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Late microvascular obstruction after acute myocardial infarction: Relation with cardiac and inflammatory markers

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ABSTRACT

Objectives: We sought to assess the relation of late microvascular obstruction (l-MVO) size as quantified by cardiac magnetic resonance (CMR) imaging with cardiac and inflammatory marker concentrations after acute myocardial infarction (AMI).

Methods: CMR was performed in 118 consecutive patients within 8 days after successful interventional reperfused first acute ST-elevation AMI. Infarct volumes and l-MVO sizes were calculated from late enhancement (LE) sequences and functional parameters were determined from short-axis cine MR sequences. Creatine kinase (CK) and cardiac troponin T (cTnT), high-sensitivity C-reactive protein (hs-CRP) as well as lactate dehydrogenase (LD) concentrations were determined serially from day 1 to day 4 after symptom onset.

Results: L-MVO was detected in 66/118 patients (55.9%) and comprised 18.2 ± 10% of infarct size and 4.7 ± 3% of left ventricle myocardial mass. Each single-point, peak and cumulative release concentration of cTnT ($r = 0.44$ to 0.73, $p < 0.0001$), CK ($r = 0.21$ to 0.76, $p < 0.0001$), LD ($r = 0.36$ to 0.82, all $p < 0.0001$) as well as hs-CRP single-point values as assessed from day 1 to day 4 and its peak and cumulative release concentrations ($r = 0.24$ to 0.49, $p < 0.003$) significantly correlated with l-MVO size. Receiver operating curve (ROC) analysis indicated a cut-off value of 4.7 μg/l cTnT to best identify the presence of l-MVO (area under the curve (AUC) 0.904; 95% CI: 0.85–0.95; $p < 0.0001$).

Conclusion: L-MVO sizes significantly correlate with cardiac and inflammatory marker concentrations as determined early after AMI. cTnT concentration of >4.7 μg/l could help to identify patients in whom l-MVO is present.

1. Introduction

Despite rapid achievement of patency in the infarct-related artery with primary percutaneous coronary intervention (p-PCI) after acute myocardial infarction (AMI), inadequate tissue perfusion may occur [1]. Microvascular obstruction (MVO) is known to be a significant and independent prognostic factor affecting outcome [2,3]. The concomitant presence of MVO in the necrotic myocardium is generated by an interaction of multiple factors, including embolization of thrombus and plaque, endothelial dysfunction, inflammation, myocardial edema and microvascular dysfunction after AMI [4–7].

Among accurate assessment of functional and morphological cardiac details, CMR with its sequences of first-pass perfusion (FFP) and late-enhancement (LE) imaging allows the detection of MVO in clinical settings [8–11]. Prevalence of hypoenhancement of MVO assessed either by FPP or LE was found to be inconsistent [12–15], which can be explained by the dynamic of the phenomenon with a slow rise of signal intensity in the first 5–10 min and a decrease of the visible MVO area on LE images [16]. Nevertheless, late MVO (l-MVO) correspond to anatomically defined areas of microvascular injury [17,18], and recently it was shown to be the better prognostic marker of left ventricular (LV) remodeling than early MVO as assessed on FPP images [12]. Its correlation with more frequent post-MI complications such as cardiovascular death, recurrent MI, congestive heart failure and stroke emphasize the clinical importance of an early identification of patients with MVO.

Cardiac magnetic resonance (CMR) data strongly support the role of cardiac marker testing for diagnostic evaluation, therapeutic decision-making and estimation of prognosis after AMI [19–21]. In contrast to cardiac imaging, measuring simple biochemical markers is a cost-effective, easy-to-implement and widely available tool. Nevertheless, clinical studies quantifying l-MVO size by LE-CMR in a large, homogeneous study population of uniformly treated ST-elevation myocardial infarction (STEMI) patients and its correlation

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with cardiac as well as with inflammatory markers are lacking. The aim of the present study was to assess the relation between biochemical markers measured early after admission, on the one hand, and l-MVO size evaluated a few days after successful interventional treatment of AMI by contrast-enhanced magnetic resonance imaging, (CE-MRI) on the other. Furthermore, we analysed which marker would be most sensitive and specific for the prediction of l-MVO presence.

2. Materials and methods

2.1. Patient population

Hundred and eighteen (n = 118) consecutive patients admitted to the coronary care unit of the Innsbruck University Hospital with the diagnosis of first AMI were investigated with CMR. Imaging scans were performed within 8 days (3.1 ± 1.5 days) after AMI.

Inclusion criteria were a) diagnosis of ST-elevation myocardial infarction (STEMI) according to the redefined ESC/ACC committee criteria [22] as first cardiac event b) pre-procedural Thrombolysis in Myocardial Infarction (TIMI) flow ≤2 and a post-procedural TIMI 3 flow and c) Killip class <2. Furthermore, only patients with d) the exact determination of time from onset of symptoms until revascularization of infarct-related artery (pain-to-balloon-time), and e) without any contraindication to MRI were eligible for this study.

2.2. Biochemical measurements

Blood samples for all markers were collected according to a standard protocol: Creatine Kinase (CK), cardiac Troponin T (cTnT), Lactate Dehydrogenase (LD) and high-sensitivity C-reactive protein (hs-CRP) concentrations were measured at least 3 times during the first 24 h after admission and subsequently on day 1 (23 ± 3 h), day 2 (45 ± 7 h), day 3 (68 ± 7 h) and day 4 (94 ± 10 h) after onset of symptoms. Cumulative release CK, cTnT, hs-CRP and LD were estimated by calculation of the cumulative sum and by dividing this value by the number of measuring time points [23]. Maximum values of these biochemical markers, defined as highest in the concentration time course, were determined from serial samples. CK activity was determined by an enzymatic assay (Roche Diagnostics) and cTnT concentrations were measured by enzyme immunoassays (Roche Diagnostics). CRP was measured using an immuno-turbidimetric assay (Tina-quant® CRPLX, Roche Diagnostics).

2.3. Electrocardiographic and TIMI myocardial perfusion grade (TMP) analysis

ST-segment resolution (STR) approximately 90 min after PCI, expressed as the percentage of maximum ST-elevation, was calculated by 2 experienced cardiologists who were unaware of the clinical and CMR findings. Based on the degree of STR, patients were categorized in group 1 with complete STR (= 100%), group 2 with partial STR (≥50%) and group 3 with no STR (<50%).

The TIMI myocardial perfusion grade was determined by 2 experienced cardiologists who were blinded to clinical and CMR findings as previously described [24].

2.4. Cardiac magnetic resonance imaging

Patients were studied in a 1.5 Tesla (T) MR scanner (Magnetom Avanto, Siemens, Erlangen, Germany) within 8 days after AMI providing a total imaging matrix and positioned to the spine array coil and covered by an 8-channel array coil, resulting in a total of 16 array elements for signal collection.

.2.4.1. First-pass perfusion-CMR protocol

First-Pass Perfusion images were obtained in three short-axis sections centered on the mid-papillary muscle using an electrocardiographically triggered T1-weighted inversion-recovery true-FISP (Fast Imaging with Steady-State Precession) sequence (repetition time (TR): 157 ms, echo time (TE): 0.89 ms, flip angle: 50°, Field of View (FoV): 390 × 259 mm, matrix of 128 × 96, voxel size (VS): 2.6 × 1.8 × 8.0 mm, slice thickness (SL): 8 mm, and interslice gap: 2 mm). A bolus injection of 0.1 mmol/kg body mass gadolinium-contrast bolus (Spectris, Medrad, Pittsburgh, PA) [25] was administered by using an infusion pump (Spectris, Medrad, Pittsburgh, PA) at 5 ml/s. Sixty dynamic images were acquired simultaneously at each of the three sections during the first pass of the contrast agent within the myocardium.

.2.4.2. Cine-MR protocol

Cine-MR images were acquired using breath-hold, with retrospective ECG-triggered trueFISP bright-blood sequences (Field of View (FoV): 380 × 310 mm, matrix of 320 × 260, voxel size (VS): 2.6 × 1.8 × 8.0 mm, echo time (TE): 1.26 ms, repetition time (TR): 53.28 ms, and flip angle: 71°) with generalized autocalibrating partial parallel acquisition (GRAPPA, acceleration factor: 2) reconstruction. The whole myocardium was covered parallel to the short axis.

.2.4.3. Contrast-enhanced CMR protocol

Ten minutes after gadolinium injection, late-enhancement (LE)-CMR was acquired by using an ECG-triggered phase-sensitive inversion recovery (PSIR) single-shot balanced steady-state free precession sequence with consecutive slices parallel to the short axis with a SL of 8 mm, an interslice gap of 2 mm, a FoV of 400 × 360 mm, a matrix of 256 × 232, a VS of 2.2 × 1.6 × 8.0 mm, a TR of 813 ms, a TE of 1.19 ms, a FA of 45°, and a GRAPPA iPat factor of 2 [25].

2.5. Data analysis

.2.5.1. Perfusion imaging

Registration of microvascular perfusion defects on FPP images was achieved with the consensus of two observers blinded to the clinical measurements. Visualization of any reduction in signal enhancement compared to remote myocardium at first-pass analysis was defined as a qualitative evaluation of perfusion defect. Microvascular obstruction was considered qualitatively to be present if a region of hypoperfusion persisted on at least 5 consecutive temporal images after contrast bolus arrival in the left ventricle and was located in the subendocardial layer of the infarct core in at least 1 of the slices. To verify that a true perfusion deficit persisted after passage of the contrast agent, all acquired phases were evaluated.

.2.5.2. Cine imaging

An observer blinded to the clinical measurements evaluated the cine-MR short axis (11 slices, slice thickness (SL): 8 mm, and interslice gap: 2 mm) images manually by contouring left ventricular endo- and epicardial borders using standard post-processing software (ARGUS, Siemens Erlangen, Germany) and obtained thereof end-diastolic- (EDV) and end-systolic-volume (ESV) as well as ejection fraction (EF) and myocardial mass (MM). Myocardial ED to ES segmental wall thickening (SWT [mm] and [% of EdWth]) analysis was performed on the basis of the same endo- and epicardial contours.

.2.5.3. Late enhancement imaging

Planimetry of LE was evaluated quantitatively for each slice and segment using a commercially available software tool (J-Vision vs. 3.3.16, TIANI Medgraph, Brunn am Gebirge, Austria). To define hyperenhancement, a threshold of + 5 SD above the signal intensity of normal myocardium in the opposite non-infarcted myocardial segment was determined [26–30]. By multiplying the hyperenhanced area with slice thickness including the inter-slice gap, the infarct volume [cm^3] was calculated, and by multiplying the volume with the specific density of cardiac muscle (1.05 g/cm^3), the infarct mass [g] was assessed. To estimate the percentage of infarcted myocardium, infarct mass was divided by a hundredth of the myocardial mass according to cine-MRI. Papillary muscles were excluded from myocardial mass (MM) and included into left ventricular volume.

Furthermore, on LE images, a persisting area of hypoenhancement, surrounded by hyper-enhanced myocardial tissue was considered as l-MVO (Fig. 1) and quantified by manual contouring of the unenhanced myocardium. L-MVO mass as well as the percentage of late MVO myocardium was calculated.

2.6. Statistical analysis

For statistical analysis, the statistical software package SPSS 17.0 (SPSS, Chicago, IL) was used. Kolmogorov–Smirnov test was used to test for normal distribution. Pearson test was used for calculation of linear correlation for selected variables if they were distributed normally; otherwise Spearman rank correlations were calculated. Data is expressed as mean ± standard error (SE) if not presented otherwise. All statistical tests were 2 tailed and a p value < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Patient population data

The mean age of the study cohort was 55.7 ± 11.7 years (range 31 to 84 years); 99 patients (83.9%) were male and 19 (16.1%) were female.

Infarct-related arteries were the right coronary artery (RCA) in 49 patients (41.5%), the left anterior descending artery (LAD) in 46 patients (39.0%) and the left circumflex artery (LCX) in 23 patients (19.5%). All patients underwent successful PCI of the culprit lesion with a median delay of 270.61 ± 264.97 (range 30 to 1440 min) minutes, 12 of them have additional prehospital fibrinolysis (Table 1). The study was approved by the local ethics committee and informed consent was obtained from each patient before inclusion in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

3.2. Clinical, angiographic and electrocardiographic data

Relevant clinical baseline characteristics of the study population are presented in Table 1.

The mean calculated infarct size (IS) was 20 ± 15 g (18 ± 13% of LVMM), average LV-EF was 41 ± 11%, and the average segmental wall thickening (SWT%) reached 56 ± 22%. Among 118 study patients, early MVO on FPP-images was seen in 81 patients (68.6%) and out of these, 66 patients (55.9%) presented l-MVO on delayed-enhancement MR. Delay in time-to-revascularisation correlated significantly with the presence of l-MVO ($r = 0.31$, $p < 0.001$), patients showing l-MVO had a significantly longer ischemia time than those without persistent MVO (322 vs. 202 min, $p < 0.001$). Furthermore, patients with and without l-MVO differed significantly ($p < 0.02$) in pre-procedural thrombolysis in myocardial infarction (TIMI) flow grade: 0.27 ± 0.6 vs. 0.54 ± 0.8, respectively. In addition, patients with l-MVO had significantly greater infarcts ($p < 0.0001$) and showed highly significant worse global ($p < 0.0001$) and regional ($p < 0.0001$) myocardial function. Nevertheless, any study patient – with or without l-MVO – survived the hospitalisation period after the acute event.

Complete STR analysis was performed in 75 patients (63.6%), for the residual 43 patients ECG before pPCI was not electronically available due to the fact that these patients were brought straight from peripheral hospitals to the catheter lab. All of the patients showing a STR <50% (17 and 22.6%) demonstrated l-MVO. Furthermore, there was a highly significant difference in l-MVO size between patients with <50% STR and patients with partial (≥50%) STR ($p < 0.0001$) as well as with patients showing complete STR ($p < 0.0001$) (Fig. 2).

Moreover, correlations between TMP grades and l-MVO size ($r = -0.60$, $p < 0.0001$) as well as with IS ($r = -0.51$, $p < 0.0001$) revealed highly significant and inverse correlations. In addition, l-MVO size ($p < 0.0001$), IS ($p < 0.0001$) as well as LV-EF ($p < 0.001$) were highly significant different in patients with TMP grade 3 (67 patients, 56.8%) and patients with TMP grade <3 (51 patients, 43.2%).

3.3. Late MVO size and correlation with biochemical marker

The quantification of l-MVO regions revealed a mean calculated l-MVO mass of 5.3 ± 4 g, and comprised 4.7 ± 3% of LVMM and

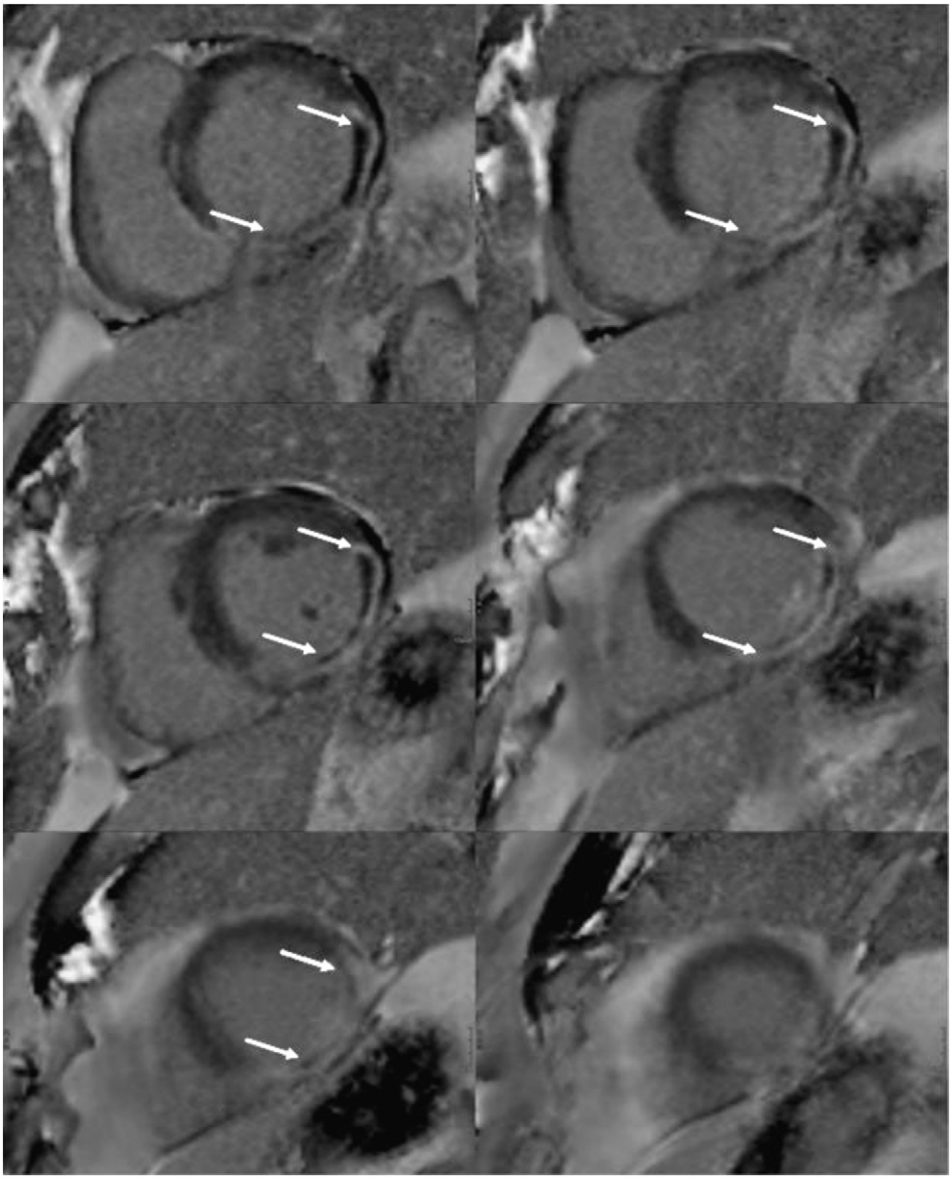

Fig. 1. Example of l-MVO in a posterior infarction depicted as a persisting area of hypoenhancement (white arrowheads) surrounded by hyperenhanced myocardial tissue on LE images.

Table 1
Clinical characteristics of the study population.

Study variable	Entire cohort n = 118 (100%)
Mean age (years)	55.7 ± 11.7
Female n	19 (16.1%)
STEMI	118 (100%)
Pain-to-ballon-time (min)	270.61 ± 264.97 (range 30–1440)
Delay AMI onset to CMR (days)	3.11 ± 1.5
Prehospital fibrinolysis	12 (10.2%)
p-PTCA	106 (89.8%)
Cardiovascular risk factor	
Hypertension	71 (60.2%)
Current smoking	68 (57.6%)
Hypercholesterolemia	95 (80.5%)
Diabetes mellitus	11 (9.30%)
Creatinine (μmol/l)	85.08 ± 1.4
Positive family history	25 (21.2%)
Infarct related artery	
Left anterior descending artery	46 (39.0%)
Right coronary artery	49 (41.5%)
Left circumflex artery	23 (19.5%)

AMI: acute myocardial infarction, CMR: cardiac magnetic resonance, n: number, and p-PCI: primary-percutaneous intervention.

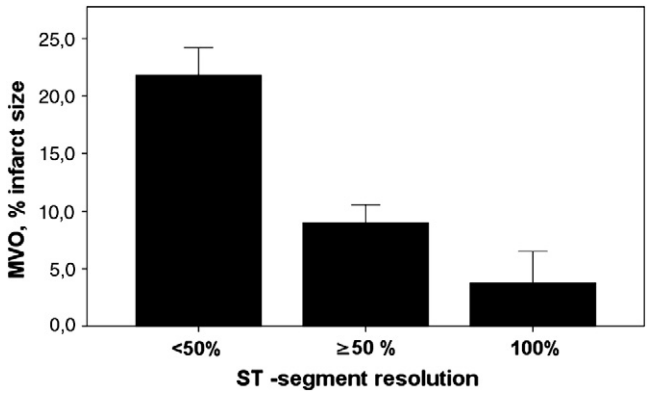

Fig. 2. There was a highly significant difference in l-MVO size between patients with <50% STR and patients with partial (≥50%) STR (p<0.0001) as well as with patients showing complete STR (p<0.0001).

18.2 ± 10% of IS. L-MVO size (gram and% of IS in gram) correlated with IS in gram (r = 0.79 and 0.48, all p<0.0001) as well as with end-diastolic (EDV) (r = 0.37 and 0.34, all p<0.004) and end-systolic volume (ESV) (r = 0.56 and 0.31, all p<0.0001) and inversely with EF (r = −0.51 and −0.47 all p<0.0001) and with segmental wall thickening (SWT%) (r = −0.51 and −0.47, all p<0.0001).

Patients with and without l-MVO significantly differed in the concentrations of measured single-time, peak and cumulative release concentration of CK (all p<0.01), cTnT (all p<0.005) and LD (all p<0.01). Furthermore, hs-CRP values of the first 48 h after symptom onset as well as their peak and cumulative release concentrations were significantly higher (all p<0.04) in patients showing microvascular perfusion defect on LE images than in those without l-MVO.

cTnT – single values (r = 0.50 to 0.73, all p<0.0001), peak (r = 0.72, all p<0.0001) and cumulative release concentrations (r = 0.68, all p<0.0001) provided significant correlations with measured l-MVO size (gram and% of infarct size in gram). Each of the CK single-point values (r = 0.21 to 0.71, all p<0.0001), its cumulative release (r = 0.68 and 0.59, p<0.0001) and peak concentrations (r = 0.76 and 0.61, p<0.0001) significantly correlated with the extent of l-MVO in gram as well as in% of infarct size in gram. Furthermore, any assessed (single-point, peak and cumulative release values) LD-(r = 0.21 to 0.82, all p<0.0001) showed significant correlations with absolute and relative l-MVO masses, respectively.

In addition, hs-CRP values as assessed from day 1 to day 4 (r = 0.23 to 0.49, all p<0.03) after symptom onset correlated with l-MVO size in gram and % of infarct size in gram as well as its peak (r = 0.50 and 0.30, all p<0.0001) and cumulative release concentrations (r = 0.49 and 0.32, all p<0.0001). Correlations of single-point, peak and cumulative release values of cTnT, CK, LD and hs-CRP with CMR-estimated l-MVO size in gram as well as l-MVO size in percent of infarct size in gram are presented in Table 2.

Furthermore, presence of early and late MVO was correlated with the biochemical measurements, resulting in consistently stronger relations of any tested marker concentrations with the presence of l-MVO than with that of early MVO (e.g.: cTnT concentrations: r = 0.34 to 0.71, all p<0.001 with presence of l-MVO; r = 0.21 to 0.50, all p<0.007 with presence of early MVO).

ROC analysis displayed the performance of peak cTnT for prediction of the presence of l-MVO (Fig. 2). The sensitivity and specificity of the assay for predicting persistent MVO was calculated at the determining limits of the ROC curves. The AUC of maximum cTnT (0.904; 95% CI, 0.852 to 0.955) with the optimal cutoff value of 4.7 μg/l revealed 78% sensitivity and 83% specificity in the prediction of the presence of late MVO (Fig. 3).

4. Discussion

The main findings of the present study are the significant correlations of l-MVO size as assessed by LE-CMR with single-point, cumulative release and peak concentrations of cTnT, CK, hs-CRP as well as of LD, measured in the first four days after AMI. In comparison to patients without l-MVO, those showing l-MVO within the hyperenhanced myocardium on LE images presented significantly higher concentrations of inflammatory and cardiac markers on the first days after the acute event. Furthermore, our results highlight the potential of maximum cTnT concentration, measured on the first four days after symptom onset, to identify patients with l-MVO with high specificity and sensitivity.

The presence of MVO has enormous clinical impact as it plays a significant role in the pathophysiology of AMI and predicts poor cardiovascular outcome after myocardial infarction [2,3]. CMR can demonstrate microcirculatory damage either with FPP or LE sequences [8–10]. Reports of prevalences of MVO assessed either with FPP or LE-imaging are inconsistent; this can be explained by the dynamics of the MVO phenomenon [12–15]. However, in agreement with the previous studies, our findings indicate that early hypoenhancement is more often observed than are hypoenhanced areas during LE. We found early MVO in 68.6% vs. late MVO in 55.9% which is analogous to the incidences described by a recently published study (70 vs. 59%), suggesting that FPP is more sensitive than LE for the identification of MVO [12]. Nevertheless, Nijveldt et al. demonstrated persistent hypoenhancement as best in determining left ventricular remodeling [12], whereas FPP imaging seems to lack in the predictive power after AMI [13]. Compared to the presence of early MVO, persistence of perfusion defects on LE imaging in the current study showed stronger correlations with the biochemical measurements, suggesting microvascular injury at late imaging may be clinically more important than the mere presence of some hypoenhanced areas that easily fill in with contrast material after a short delay.

Elevated levels of CRP may promote inflammatory processes occurring in the vasculature, reflect unstable coronary lesion in patients with unstable angina [31,32] and are associated with AMI [33]. Furthermore, parenteral injection of human CRP in a rat model was shown to enhance tissue damage, whereas inhibition of complement-dependent mechanism attenuates the infiltration of neutrophils into the jeopardized myocardium and reduces infarct size [34]. Moreover, independently of markers of infarct size, CRP is known to be associated with an increased risk of short-term mortality and

Table 2
Correlations of single-point, peak and cumulative release values of cTnT, CK, LD and CRP with CMR-estimated l-MVO size in gram as well as with l-MVO size in % of infarct size.

Time, hours			Correlation to l-MVO, gram				Correlation to l-MVO, % of infarct size			
Point	Mean	SD	cTnT, μg/l	CK, U/l	LD, U/l	CRP, mg/dl	cTnT, μg/l	CK, U/l	LD, U/l	CRP, mg/dl
Admission	2.6	1.6	0.500**	0.577**	0.420**	0.109	0.437**	0.411**	0.362**	0.108
8 h	6.9	2.5	0.551**	0.714**	0.441**	0.143	0.444**	0.495**	0.501**	0.110
16 h	12.2	3.4	0.704**	0.707**	0.822**	0.203	0.653**	0.555**	**0.770****	0.124
24 h	23.0	3.5	0.642**	0.638**	**0.829****	0.455**	0.611**	0.483**	0.654**	0.247*
48 h	45.2	6.8	0.625**	0.522**	0.779**	0.480**	0.591**	0.405**	0.603**	0.250*
72 h	68.1	7.2	0.656**	0.461**	0.777**	0.409**	0.634**	0.381**	0.625**	0.238*
96 h	94.3	10.3	**0.738****	0.307**	0.543**	**0.493****	0.657**	0.215**	0.566**	0.290*
Maximum	–	–	0.720**	**0.764****	0.821**	0.501**	0.643**	**0.610****	0.644**	0.300**
Mean	–	–	0.688**	0.684	0.786**	0.490**	**0.674****	0.594**	0.629**	**0.329****

cTnT: cardiac troponin T, CK: Creatine Kinase, CRP: c-reactive protein, LD: lactate dehydrogenase, and l-MVO: late microvascular obstruction.
* $p<0.05$.
** $p<0.005$.

development of heart failure [35,36], reflecting the inflammatory processes associated with infarct healing or expansion and post-infarction ventricular remodeling [36–38]. Several studies reported CRP to be related to the degree of myocardial necrosis assessed either by echocardiography or by cardiac marker testing [39,40]. In our study, infarct size as well as extent of l-MVO as determined by CMR was strongly related to serial measurements of hs-CRP. Highest correlations were found for maximum hs-CRP concentrations measured in the first four days after AMI with l-MVO size in gram as well as for cumulative hs-CRP concentration with l-MVO size in % of infarct size. To the best of our knowledge, this is the first study to demonstrate in a large population a correlation between hs-CRP and the extent of l-MVO.

Recent data using both scintigraphy and CMR demonstrated that both cTnT and CK values as determined within 96 h after AMI correlate optimally with infarct size assessed by imaging approaches [19,20,41,42]. However, to date clinical trials correlating l-MVO size with biomarkers of myocardial damage in a homogeneous and large study population of STEMI patients are lacking. Additionally to the relation of hs-CRP and l-MVO size, our data highlight significant correlations of currently used (cTnT and CK) and conventional (LD) cardiac markers with the extent of l-MVO.

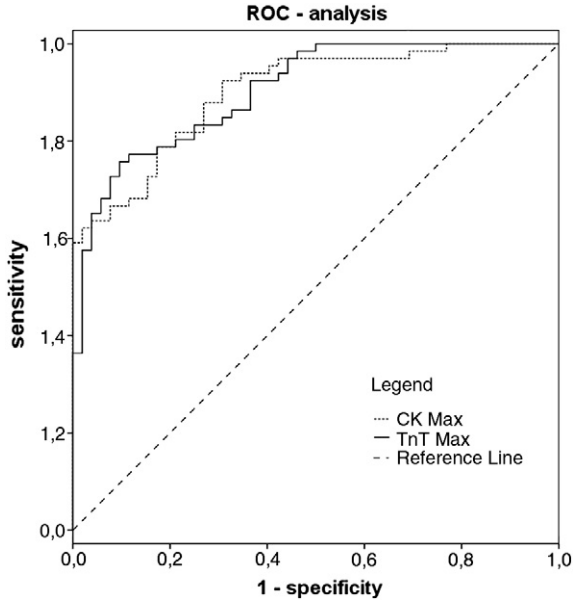

Fig. 3. Receiver-operator characteristic (ROC) curve for determining the optimum cut-off value for prediction of l-MVO presence with maximum cTnT and maximum CK concentrations within 4 days after symptom onset of acute myocardial infarction. The AUC of maximum cTnT (0.904; 95% CI, 0.852 to 0.955) with the optimal cutoff value of 4.7 μg/l had 78% sensitivity and 83% specificity in the prediction of the presence of late MVO. For maximum CK, the AUC with the optimal cutoff value of 1618 U/l had 80% sensitivity and 79% specificity in the prediction of the presence of late MVO.

Many factors contribute to the complex process of microvascular dysfunction. Beside erythrocyte stasis of microvasculature, compression of capillaries by edematous and necrotic myocytes, arteriolar spasm and progressive endothelial abnormalities, the ultrastructural damage due to the ischemia itself and its subsequent global inflammatory response mediated by cytokine release are well investigated [4–7]. Despite the impaired microcirculation in the infarct core due to MVO, necrotic debris and inflammatory mediators may slowly diffuse from the infarct zone to systemic circulation and subsequently the hepatic release of acute phase reactant such as CRP is increased.

Furthermore, our study is in accordance with a report suggesting that incomplete STR is strongly associated with the presence of l-MVO and that the extent of STR correlates with the l-MVO size [43]. L-MVO size in patients with STR <50% was highly significantly greater than in those with >50% or complete STR.

In conclusion, either single analysis, cumulative or peak concentrations of modern (cTnT and CK) and conventional cardiac markers (LD) as well as hs-CRP measurements of the first 4 days after AMI correlate well with extent of l-MVO as determined by CMR.

Our results suggest that cardiac marker testing in the acute phase of STEMI may be a useful tool in estimating microcirculatory damage. In addition, a cTnT concentration of >4.7 μg/l seems to predict the presence of l-MVO with a high sensitivity and specificity. These facts provide a cost-effective, convenient and thus widely applicable tool for clinicians to get an early risk stratification and important prognostic information in patients with an acute myocardial infarction.

Conflict of Interest

None.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [44].

References

[1] Lepper W, Hoffmann R, Kamp O, et al. Assessment of myocardial reperfusion by intravenous myocardial contrast echocardiography and coronary flow reserve after primary percutaneous transluminal coronary angioplasty [correction of angiography] in patients with acute myocardial infarction. Circulation 2000;101:2368–74.

[2] Wu KC, Zerhouni EA, Judd RM, et al. Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 1998;97:765–72.
[3] Ito H, Tomooka T, Sakai N, et al. Lack of myocardial perfusion immediately after successful thrombolysis. A predictor of poor recovery of left ventricular function in anterior myocardial infarction. Circulation 1992;85:1699–705.
[4] Kloner RA, Ganote CE, Jennings RB. The "no-reflow" phenomenon after temporary coronary occlusion in the dog. J Clin Invest 1974;54:1496–508.
[5] Braunwald E, Kloner RA. Myocardial reperfusion: a double-edged sword? J Clin Invest 1985;76:1713–9.
[6] Gibson CM, Ryan KA, Murphy SA, et al. Impaired coronary blood flow in nonculprit arteries in the setting of acute myocardial infarction. The TIMI study group. Thrombolysis in myocardial infarction. J Am Coll Cardiol 1999;34:974–82.
[7] Roe MT, Ohman EM, Maas AC, et al. Shifting the open-artery hypothesis downstream: the quest for optimal reperfusion. J Am Coll Cardiol 2001;37:9–18.
[8] Lima JA, Judd RM, Bazille A, Schulman SP, Atalar E, Zerhouni EA. Regional heterogeneity of human myocardial infarcts demonstrated by contrast-enhanced MRI. Potential mechanisms. Circulation 1995;92:1117–25.
[9] Judd RM, Lugo-Olivieri CH, Arai M, et al. Physiological basis of myocardial contrast enhancement in fast magnetic resonance images of 2-day-old reperfused canine infarcts. Circulation 1995;92:1902–10.
[10] Hombach V, Grebe O, Merkle N, et al. Sequelae of acute myocardial infarction regarding cardiac structure and function and their prognostic significance as assessed by magnetic resonance imaging. Eur Heart J 2005;26:549–57.
[11] Klug G, Trieb T, Schocke M, et al. Quantification of regional functional improvement of infarcted myocardium after primary PTCA by contrast-enhanced magnetic resonance imaging. J Magn Reson Imaging 2009;29:298–304.
[12] Nijveldt R, Hofman MB, Hirsch A, et al. Assessment of microvascular obstruction and prediction of short-term remodeling after acute myocardial infarction: cardiac MR imaging study. Radiology 2009;250:363–70.
[13] Baks T, van Geuns RJ, Biagini E, et al. Recovery of left ventricular function after primary angioplasty for acute myocardial infarction. Eur Heart J 2005;26:1070–7.
[14] Nijv eldt R, Beek AM, Hofman MB, et al. Late gadolinium-enhanced cardiovascular magnetic resonance evaluation of infarct size and microvascular obstruction in optimally treated patients after acute myocardial infarction. J Cardiovasc Magn Reson 2007;9:765–70.
[15] Lund GK, Stork A, Muellerleile K, et al. Prediction of left ventricular remodeling and analysis of infarct resorption in patients with reperfused myocardial infarcts by using contrast-enhanced MR imaging. Radiology 2007;245:95–102.
[16] Raff GL, O'Neill WW, Gentry RE, et al. Microvascular obstruction and myocardial function after acute myocardial infarction: assessment by using contrast-enhanced cine MR imaging. Radiology 2006;240:529–36.
[17] Rochitte CE, Lima JA, Bluemke DA, et al. Magnitude and time course of microvascular obstruction and tissue injury after acute myocardial infarction. Circulation 1998;98:1006–14.
[18] Wu KC, Kim RJ, Bluemke DA, et al. Quantification and time course of microvascular obstruction by contrast-enhanced echocardiography and magnetic resonance imaging following acute myocardial infarction and reperfusion. J Am Coll Cardiol 1998;32:1756–64.
[19] Steen H, Giannitsis E, Futterer S, Merten C, Juenger C, Katus HA. Cardiac troponin T at 96 hours after acute myocardial infarction correlates with infarct size and cardiac function. J Am Coll Cardiol 2006;48:2192–4.
[20] Giannitsis E, Steen H, Kurz K, et al. Cardiac magnetic resonance imaging study for quantification of infarct size comparing directly serial versus single time-point measurements of cardiac troponin T. J Am Coll Cardiol 2008;51:307–14.
[21] Ingkanisorn WP, Rhoads KL, Aletras AH, Kellman P, Arai AE. Gadolinium delayed enhancement cardiovascular magnetic resonance correlates with clinical measures of myocardial infarction. J Am Coll Cardiol 2004;43:2253–9.
[22] Alpert JS, Thygesen K, Antman E, Bassand JP. Myocardial infarction redefined — a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. J Am Coll Cardiol 2000;36:959–69.
[23] Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. Bmj 1990;300:230–5.
[24] Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. Circulation 2000;101:125–30.
[25] Metzler B, Schocke MF, et al. Decreased high-energy phosphate ratios in the myocardium of men with diabetes mellitus type I. J Cardiovasc Magn Reson 2002;4:493–502.
[26] Nowosielski M, Schocke M, Mayr A, et al. Comparison of wall thickening and ejection fraction by cardiovascular magnetic resonance and echocardiography in acute myocardial infarction. J Cardiovasc Magn Reson 2009;11:22.
[27] Beek AM, Kuhl HP, Bondarenko O, et al. Delayed contrast-enhanced magnetic resonance imaging for the prediction of regional functional improvement after acute myocardial infarction. J Am Coll Cardiol 2003;42:895–901.
[28] Bondarenko O, Beek AM, Hofman MB, et al. Standardizing the definition of hyperenhancement in the quantitative assessment of infarct size and myocardial viability using delayed contrast-enhanced CMR. J Cardiovasc Magn Reson 2005;7: 481–5.
[29] Kim RJ, Wu E, Rafael A, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000;343: 1445–53.
[30] Mayr A, Mair J, Schocke M, et al. Predictive value of NT-pro BNP after acute myocardial infarction: Relation with acute and chronic infarct size and myocardial function. Int J Cardiol 2009 Nov. 5 [Epub ahead of print].
[31] Morrow DA, Rifai N, Antman EM, et al. C-reactive protein is a potent predictor of mortality independently of and in combination with troponin T in acute coronary syndromes: a TIMI 11A substudy. Thrombolysis in myocardial infarction. J Am Coll Cardiol 1998;31:1460–5.
[32] Buffon A, Biasucci LM, Liuzzo G, D'Onofrio G, Crea F, Maseri A. Widespread coronary inflammation in unstable angina. N Engl J Med 2002;347:5–12.
[33] Biasucci LM, Vitelli A, Liuzzo G, et al. Elevated levels of interleukin-6 in unstable angina. Circulation 1996;94:874–7.
[34] Weisman HF, Bartow T, Leppo MK, et al. Soluble human complement receptor type 1: in vivo inhibitor of complement suppressing post-ischemic myocardial inflammation and necrosis. Science 1990;249:146–51.
[35] Pietila KO, Harmoinen AP, Jokiniitty J, Pasternack AI. Serum C-reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment. Eur Heart J 1996;17:1345–9.
[36] Suleiman M, Aronson D, Reisner SA, et al. Admission C-reactive protein levels and 30-day mortality in patients with acute myocardial infarction. Am J Med 2003;115:695–701.
[37] Maekawa Y, Anzai T, Yoshikawa T, et al. Prognostic significance of peripheral monocytosis after reperfused acute myocardial infarction:a possible role for left ventricular remodeling. J Am Coll Cardiol 2002;39:241–6.
[38] Entman ML, Michael L, Rossen RD, et al. Inflammation in the course of early myocardial ischemia. FASEB J 1991;5:2529–37.
[39] Anzai T, Yoshikawa T, Shiraki H, et al. C-reactive protein as a predictor of infarct expansion and cardiac rupture after a first Q-wave acute myocardial infarction. Circulation 1997;96:778–84.
[40] Pietila K, Harmoinen A, Hermens W, Simoons ML, Van de Werf F, Verstraete M. Serum C-reactive protein and infarct size in myocardial infarct patients with a closed versus an open infarct-related coronary artery after thrombolytic therapy. Eur Heart J 1993;14:915–9.
[41] Licka M, Zimmermann R, Zehelein J, Dengler TJ, Katus HA, Kubler W. Troponin T concentrations 72 hours after myocardial infarction as a serological estimate of infarct size. Heart 2002;87:520–4.
[42] Panteghini M, Cuccia C, Bonetti G, Giubbini R, Pagani F, Bonini E. Single-point cardiac troponin T at coronary care unit discharge after myocardial infarction correlates with infarct size and ejection fraction. Clin Chem 2002;48:1432–6.
[43] Kim JS, Ko YG, Yoon SJ, et al. Correlation of serial cardiac magnetic resonance imaging parameters with early resolution of ST-segment elevation after primary percutaneous coronary intervention. Circ J 2008;72:1621–6.
[44] Shewan LG and Coats AJ. Ethics in the authorship and publishing of scientific articles. Int J Cardiol 2010;144:1–2.