The Sum of ST-Segment Elevation Is the Best Predictor of Microvascular Obstruction in Patients Treated Successfully by Primary Percutaneous Coronary Intervention. Cardiovascular Magnetic Resonance Study

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Introduction and objectives. The usefulness of ST-segment elevation resolution (STR) for predicting epicardial reperfusion is well established. However, it is still not clear how ST-segment changes are related to microvascular obstruction (MVO) observed by cardiovascular magnetic resonance (CMR) after primary percutaneous coronary intervention (pPCI) for ST-segment elevation myocardial infarction (STEMI).

Methods. The study involved 85 consecutive patients admitted for a first STEMI and treated by pPCI who had a patent infarct-related artery. An ECG was recorded on admission and 90 min and 6, 24, 48 and 96 h after pPCI. Thereafter, STR and the sum of ST-segment elevation (sumSTE) in all leads were determined.

Results. Overall, CMR revealed MVO in 37 patients. In infarcts with MVO, sumSTE was greater both before and after revascularization than in infarcts without MVO (P ≤ 0.001 at all times). In contrast, there was no significant difference in the magnitude of STR between infarcts with and without MVO 90 min after revascularization (P = 1.0), though there was after 6 h (P ≤ 0.05 at all times). The area under the receiver operating characteristic curve for detecting MVO was greater for sumSTE than STR (P ≤ 0.05 for all measurements). On multivariate analysis, after adjusting for clinical, angiographic and ECG characteristics, a sumSTE >3 mm 90 min after pPCI was an independent predictor of MVO on CMR, while an STR sumSTE >3 mm 90 min after pPCI was an independent predictor of MVO on CMR, while an STR

Conclusions. MVO was associated with a significantly increased sumSTE at all times after revascularization. The difference in the magnitude of STR between infarcts with and without MVO was significant only >6 h after revascularization. The best predictor of MVO was a sumSTE >3 mm 90 min after pPCI.

Key words: Cardiovascular magnetic resonance. Microvascular obstruction. ST-segment resolution. Sum of ST-segment elevation. ST-segment elevation myocardial infarction.
We analyzed the usefulness of STR and the extent of the sum of ST-segment elevation (sumSTE) for detecting CMR-derived MVO in a consecutive group of patients with STEMI treated with pPCI and re-established TIMI flow grade 3 in the infarct related artery.

**METHODS**

**Patients**

We prospectively included 100 consecutive patients admitted to a university hospital for a first STEMI treated with pPCI within 12 hours after the onset of chest pain. The inclusion criteria were: a) stable clinical course without complications during hospitalization; b) no contraindications to CMR; and c) TIMI flow grade 3 in the infarct related artery after revascularization. We excluded 4 patients because of claustrophobia and 7 patients due to TIMI flow grade ≤2 after pPCI. Patients with inconclusive ECG (bundle branch block or ventricular pacing) were excluded (4 cases). Therefore, the final study group comprised 85 patients. All patients gave written informed consent and the study protocol was approved by the local ethics committee.

**Percutaneous Coronary Intervention and Angiography**

pPCI was performed within 12 hours of symptom onset in all patients. TIMI flow grade\(^{12}\) before and after the procedure was assessed. Myocardial blush grade\(^{13}\) was evaluated after pPCI. Angiographic data was analyzed by an experienced investigator unaware of patient identity, ECG and CMR results using standard software (HM3000, Philipps, Best, The Netherlands).

**ECG Analysis**

A standard 12 lead ECG was recorded upon admission and at 90 minutes, 6 hours, 24 hours, 48 hours, and 96 hours after pPCI at a paper speed of 25 mm/s and an amplification of 10 mm/mV. ECG data was evaluated by an observer unaware of patient identity, angiographic data and CMR results. The isoelectric line was defined as the level of the preceding TP-segment. Extent of ST-segment elevation was measured 20 ms after the J-point in every lead. The following ECG parameters were determined:

- Sum of ST-segment elevation (sumSTE): sumSTE was manually calculated as the sum of elevation in V1–6,
I, and aVL for anterior infarction and as the sum of elevation in leads II, III, aVF, V5, and V6 for non-
anterior infarction.17,14,15 For dichotomic univariate
analysis of sumSTE we implemented cut-off values
established on the basis of the area under the
receiver operating characteristics curves (AUC) for
predicting MVO by maximizing the observed overall
diagnostic accuracy (minimizing the number of false
positives plus the number of false negatives).
– ST-segment resolution: STR was defined as
the percent reduction in the sumSTE obtained on
admission and each time point following pPCI. Complete STR was considered for a reduction of
≥70%,7,15

Cardiovascular Magnetic Resonance Imaging

CMR (1.5-T scanner, Sonata Magnetom, Siemens,
Erlangen, Germany) was performed at least 48 hours
after cardiac catheterization in accordance with our
laboratory protocol.16,17 Images were acquired by a
phased-array body surface coil during breath-holds
and were ECG-triggered. Cine images (steady-state
free precession sequence; repetition time / echo time:
3.2/1.6 ms, flip angle: 61 degrees, matrix: 256×128,
slice thickness: 6 mm, temporal resolution: 26 ms)
were acquired in 2-, 3-, 4-chamber views and every 1
cm in short-axis views.

Late enhancement imaging was performed in the
same projections used for cine images at least 10
minutes after administering 0.1 mmol/kg of
gadolinium-diethylenetriaminepentaacetic acid
(Magnograf, Juste S.A.Q.F., Madrid, Spain). A
segmented inversion recovery imaging with steady
state free precession sequence was used (repetition
time / echo time: 2.5/1.1 ms, slice thickness: 6 mm,
flip angle: 50 degrees, matrix: 195×192) nullifying
myocardial signal.

Cardiovascular Magnetic Resonance Imaging
Data analysis

CMR studies were analyzed by an experienced
observer blinded to all patient, angiographic and
ECG data using customized software (QMASS MR
6.1.5, Medis, Leiden, The Netherlands). Segment
location was defined according to the 17-segment
model18. Left ventricular mass (g/m²), ejection
fraction (%), and volumes (mL/m²) were quantified
by manual definition of endocardial borders of all
short-axis slices in cine-images. Late gadolinium
enhancement was considered in the case of signal
intensity >2 standard deviations with respect to a
remote non-infarcted area in late gadolinium
enhancement imaging.16,19 Infarct size was calculated
as the percentage of left ventricular mass showing
late gadolinium enhancement.17

Microvascular obstruction: on a segmental basis
MVO was visually defined in late enhancement
imaging as a lack of contrast uptake in the core
of a segment surrounded by tissue showing late
enhancement2 (Figure 1). On a patient basis,
significant microvascular obstruction was considered
if it was detected in at least 1 segment. Intraobserver
variability for the detection of MVO using this
criterion in our laboratory was 1%.

Statistical Analysis

All data were tested for normal distribution
using the one-sample Kolmogorov-Smirnov test.
Continuous normally distributed data were expressed
as the mean (standard deviation) and compared
using Student's t test. Non-parametric data were
expressed as the median with the interquartile range
(IQR) and were compared with the Mann-Whitney
U test. Group percentages were compared using the
χ² test or Fisher's exact test where appropriate.

Receiver operating characteristic curve analysis
for predicting MVO was performed for STR
and sumSTE at all time points. The areas under
the receiver operating characteristic curve were
compared.

In order to determine the predictive value of
sumSTE and STR, a logistic regression model was
applied, adjusted by variables showing a P-value
<.1 in univariate analyses (Table 1). These variables
were: systolic blood pressure, anterior infarction
and peak creatine kinase MB. Odds ratios with the
respective 95% confidence intervals were computed.

Statistical significance was considered for 2-tailed
P-value <.05. SPSS 13.0 (SPSS Inc, Chicago, Illinois,
USA) and STATA 9.0 (StataCorp, College Station,
Texas, USA) were used.

RESULTS

The baseline characteristics and angiographic
data of all patients are displayed in Table 1. The
mean age was 60 (13) years (range, 31-90) with the
majority of the patients being male (81%). Median
time from pain onset to revascularization was 210
minutes [141-420]. Abnormal TIMI flow grade (0-2)
was present in 87% prior to pPCI with an occluded
infarct related artery in 78% of the cases. A stent
was placed in 96% of patients and TIMI flow grade 3
in the infarct related artery was established in all cases.
Myocardial blush grade 2-3 was observed in 77%
after pPCI.

The evolution of sumSTE and STR over time in
the entire patient population is displayed in Figure
2. The median sumSTE on arrival was 9.0 mm [6.0-
14.0] and dropped to 3.0 mm [0.0-6.0] after pPCI
(Figure 2A). Accordingly, the median STR at 90
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On CMR imaging, patients with MVO-infarctions showed a larger infarct size (37 [23%] vs 11 [9]; \( P < .0001 \)), a lower left ventricular ejection fraction (44 [13%] vs 59 [12]; \( P < .0001 \)), and larger end-systolic (54 [31] mL/m² vs 29 [14]; \( P < .0001 \)) and end-diastolic (93 [33] mL/m² vs 70 [18]; \( P < .0001 \)) left ventricular volumes and mass (81 [19] g/m² vs 65 [15]; \( P < .0001 \)).

**Cardiovascular Magnetic Resonance Imaging Results**

CMR imaging was performed 6 (2) days after pPCI. The clinical course between both examinations was stable in all patients. MVO was present in 37 patients (44%). Clinical and angiographic characteristics of the patients with and without evidence of MVO on CMR imaging are displayed in Table 1.

Patients with MVO-infarctions were younger (56 [14] years vs 63 [12]; \( P = .02 \)), had more anterior infarctions (68% vs 33%; \( P = .002 \)), a larger median peak creatine kinase MB 334 [162-503] ng/mL vs 85 [44-197]; \( P < .0001 \)) and there was a trend towards a lower systolic blood pressure (119 [26] mmHg vs 130 [25]; \( P = .05 \)).

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**Relationship of SumSTE and STR With Microvascular Obstruction**

In MVO-infarctions, the extent of sumSTE was significantly larger before and at all time points after revascularization compared to non-MVO-infarctions (\( P \leq .001 \) at all time points). In patients with MVO-infarctions, the median sumSTE at 24 hours after revascularisation smoothly reached 3 mm and did not drop further during the following measurements. In patients without MVO the median sumSTE at 6 hours reached 0 mm (Figure 3A). The amount of STR did not differ significantly at 90 min after pPCI between MVO
and non-MVO infarctions (*P*=.1). In the following measurements patients with non-MVO infarctions had a significant larger amount of STR than did patients with MVO infarctions (*P*≤.02 from 6 h to 96 h) (Figure 3B).

Table 2 shows the areas under the receiver operating characteristic curve of sumSTE and STR at all time points for predicting MVO. SumSTE yielded a significantly larger area under the curve at every measurement compared to the corresponding STR at that time point. Since STR is habitually dichotomized according to complete (≥70%) versus incomplete (<70%) the following analyses were carried out: When dichotomized according to complete STR (≥70% vs <70%) there was no significant difference in the prevalence of MVO between the 2 groups at 90 minutes (36% vs 52%; *P*=.1). Only from 24 hours after revascularization onwards, patients with complete STR displayed a significantly lower prevalence of MVO (Table 3).

According to the best cut-off derived from the area under the receiver operating characteristic curve, sumSTE at 90 minutes after pPCI was dichotomized (sumSTE ≤3 vs sumSTE >3 mm). Patients with sumSTE >3 mm had a higher prevalence of MVO than patients with sumSTE ≤3 (63% vs 28%; *P*=.001). The diagnostic accuracy of sumSTE >3 and complete STR (≥70%) at 90 minutes after pPCI is displayed in Table 4. SumSTE >3 mm yielded a higher diagnostic accuracy for predicting MVO than STR≥70%.

**Multivariable Analysis**

A multivariate logistic regression model for predicting MVO at 90 minutes after pPCI, adjusted for those variables showing a *P*-value <.1 in the univariate analyses, was performed. The variables included were: age, diabetes, smoker, systolic blood pressure, anterior infarction, median peak creatine kinase MB, involvement of the proximal left anterior descending artery, sumSTE >3 mm at 90 min and STR ≥70% at 90 min. Anterior infarction (OR, 4.2; 95% CI, 1.8-11.2; *P*=.04) and sumSTE >3 mm at 90 min after pPCI (OR, 3.1; 95% CI, 1.2-8.4; *P*=.02) were the only parameters associated with the presence of MVO on CMR imaging.

**DISCUSSION**

The main finding of the present study is that monitoring of ST-segment characteristics is useful for predicting MVO in patients with STEMI treated with pPCI and re-established TIMI flow grade 3 in the infarct related artery. The amount of SumSTE at 90 min after pPCI was shown to be a simple
predictor of MVO even after adjustment for baseline characteristics and angiographic data.

Microvascular Obstruction

In spite of restoration of epicardial blood flow in STEMI, impairment at the microvascular level can occur, a phenomenon referred to as MVO. It has been demonstrated that patients with MVO-infarctions have poor recovery of left ventricular function and are at high risk for development of heart failure and death. Several non-invasive and invasive indexes such as angiographic parameters,
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In the present study, SumSTE was significantly larger throughout all measurements in patients with MVO-infarctions. When dichotomized (>3 mm vs ≤3 mm) sumSTE at 90 minutes after pPCI yielded a higher diagnostic accuracy for detecting MVO than complete STR and accordingly MVO was more frequent in patients displaying a high sumSTE.
Sum of ST-Segment Elevation Predicts Microvascular Obstruction on admission yielded the largest AUC for predicting MVO. The exact implications of this finding remain to be determined.

STR highly depends on pre-procedural extent of sumSTE. As a relative measure, STR reflects (>3 mm)(63% vs 28%; \( P=.001 \)). In a multivariate analysis adjusted for clinical and angiographic parameters, the presence of an elevated sumSTE (>3 mm) at 90 minutes after revascularization was an independent predictor of MVO. Of note, sumSTE on admission yielded the largest AUC for predicting MVO. The exact implications of this finding remain to be determined.

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resolution of the initial sumSTE not taking into account the absolute extent of sumSTE neither on admission nor after pPCI, thus not incorporating the remaining microvascular injury after revascularization. At the first measurement after revascularization we did not detect a significant association of STR with MVO neither as a continuous variable nor as a binary variable using a well established cut-off (≥70% vs <70%). Nevertheless at 24 hours after revascularization the association of STR with MVO reached statistical significance. The lower discriminative value of STR might be owed to several reasons. For example, a patient who displays complete STR might still have a significant amount of sumSTE after pPCI and thus have a higher probability of MVO. Of note and of implications for clinical practice is, that sumSTE constitutes a simple index that yields a better diagnostic accuracy and can be obtained with one single measurement compared with 2 measurements (on arrival and at a later time point) necessary in order to determine STR for predicting MVO. Moreover, the information on the status of the microcirculation after pPCI offered by sumSTE is already available at an early time point (90 minutes after revascularization) when this information is most appreciated by the clinician.

It has been demonstrated that myocardial microcirculation displays a dynamic behaviour within the first days and months after STEMI. These dynamic changes in abnormal perfusion are likely reflected by the smooth normalization in the extent of sumSTE observed in our study, advocating the ECG as a non-invasive tool for assessing the status of the microcirculation in the first phase after STEMI. This observation highlights the value of serial electrocardiographic examinations after STEMI since the behaviour of the microcirculation, mirrored by ST-segment changes, displays marked differences between patients with MVO and without MVO.

Limitations and Strengths of the Study

The results of our study have to be interpreted with caution because of the small sample size. Nevertheless, CMR is a highly reproducible modality with a very low interobserver and intraobserver variability accounting for a smaller number of patients necessary to detect significant differences. Since CMR data were evaluated by one experienced observer, interobserver variability for the CMR indexes is not available.

Of note, myocardial blush grade was not significantly associated with the presence of CMR-derived MVO. The focus of the present study was to investigate the association of ST-segment changes with MVO. A possible explanation for the finding that myocardial blush grade was not associated with MVO might be that this variable is more operator-dependent and might have yielded better results if evaluated in a core laboratory.

CONCLUSIONS

Our study demonstrates the value of ST-segment monitoring for prediction of CMR-derived MVO. MVO was best predicted by the extent of sumSTE. Therefore, the assessment of ST-segment changes should not only involve the evaluation of STR after pPCI but should also focus on the remaining sumSTE. This simple bedside measure provides information on the quality of microvascular reperfusion after pPCI.

REFERENCES