in a study of seven dogs. The development of MO has been observed as a dynamic process that showed its largest extent 3.5 hours after reperfusion in dogs (15). In addition, Wu et al. (11) described an unchanged extent of MO at two and nine days after reperfused myocardial infarction in ten dogs. Reffelmann et al. (16) demonstrated persisting MO one month after reperfused ischemia in 29 female Fisher rats.

Our data showed that infarct size decreases both in patients with MO and in the control group during the follow-up. These data are consistent with the findings of Ibrahim et al. (17), who evaluated the time course of LGE without MO in a serial cardiac MRI study of 17 patients and demonstrated that the infarct size decreased significantly during the first week after infarction.

Furthermore, we observed that total infarct size declines significantly in patients with MO, compared with the control group. A possible reason could be the total reduction of MO size, which is included in the calculation of the total infarct size. Another aspect could be the development of shrinking myocardial scars. Wu et al. (3) observed that the presence of early MO was associated with fibrous scar formation including wall thinning in five of eight patients. The significant reduction of infarct size in our patients with MO could be explained by the progression of myocardial wall thinning, which might reduce the enhancement uptake. Corresponding to the additional findings of Wu et al. (3) we observed larger infarct-sizes in patients with MO compared with the control group. This may indicate that MO is associated with more severe infarction, as previously hypothesized by Bekkers et al. (18). They identified larger infarct sizes in patients with MO in an examination of 90 patients after acute myocardial infarction.

Previous data demonstrated the independent predictive value of MO, even after adjusting for the respective infarct size (3, 10). We found a lower mean LVEF in patients with MO compared with the control group, in the initial cardiac MRI as well as in the follow-up. These data are consistent with other studies that emphasize the prognostic value of MO and the association to left ventricular remodeling after acute myocardial infarction (8, 9, 19, 20). The findings of Wong et al. (20) suggest MO as a strong predictor for left ventricular function following STEMI. Bruder et al. (7) found MO to be independently related to prognosis in 67 patients after acute myocardial infarction treated by PCI. However, we observed a slight improvement of the LVEF both in patients with MO and the control group. These findings are consistent with the data of Bekkers et al. (18), who examined 90 patients based on the presence and absence of MO and intramyo-

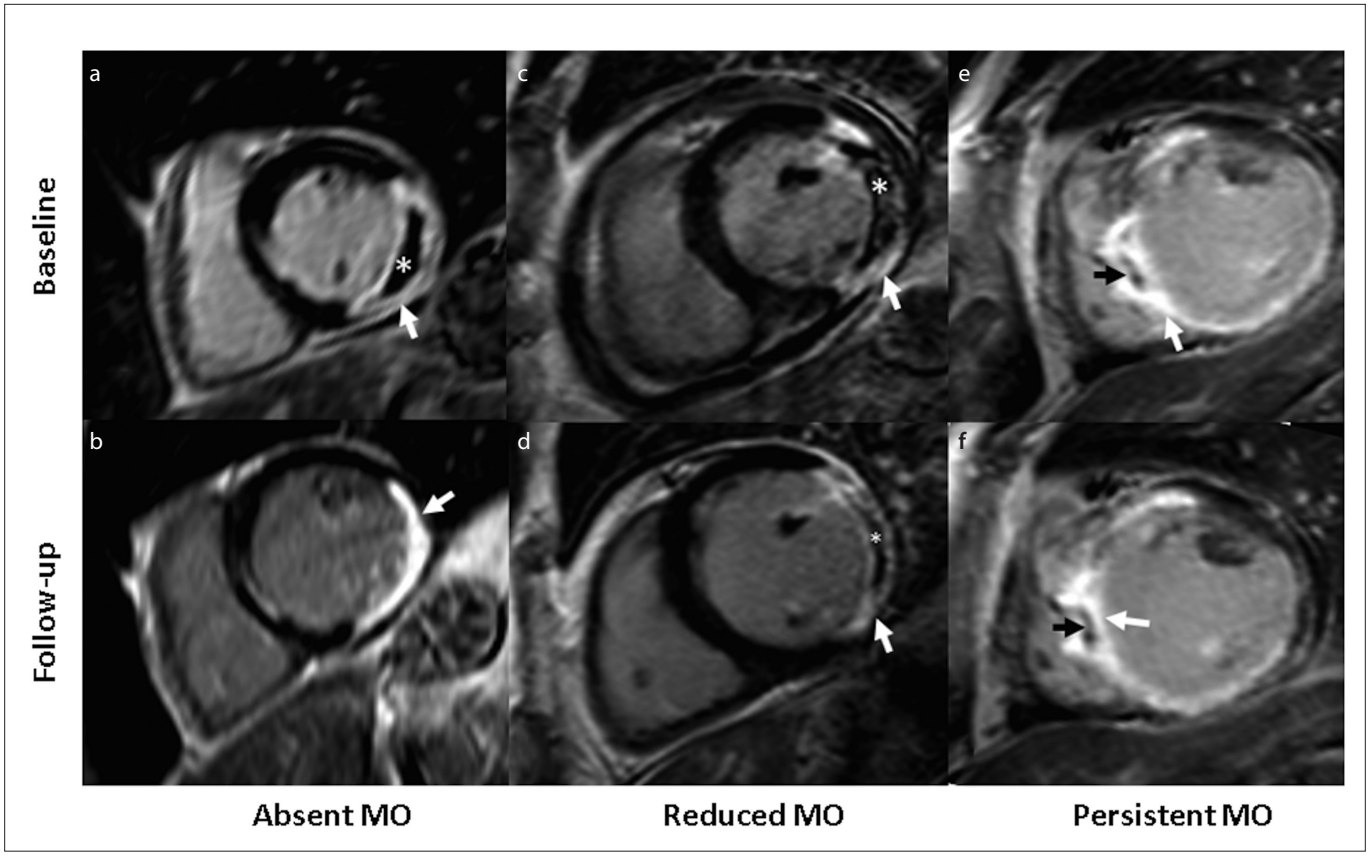

Figure 2. a-f. Examples of short axis views with microvascular obstruction (MO, *white asterisks)* and transmural late gadolinium enhancement (LGE, *white arrows)* in patients with acute myocardial infarction in the initial **(a, c, e)** and follow-up **(b, d, f)** scans. Initial MO **(a)** disappeared in the follow-up scan **(b)** and a transmural LGE *(white arrows)* remained. Another patient with MO (**c,** *white asterisks)*, who showed reduced MO size in the follow-up scan (**d,** *white asterisks)*. Images **(e)** and **(f)** show persistent MO *(black arrows)* in the initial **(e)** and follow-up **(f)** scans.

cardial hemorrhage and showed that LVEF increased in all subgroups. Morphologic analyses on MO extent were not performed in these previous studies.

Postinterventional results differed between patients with MO and patients without MO in the control group. Interestingly, only 74% of patients with MO showed a postinterventional TIMI-III-flow, while successful revascularization (TIMI-III-flow) was achieved in all patients of the control group. To elucidate the relation between reperfusion and the development of MO, larger patient numbers are necessary.

Main limitations of the study are the monocentric design and the relatively small sample size. Consequently, multicenter studies with higher patient numbers are required to confirm our acute myocardial infarction follow-up data.

In conclusion, to the best of our knowledge, we present the first cardiac MRI analysis on the temporal course of microvascular obstruction in patients with acute myocardial infarction. We observed a massive reduction of MO in the follow-up examinations. In addition, patients with MO showed larger infarct sizes compared with patients without MO.

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Conflict of interest disclosure

The authors declared no conflicts of interest.

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