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Late Gadolinium-Enhanced Cardiovascular Magnetic Resonance Evaluation of Infarct Size and Microvascular Obstruction in Optimally Treated Patients after Acute Myocardial Infarction

Robin Nijveldt, MD,[1,2] Aernout M. Beek, MD,[1] Mark B.M. Hofman, PhD,[3] Victor A.W.M. Umans, MD, PhD,[4] Paul R. Algra, MD, PhD,[5] Marieke D. Spreeuwenberg, MSc,[6] Cees A. Visser, MD, PhD,[1,2] and **Albert C. van Rossum, MD, PhD[1,2]**

Department of Cardiology, VU University Medical Center, Amsterdam, The Netherlands,[1] Interuniversity Cardiology Institute of the Netherlands, Utrecht, The Netherlands,[2] Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, The Netherlands,[3] Department of Cardiology, Medical Center Alkmaar, Alkmaar, The Netherlands,[4]; Department of Radiology, Medical Center Alkmaar, Alkmaar, The Netherlands[5] Department of Clinical Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands[6]

ABSTRACT

Purpose: **Cardiovascular magnetic resonance (CMR) is considered the standard imaging modality in clinical trials to monitor patients after acute myocardial infarction (AMI). However, limited data is available with respect to infarct size, presence, and extent of microvascular injury (MVO), and changes over time, in relation to cardiac function in these optimally treated patients. In this 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.** ***Methods:*** **Forty patients underwent cine and late gadolinium-enhanced CMR within 9 days and at 4 months after primary stenting. Left ventricular ejection fraction (LVEF), infarct size (IS) and MVO size were calculated.** ***Results:*** **IS decreased with 19.0% at follow-up ($p < 0.01$). The 23 (57.5%) patients with MVO had larger infarct size, higher left ventricular volumes and lower LVEF and more involution of IS at follow-up. Overall, LVEF improved from $42.3 \pm 9.8\%$ to $44.0 \pm 9.8\%$ ($p = 0.06$), irrespective of presence or size of MVO.** ***Conclusion:*** **Infarct size reduces over time by 19.0% in optimally treated patients after AMI. Despite optimal reperfusion, MVO was found in the majority of patients. Although patients with MVO had larger infarcts and worse indices of left ventricular remodelling, functional change at follow-up was comparable to patients without MVO.**

INTRODUCTION

Cardiovascular magnetic resonance (CMR) allows a complete and accurate assessment of left ventricular status in patients after acute myocardial infarction (AMI) (1). Functional CMR allows highly reproducible quantification of left ventricular function, and late gadolinium-enhanced (LGE) CMR visualizes and quantifies infarct size and microvascular obstruction (MVO) in vivo (2, 3). Therefore, CMR is considered the standard imaging technique in clinical trials to monitor changes in left ventricular function and infarct size in patients after AMI (4–6). Recent clinical studies have demonstrated an absolute improvement in ventricular function of 4–7% and a 26–31% infarct size involution during follow-up in patients after AMI (7–10). However, these studies were performed in heterogeneous patient groups with a variety of revascularization strategies (primary percutaneous coronary intervention [PCI], thrombolysis with or without rescue PCI, spontaneous reperfusion), and lacked detailed information on (anti-thrombotic) medication. Limited data are available about infarct size, presence and size of MVO and changes over time in patients with AMI that received uniform, optimum medical treatment, including primary stenting, abciximab, clopidogrel and statin therapy.

The aim of our study was, therefore, to prospectively investigate infarct size, presence, extent of microvascular damage, and

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Correspondence to:
Robin Nijveldt, MD
VU University Medical Center
Department of Cardiology, Room 5F003
De Boelelaan 1117, 1081 HV, Amsterdam, The Netherlands
tel: +31 20 444 22 44; fax: +31 20 444 33 95
email: R.Nijveldt@vumc.nl

changes over time in relation to left ventricular function in an optimally treated patient group after AMI.

METHODS

Patient population

Patients were eligible for the study if they were admitted with a first ST-elevation AMI, according to standard electrocardiographic and enzymatic criteria (11), and had undergone angiographically successful (no residual stenosis) primary PCI with stent implantation of the infarct related artery. Exclusion criteria were hemodynamic or other clinical instability, failure to give written informed consent, or (relative) contraindications for CMR. All patients were treated with aspirin, heparin, abcximab, clopidogrel, statins, beta-blockade and ACE-inhibitors, according to ACC/AHA practice guidelines (12). The study was approved by the local ethics committee. Forty-five consecutive patients were prospectively enrolled in the study. Five patients did not complete follow-up study and were, therefore, excluded from analysis (refusal of follow-up CMR in 3, claustrophobia in 1, and non-cardiac death in 1).

CMR protocol

CMR examination was performed on a 1.5-T clinical scanner (Sonata/Symphony, Siemens, Erlangen, Germany) using a four-element phased array cardiac receiver coil. Baseline scan was scheduled between 2 and 9 days after reperfusion, when infarct size and MVO size will not be affected by the precise time point of scanning (13, 14). Follow-up scan was performed at 4 months. ECG-gated images were acquired during repeated breath-holds of approximately 10 seconds. Left ventricular function was determined with cine imaging, using a segmented steady state free precession pulse sequence in multiple short axis views every 10 mm covering the entire left ventricle. Average in plane resolution was 1.6×2.1 mm^2, with slice thickness of 5.0–6.0 mm (repetition time/echo time = 3.2/1.6 ms, flip angle 60°, matrix 256×156, temporal resolution 35–50 ms). LGE images were obtained between 12 to 15 minutes after injection of a gadolinium-based contrast agent (Magnevist, Schering AG, Berlin, Germany)(0.2 mmol/kg) using a 2D segmented inversion recovery gradient-echo pulse sequence, with slice locations identical to the cine images, covering the whole left ventricle. Average in plane resolution was 1.4×1.8 mm^2, with slice thickness of 5.0–6.0 mm (repetition time/echo time = 9.6/4.4 ms, flip angle 25°, matrix 256×166, triggering to every other heart beat). The inversion time was set to null the signal of viable myocardium and typically ranged from 240 to 300 ms.

Data analysis and definitions

All CMR data were analyzed on a separate workstation using dedicated software (Mass, Medis, Leiden, the Netherlands). Cine and LGE images acquired during the same imaging session were matched by using slice position. Registration of follow-up to baseline cine and LGE images was achieved by consensus of two observers (RN, AMB) using anatomic landmarks, such as papillary muscles and right ventricular insertion sites. On all short axis cine slices, the endocardial and epicardial borders were outlined manually on end-diastolic and end-systolic images, excluding trabeculae and papillary muscles (15). From these left ventricular volumes, ejection fraction (LVEF) and mass were calculated.

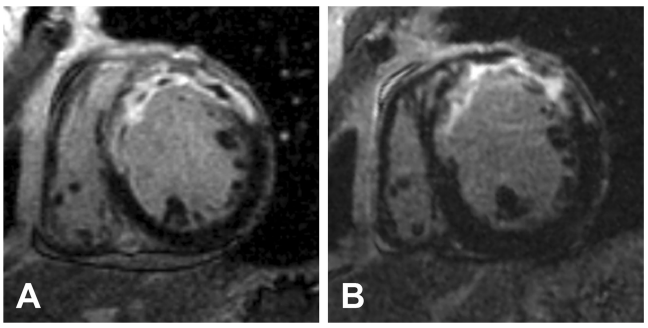

Figure 1. Late gadolinium-enhanced images of the same patient at baseline (panel A) and follow-up (panel B). Panel A demonstrates an example of a short axis slice with MVO size around 5% of the total infarct size. At follow-up (B), the area of MVO has disappeared.

The assessment of LGE images and infarct size was done as previously described (16, 17). Total infarct size was calculated by summation of all slice volumes of hyperenhancement. On LGE images, MVO was defined as any region of hypoenhancement within the hyperenhanced, infarcted area (9). MVO was included in the calculation of total infarct size. MVO size was calculated by subtraction of the hyperenhanced area from the total infarct size and expressed as a percentage of total infarct size. To study the significance of MVO size, the median percentage MVO of total infarct size was used as cut off value to distinguish between small (<median MVO size) and large areas of MVO (>median MVO size) (Fig. 1).

Images were analyzed by two observers (RN, AMB) who were blinded to patient data and clinical status.

Statistical analysis

Continuous data are expressed as mean ± SD. Student's paired sample *t* tests with Bonferroni correction were used to compare temporal change in infarct size, global LV volumes, LV mass and LVEF between baseline and follow-up study for the entire patient group. Pearson's correlation coefficients (r) were calculated, for the relation between MVO size, peak CK, LVEF, total infarct size and symptom-to-balloon time. Analysis of variances (ANOVA) was used to compare differences between patient groups with no, small, and large areas of MVO at baseline. Multivariate analysis with dummy coding for group membership for no, small, and large areas of MVO was used to study differences in temporal change between the three groups. Multiple regression analysis was used to test multiple variables (LVEF at baseline, total infarct size at baseline, extent of MVO, creatine kinase and symptom-to-balloon time) for their ability to predict change in LVEF and decrease in infarct size at follow-up. All statistical tests were two-sided with a

Table 1. Patient characteristics. Values are presented as number (%) or mean ± standard deviation

Number of patients	40
Age	56.7 ± 10.3
Risk factors	
Men	35 (87.5)
BMI (kg/m^2)	25.5 ± 2.4
Diabetes mellitus	2 (5)
Hyperlipidaemia	11 (27.5)
Hypertension	12 (30)
Smoking	25 (62.5)
Prior myocardial infarction	0 (0)
Infarct related artery	
LAD	22 (55)
LCx	8 (20)
RCA	10 (25)
Symptom-to-balloon time (hr)	3.8 ± 3.9
Bare metal stent	40 (100)
Platelet glycoprotein IIb/IIIa inhibitors	36 (90)
Maximum total creatine kinase (U/L)	2928 ± 1905
TIMI flow post-PCI (TIMI 2/TIMI 3)	
TIMI 2	3 (7.5)
TIMI 3	37 (92.5)
Medication at discharge	
Aspirin	40 (100)
Clopidogrel	40 (100)
Beta-blockade	40 (100)
Statins	40 (100)
ACE-inhibitors/ATII-antagonists	32 (80)

significance level of $p \leq 0.05$. SPSS 12.0.1 for Windows (SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

Baseline characteristics and medication are listed in Table 1. Twenty-two patients had anterior AMI, and 18 patients had inferior or lateral wall AMI. All patients had single-vessel disease. The mean time to treatment was 3.8 ± 3.9 hours. Thirty-seven patients had TIMI flow grade 3 (92.5%), and 3 patients had TIMI flow grade 2 (7.5%). All patients were on aspirin, clopidogrel, beta-blockade and statins at discharge. CMR examination was performed 5 ± 2 days and 116 ± 24 days after primary PCI. No cine or LGE images were excluded from analysis because of insufficient image quality.

Global infarct size and LV function

All patients showed hyperenhancement on LGE images at baseline and follow-up, and, in all patients, the area of hyperenhancement corresponded to the electrocardiographic infarct location. There was good correlation between baseline infarct size and peak creatine kinase ($r = 0.70$, $p < 0.01$), and baseline LVEF ($r = -0.68$, $p < 0.01$). At follow-up, infarct size decreased from 15.0 ± 10.1% to 13.0 ± 10.0% ($p < 0.01$), a mean reduction of 19.0%. Total LV myocardial mass decreased by 6.4 ± 11.1% ($p < 0.01$).

There was a non-significant trend towards improvement in LVEF from 42.3 ± 9.8% at baseline to 44.0 ± 9.8% at follow-up ($p = 0.06$). No statistical differences were found in left ventricular volumes between baseline and follow-up (Table 2). LVEF at follow-up was strongly related to LVEF at baseline ($r = 0.86$, $p < 0.01$).

Table 2. Changes in LV volumes, global function and infarct size

	Baseline	Follow-up	p-value
LVEDV (mL)	193.8 ± 55.7	194.4 ± 67.9	0.91
LVEDVi (mL/m^2)	98.6 ± 24.8	98.6 ± 31.0	0.98
LVESV (mL)	114.8 ± 48.3	112.7 ± 54.7	0.56
LVESVi (mL/m^2)	58.3 ± 22.4	57.0 ± 25.7	0.52
LVEF (%)	42.3 ± 9.8	44.0 ± 9.8	0.06
EDM (g)	126.4 ± 31.0	118.7 ± 32.5	<0.01
EDMi (g/m^2)	64.3 ± 13.4	60.3 ± 15.1	<0.01
IS (g)	19.3 ± 15.7	15.8 ± 16.0	<0.01
IS (g/m^2)	9.8 ± 7.6	8.0 ± 8.0	<0.01
IS (% of LV)	15.0 ± 10.1	13.0 ± 10.0	<0.01

LVEDV: left ventricular end-diastolic volume, LVESV: left ventricular end-systolic volume, LVEF: left ventricular ejection fraction, EDM: end-diastolic mass, IS: infarct size, -i: indexed for body surface area.

Microvascular obstruction

Twenty-three patients (57.5%) had evidence of MVO on LGE images at baseline, and no patient demonstrated MVO at follow-up.

Patients with MVO had significantly higher peak creatine kinase, higher end-systolic volumes, lower LVEF, and larger infarct size at baseline and follow-up, and higher end-diastolic volumes at follow-up ($p < 0.05$) (Fig. 2). Infarct size reduction was significantly larger in patients with MVO (20.4 ± 8.7% to 18.0 ± 9.5%) than in patients without (7.7 ± 6.9% to 6.0 ± 5.6%) ($p < 0.01$).

The median MVO size was 5.2% of total infarct size (25th to 75th percentile, 1.4–12.6%). A modest correlation was found between MVO size and infarct size at baseline ($r = 0.47$, $p < 0.01$) (Fig. 3), peak creatine kinase ($r = 0.41$, $p < 0.01$) and LVEF ($r = -0.36$, $p < 0.05$). The significance of MVO size was explored by dividing the patients with MVO into 2 groups, using the median percentage MVO of total infarct size (5.2%) as a cut off value: 11 patients had MVO size <5% (mean MVO size 2.5 ± 1.6%) and 12 patients had MVO >5% (mean MVO size 12.1 ± 5.6%). There were no significant differences in peak creatine kinase, infarct size, and LVEF between patients with small and large areas of MVO. Furthermore, even though the absolute decrease in infarct size in percentage of the LV mass at follow-up was larger in patients with MVO than in patients without MVO, there was no difference in relative decrease, and both absolute and relative decrease was comparable in patients with small and large areas of MVO.

All patients, irrespective of presence or size of MVO, revealed a non-significant trend towards improvement of LVEF at follow-up ($p = ns$) (Fig. 4). Baseline LVEF proved to be the only predictor of LVEF at follow-up ($ß = 0.80$, $p < 0.01$). After adjusting for peak creatine kinase, baseline infarct size and baseline LVEF, MVO size predicted the decrease in infarct size at follow-up ($ß = -0.53$, $p < 0.01$).

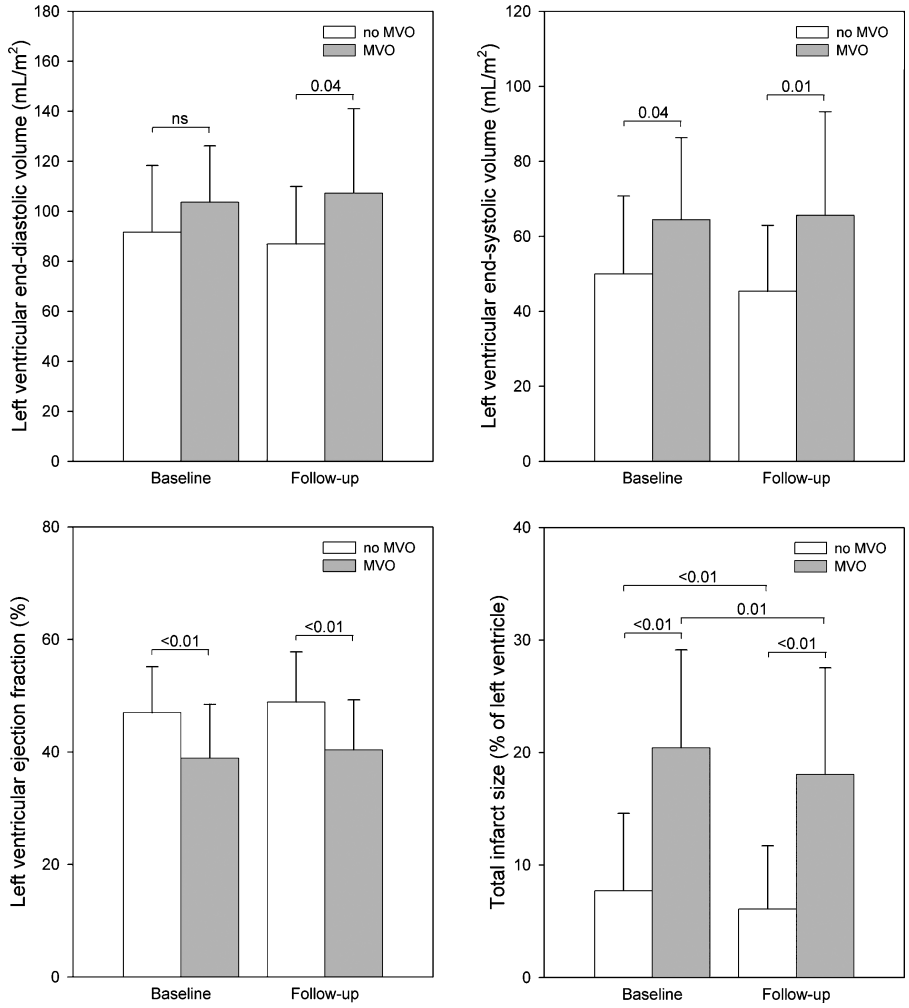

Figure 2. Subgroup analysis between patients with (gray bars) and without MVO (white bars) at baseline and follow-up. There was no significant improvement or difference between baseline and follow-up in left ventricular volumes and ejection fraction, in patients with or without MVO.

DISCUSSION

In this paper we evaluated presence, extent and temporal changes of infarct size and microvascular injury in relation to left ventricular volumes and function in a patient group with AMI, optimally treated according to current guidelines. We found a significant 19% decrease in total infarct size in 4 months. MVO was present in the majority of patients after AMI (57.5%), despite early and optimal reperfusion therapy and was associated with larger infarct size, higher left ventricular volumes and lower LVEF. There was a small, non-significant improvement in LVEF in all patients, irrespective of presence or size of MVO.

Previous publications using LGE CMR have already demonstrated that infarct volume is larger in the early phase than in the chronic phase (18) and that infarct size reduces over time (2, 8–10). This is attributed to the presence of hemorrhage and inflammation in necrotic myocardium and infarct associated edema in the early phase, which comprises a larger volume than collagenous scar tissue in the chronic phase. In addition, myocardial infarction leads to myocyte loss, which also contributes to the decline in infarct size. This may also explain the higher degree of infarct size involution in patients with MVO compared to patients without, as these infarcts contain more cellular debris due to necrosis of both myocytes and capillaries (19, 20). In our study population, baseline infarct size was comparable to previously reported data (15.6% vs 11–26%), although the degree of infarct size reduction at follow-up was smaller (19% vs 26–31%). This may be partly explained by the strict standardization of image acquisition and analysis in our study. In patients, signal intensities in hyperenhanced myocardium were at least 5 SD above remote, non-enhancing myocardium (2, 17). Contrary to previous studies, we used objective predefined criteria to measure infarct size, which is of particular concern in the early phase after myocardial infarction, when patchy and vaguely delineated hyperenhanced areas can easily overestimate infarct size calculation (17). This method is a more objective approach, however, head-to-head comparison with other studies is difficult since these studies used subjective analysis criteria. Additionally, one

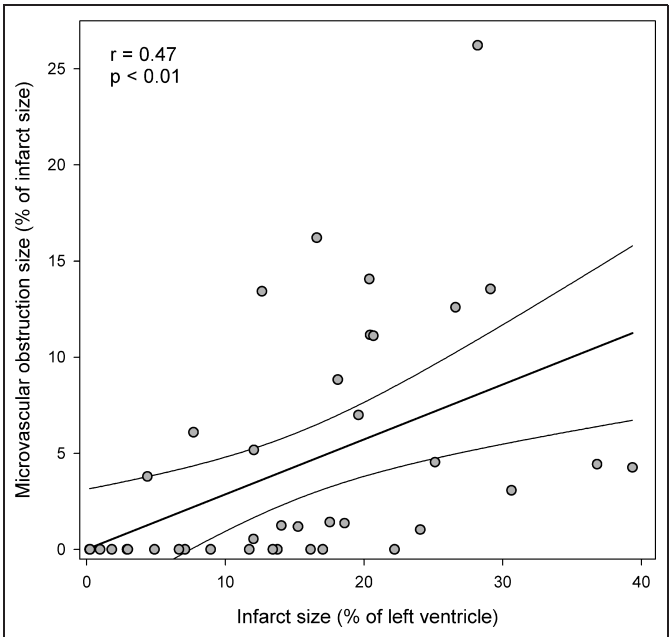

Figure 3. Correlation between MVO size and infarct size (Pearson's correlation coefficient r = 0.47, p < 0.01).

may speculate that the optimal infarct treatment in our patient group may have limited the acute inflammatory response and edema formation. This, in turn, may have led to reduced infarct shrinkage at follow-up.

Since gadolinium enhancement is a dynamic process, the size of MVO depends on the degree of microvascular injury and the related wash-in of contrast over time (21, 22). Slow, but ongoing diffusion of gadolinium into regions with less extensive microvascular injury may lead to lower incidence and smaller size of MVO at LGE compared to early gadolinium-enhanced images (23). In our study, MVO size was calculated on LGE images because this technique provides high spatial resolution and coverage of the whole left ventricle, resulting in reliable quantification of the extent of MVO. Despite the optimal treatment, we found that 57.5% of the patients had evidence of MVO. Patients with MVO had larger infarcts, demonstrated by higher peak enzyme release, larger infarct size, higher left ventricular volumes, and lower LVEF at baseline and follow-up. In our study population, MVO did not lead to left ventricular remodelling or decreased LVEF. Although function of segments with MVO has a very low likelihood of recovery, recent studies showed that global LVEF in patients with MVO is generally preserved and may actually improve at follow-up (9). In addition, we saw no difference between patients with small or large areas of MVO, both showing comparable changes in infarct size, left ventricular volumes and LVEF. The lack of adverse remodelling in patients with MVO is intriguing, since several studies in the past have clearly shown the negative impact of microvascular damage on functional outcome and prognosis (24, 25). One explanation may be that the increased sensitivity of newer imaging techniques picks up smaller degrees of microvascular injury. For example, Wu et al. found MVO in only 25% of patients, using a technique with a $1.4 \times 3.7 \times 10\ mm^3$ voxel size (average voxel size of LGE imaging as used in our study was approximately 4 times smaller) (25). Furthermore, infarct treatment has changed drastically, and the use of primary stenting and an extensive regimen of intravenous and oral platelet inhibitors has resulted in increased myocardial salvage. Thus, MVO, visualized and quantified by current LGE imaging techniques in patients after optimal treatment for AMI, may have less clinical significance than previously reported.

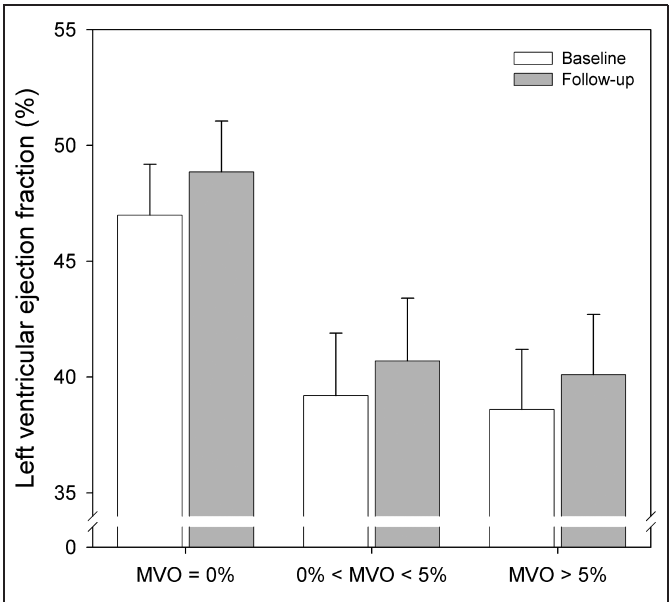

Figure 4. Multivariate analysis of patients with no, small or large areas of MVO at baseline (white bars) and follow-up (gray bars).

In conclusion, in this study we used LGE and functional CMR to monitor infarct size, microvascular damage, and left ventricular volumes and function in a patient group with AMI that received uniform, optimum medical treatment. Using standardized analysis, we found a significant involution of infarct size of 19% at 4 months. MVO was present in the majority of patients despite optimal reperfusion therapy. Although its presence identified patients with larger infarct size, higher left ventricular volumes, lower LVEF and larger infarct size involution at follow-up, it was not associated with remodelling or adverse functional outcome. Further study is necessary to evaluate long-term outcome of patients with MVO, and the prognostic significance of its extent.

Limitations

A limitation of the study is the relatively small number of patients that were used to evaluate the significance of MVO extent. This study suggested that the mere presence of MVO may be clinically more relevant than its extent, but future research should confirm these data in larger patient populations.

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