VNIVERSITAT DE VALÈNCIA

OBSTRUCCIÓN MICROVASCULAR DERIVADA DE LA RESONANCIA MAGNÉTICA CARDIACA TRAS UN INFARTO MIOCÁRDICO CON ELEVACIÓN DEL ST –ASOCIACIÓN CON MARCADORES DE NECROSIS CARDIACA Y CAMBIOS DEL SEGMENTO ST

TESIS DOCTORAL INTERNACIONAL

Presentada por:

Oliver Husser

Dirigida por:

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Departament de Medicina, Facultat de Medicina i Odontologia, Universitat de València

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Departament de Medicina

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CARDIOVASCULAR MAGNETIC RESONANCE DERIVED MICROVASCULAR OBSTRUCTION AFTER ST-ELEVATION MYOCARDIAL INFARCTION – ASSOCIATION WITH CARDIAC NECROSIS MARKERS AND ST-SEGMENT CHANGES

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A mi familia.

Mi agradecimiento

A Vicente Bodí, el director de esta tesis, por su respaldo y los tónicos de la voluntad. Sin su apoyo no existiría este trabajo.

A Julio Núñez quien a la vez es un gran tutor y un mejor amigo.

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1 List of Abbreviations

STEMI = ST-segment elevation myocardial infarction

PCI = Percutaneous coronary intervention

MVO = microvascular obstruction

CMR = cardiovascular magnetic resonance imaging

LGE = late gadolinium enhancement

LV = left ventricle

SumSTE = Sum of ST-segment elevation

STR = ST-segment resolution

CK-MB = creatine kinase MB

2 List of Tables and Figures

3 Summary

3.1 English Summary

This work is divided into 3 parts and assesses the association of cardiovascular magnetic resonance (CMR)-derived microvascular obstruction (MVO) with readily available biomarkers after ST-elevation myocardial infarction (STEMI).

CMR allows for a comprehensive assessment of patients with STEMI. Out of a wide range of myocardial infarction parameters especially MVO has emerged as a strong predictor of adverse outcome in terms of major adverse cardiovascular events and adverse remodeling after STEMI.

In the first part the association of ST-segment changes, especially the sum of ST-segment elevation and ST-segment resolution, with MVO is investigated. There was a strong relationship of ST-segment changes with the presence of MVO. The sum of ST-segment elevation at 90 minutes after reperfusion via primary percutaneous coronary intervention was the ECG parameter most strongly associate with MVO.

The second part of this work investigates the association of cardiac necrosis markers, in detail troponin, creatine kinase and myoglobin, with the occurrence of MVO after STEMI. We found a larger release of cardiac necrosis markers in patients with MVO. Troponin was the cardiac necrosis marker, which possessed the strongest predictive capability for MVO.

Finally, we sought to determine the predictive value of parameters available on patient admission for the prediction of MVO in STEMI. A simple score was constructed using only clinical and ECG variables, which are the timeliest available variables, on patient admission.

3.2 Resumen castellano

Este trabajo, que se dividió en tres partes, pretendió determinar la asociación entre la obstrucción microvascular (MVO) estimada mediante resonancia magnética cardiaca (RMC) con determinados marcadores ampliamente disponibles en el contexto del infarto agudo de miocardio con elevación del segmento-ST (IAMCEST).

La RMC permite una exhaustiva evaluación de los pacientes con IAMCEST. En este sentido, la aparición de MVO ha mostrado ser un factor asociado a episodios cardiovasculares adversos mayores y remodelado negativo tras un IAMCEST.

En la primera parte de este trabajo, pretendimos explorar la asociación entre el sumatorio de las derivaciones con ST elevado (sum-ST) y la resolución del segmento ST con la presencia de MVO. Se observó que el sum-ST determinado a los 90 minutos tras la reperfusión mediante angioplastia primaria fue el parámetro más intensamente asociado a la MVO.

En una segunda etapa, determinamos la asociación entre la liberación de los marcadores de necrosis miocárdica (troponina, creatin kinasa y mioglobina) con la aparición de MVO tras un IAMCEST. Con respecto a este punto, observamos una mayor liberación plasmática de marcadores de necrosis en los pacientes con MVO; concretamente, la troponina fue el marcador que mas inmensamente asociado a la MVO.

Finalmente, pretendimos evaluar el valor de parámetros clínicos habituales determinados al ingreso para predecir MVO. Así, desarrollamos una puntuación simple de riesgo que incluyó variables clínicas y electrocardiográficas, todas ellas de fácil adquisición en el momento del ingreso.

4 Introduction

In ST-segment elevation myocardial infarction (STEMI) timely reperfusion of the infarct related artery by means of percutaneous coronary intervention (PCI) or thrombolysis is the primary therapeutic goal the primary therapeutic in order to restore of tissue perfusion (1-3). Nevertheless, despite of a patent infarct related artery reperfusion at the microvascular level is not always achieved, a phenomenon referred to as microvascular obstruction (MVO) (4). In patients with an open infarct-related artery, a lack of reperfusion at the microvascular level has been related to worse outcome (1; 2; 5; 6).

CMR has become the gold standard in cardiovascular imaging and allows for a comprehensive assessment of a wide range of parameters in patients with STEMI (5), including infarct size and MVO (4; 7). MVO appears as dark areas within the core of the infarct zone and is believed to result from impaired microvascular perfusion due to multifactorial causes including edema, microembolization and inflammatory response (8; 9). The presence of MVO on CMR imaging has been shown to predict less functional recovery (10)and post infarction complications independent of infarct size (11). Moreover the presence of MVO on CMR has been associated with worse outcome and left ventricular remodelling compared to non-MVO infarctions (7; 11-13).

Apart from these sequences, using cine sequences, CMR allows for the analysis of myocardial mass, volumes and segmental wall thickening and has emerged as the gold standard for these purposes (14).

Finally, CMR allows for an exact delineation of infarct size and mass in late gadolinium enhancement (LGE) sequences (15). The multitude of CMR-derived parameters of myocardial infarction is summarized in figure 1.

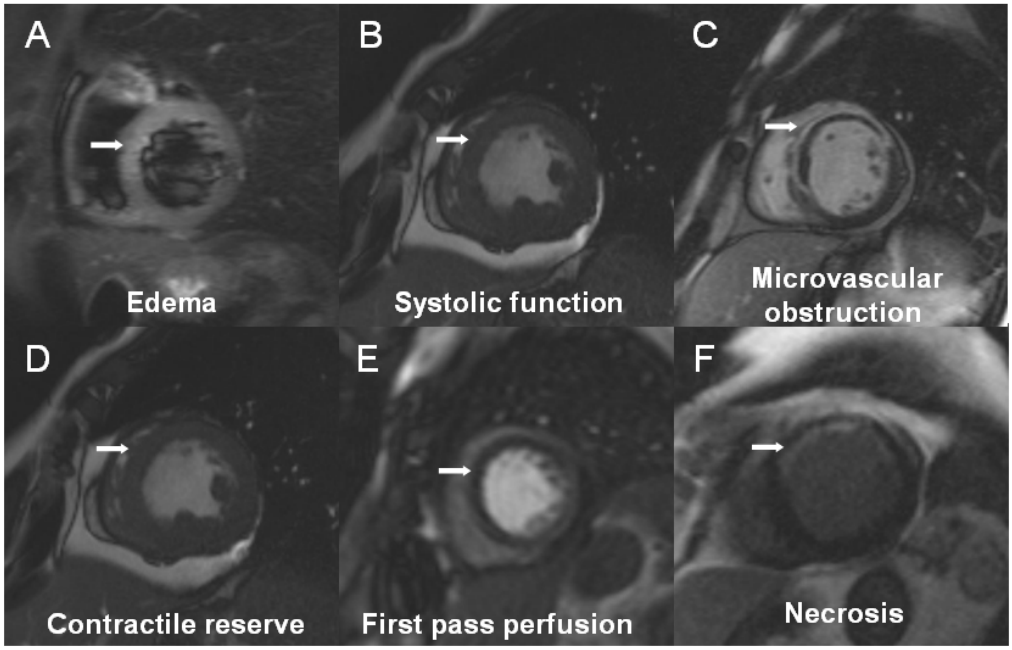


Fig. 1 - Summary of CMR-derived parameters after ST-elevation myocardial

Out of this multitude of CMR-derived infarct parameters, especially MVO has shown to be associated with outcome after STEMI.

We hypothesized that biomarkers as the ECG and cardiac necrosis markers might show a significant association with MVO. Therefore the aim of this work was to investigate the association of CMR-derived MVO with readily accessible biomarkers after STEMI and to determine their predictive value.

Firstly, the electrocardiogram represents a useful tool, which is virtually omnipresent in the clinical environment. Monitoring of ST-segment changes, especially ST-segment resolution (STR), has been employed in the past as a simple measure of epicardial reperfusion quality in STEMI (16). So far the relationship between ST-segment changes and CMR-derived measures of MVO remains to be clarified. The first part of this work aims to analyze 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 primary percutaneous coronary intervention and re-established blood flow the infarct related artery.

Secondly, Cardiac necrosis markers, especially troponin quantification, have been incorporated into daily practice for diagnostic and risk stratification purposes (17-20). In non-ST-elevation myocardial infarction, worse prognosis of troponin-positive patients seems to be related to the presence of coronary thrombi and microvascular embolization (21; 22). Classically, a larger and faster release of cardiac necrosis markers has been considered an indicator of successfully recovered epicardial coronary flow (23; 24) and the close relationship between troponin release and infarct size has been well established (25). Nevertheless, the relationship between the temporal evolution of cardiac necrosis marker release and reperfusion at the microvascular level is unknown. Moreover, a simultaneous assessment of the relationship of the 3 most widely used necrosis markers, namely troponin, creatine kinase MB mass (CK-MB) and myoglobin, with the state of microvasculature after reperfused STEMI has not been performed so far.

Finally, we aimed to investigate the capability of clinical parameters and the biomarkers already available (including ECG parameters and cardiac necrosis markers) on patient admission for prediction of MVO. The prediction of MVO at such a pivotal time point for therapeutic decision making has not been attempted before and is desirable since it bears the potential of early risk stratification and might have therapeutic implications for therapies aiming at the reduction of MVO before reperfusion therapy is initiated.

4.1 Original Contribution of the Author

The author of this work has performed data acquisition and analysis. All three parts of this cumulative international thesis have been published in international peer reviewed journals endorsed with an impact factor. The author of this work has written all articles and features as the first author.

5 Materials and Methods

5.1 Patients and CMR Protocol

The methodology of this work and the characteristics of the patient population can be consulted in detail in the attached published manuscripts. In short, the materials and methods used in all parts of this work are displayed here, while individual methods relevant for parts of the work are exposed in the respective parts.

We prospectively included consecutive patients admitted with a first STEMI. The Reperfusion strategy and medical treatment were left to the discretion of the attending cardiologists. A pharmacoinvasive strategy (26) consisting of thrombolysis with timely angiography or primary PCI were used. A minority of patients did not receive timely reperfusion therapy (within 12 hours of symptom onset).

Patients underwent CMR (1.5-T, Sonata Magnetom, Siemens, Erlangen, Germany) at 1 week and, in order to evaluate LV remodeling, at 6 months after STEMI according to our laboratory protocol (6; 27).

All images were acquired by a phased-array body surface coil during breath-holds and were ECG-triggered. First, we obtained cine images. Then, first pass perfusion imaging was performed administering 0.1 mmol/kg of gadoliniumdiethylenetriaminepentaacetic acid (Magnograf, Juste S.A.Q.F., Madrid, Spain). LGE imaging was performed at least 10 min after contrast administration.

5.2 CMR Analysis

CMR studies were analysed offline by an experienced observer blinded to all patient data using customized software (QMASS MR 6.1.5, Medis, Leiden, The Netherlands). The 17-segment model, excluding the apex, was applied (28).

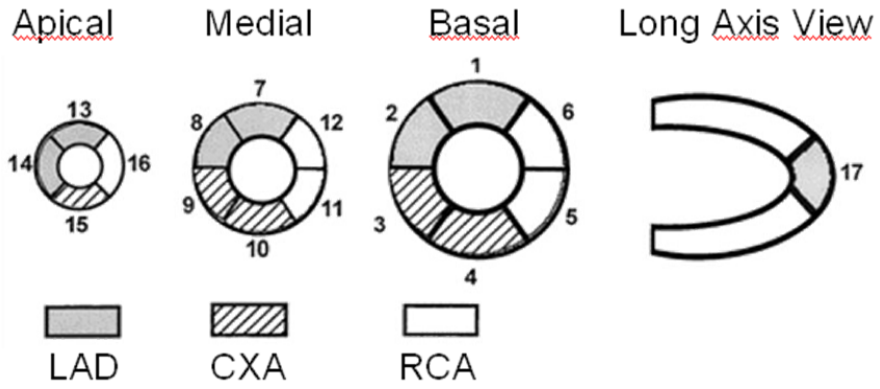


Fig. 2 - The 17-segment model for segmental evaluation of myocardial infarction parameters (28).

LV ejection fraction (%), end-diastolic and end-systolic volume indexes (ml/m^2) and mass (g/m^2) were calculated by manual planimetry of endocardial and epicardial borders in all short-axis views cine images.

LGE was considered present if signal intensity was >2 standard deviations with respect to a remote non-infarcted area in LGE imaging (6). Infarct size was calculated as the percentage of LV mass showing LGE. Additionally, the number of segments showing transmural (>50% of wall thickness) was calculated.

MVO was visually defined on a segmental basis as a lack of contrast uptake in the core of a segment surrounded by tissue showing LGE. On a patient basis, significant MVO was considered if it was detected in more than one segment (figure 3).

The intraobserver variability for the determination these CMR parameters in our group is less than 5% (29; 30).

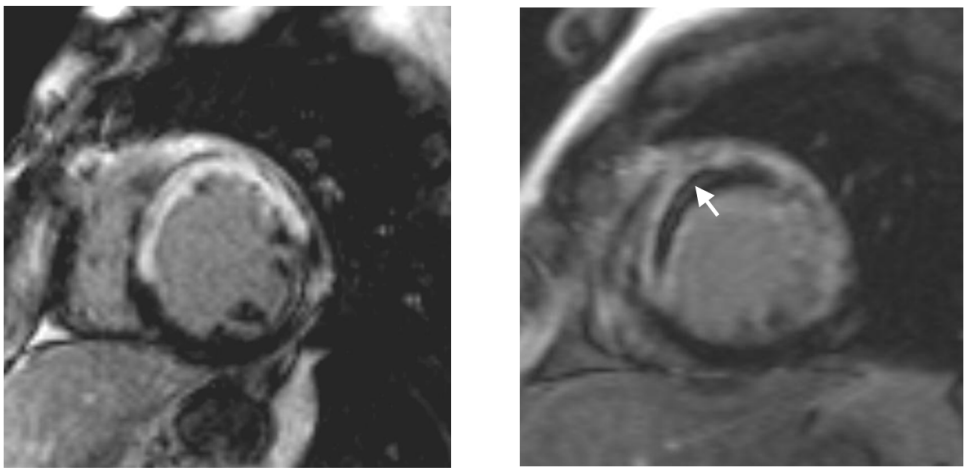


Fig. 3 - Short-axis view of late enhancement imaging in two patients with anterior infarction of comparable size. Left: Normal contrast uptake in the infarcted zone. Right: Lack of contrast uptake in the core of the infarcted area indicating microvascular obstruction (arrow).

6 Results

6.1 Sum of ST-Segment Elevation Best Predicts Microvascular Obstruction in Patients Successfully Treated with Primary Percutaneous Coronary Intervention – A Cardiovascular Magnetic Resonance Study. (Appendix 1)

Aim: We aimed to analyze the usefulness of ST-segment resolution (STR) and of the extent of summatory ST-Segment elevation (sumSTE) for detecting CMR-derived MVO in a consecutive group of patients with STEMI treated with primary percutaneous coronary intervention and re-established TIMI flow grade III in the infarct related artery.

Methods: We studied 52 consecutive patients admitted for a first STEMI treated with primary PCI and a patent infarct related artery represented by TIMI flow grade 3. A 12-lead ECG was recorded on admission and at 90 minutes, 6, 24, 48 and 96 hours after PCI. STR and the sum of ST-elevation (sumSTE) in all leads were calculated.

Results: CMR imaging was performed 9±6 days after primary percutaneous coronary intervention. MVO was present in 21 patients (40%). On CMR imaging, MVO was present in 21 patients. Patients with MVO-infarctions tended to be younger (56 ± 13 years vs. 61 ± 11 years, p=.167) and had more anterior infarctions (76% vs. 36%, p=.004), a lower systolic blood pressure (113 ± 23 mmHg vs. 128 ± 23 mmHg, p=.031) and a larger median peak creatine kinase MB (432 ng/ml (364) vs. 97 ng/ml (198), p<.0001).

In MVO-infarctions, the extent of sumSTE was significantly larger before and at all times after revascularization compared to non-MVO infarctions (p<.03 at all times). In patients with MVO-infarctions, the median sumSTE at 24 hours after revascularisation smoothly reached 4 mm and did not drop further during the following measurements. In patients without MVO the median sumSTE at 96 hours reached 0 mm (figure 4a). In contrast, there was only a weak difference in the amount of STR between MVO and non-MVO infarctions (p= ns at all

times) albeit with a certain, non-significant, trend to a larger median amount of STR in patients without MVO-infarctions (figure 4b).

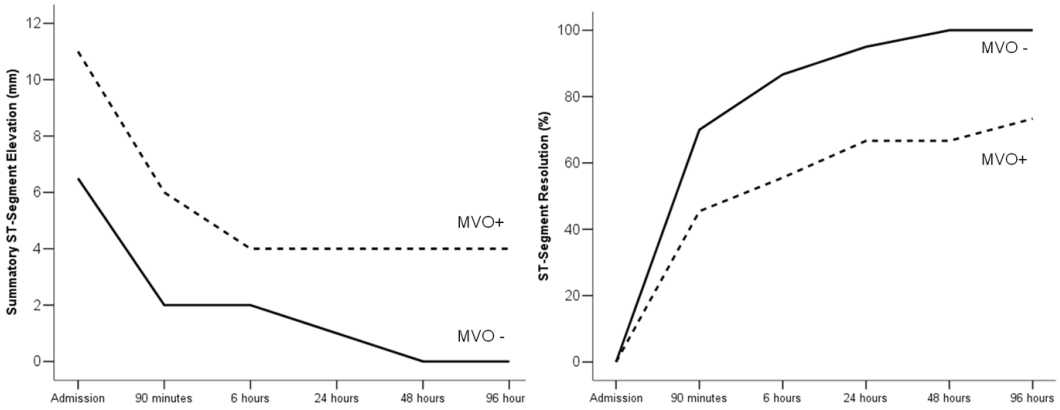


Fig. 4 - Time course of summatory ST-Segment elevation (left panel) and ST-Segment resolution (right panel) according to the presence of MVO on CMR.

As a continuous variable, the extent of sumSTE at all times correlated with the number of segments showing MVO on CMR (Spearman's rho = .360 to .413, p.≤01 at all times) while there was a weak, non significant correlation between STR and extent of MVO (Spearman's rho = -.254 to -.197, p=ns at all times).

A multivariate logistic regression model for predicting MVO, adjusted for those variables showing a p-value <0.1 in the univariate analyses, was performed. The variables included were: systolic blood pressure, anterior infarction, peak creatine kinase MB and sumSTE and STR at all time points. SumSTE at 90 min after percutaneous coronary intervention was the only parameter associated with the presence of MVO on CMR imaging (OR 1.3 95%CI [1.1-1.6], per millimeter, p=.008.)

6.2 Release of Necrosis Markers and Cardiovascular Magnetic Resonance-derived Microvascular Perfusion in Reperfused ST-Elevation Myocardial Infarction. (Appendix 2)

Aim: We analyzed the association of the dynamics of troponin, creatine kinase MB (CK-MB) and myoglobin release with CMR-derived abnormal microvascular perfusion after STEMI.

Methods: We studied 163 patients with a first ST-elevation myocardial infarction and a patent infarct-related artery treated with thrombolysis (67%) or primary angioplasty (33%). Using first-pass perfusion CMR, abnormal perfusion (MVO) was defined as a lack of contrast arrival into the infarct area in >1 segment. Troponin I, creatine kinase MB and myoglobin were measured upon arrival and at 6, 12, 24, 48 and 96 hours after reperfusion.

Results: Abnormal perfusion was detected in 75 patients (46%). Abnormal perfusion related to a larger release of all three cardiac necrosis markers after reperfusion and higher peak values (figure 5). The most significant differences were detected in all cases at 6 hours post-reperfusion. Out of the 3 markers, troponin levels at 6 hours after reperfusion yielded the largest area under the receiver operating characteristic curve for prediction of abnormal perfusion (troponin: 0.69, creatine kinase MB: 0.65 and myoglobin: 0.58). Patients were categorized according to the median troponin level at 6 hours after reperfusion (lower troponin 0-42 ng/ml and high troponin >42 ng/ml). Abnormal perfusion was more frequent in patients with high troponin levels (50/81 (62%) vs. 25/82 (31%), p<.0001).

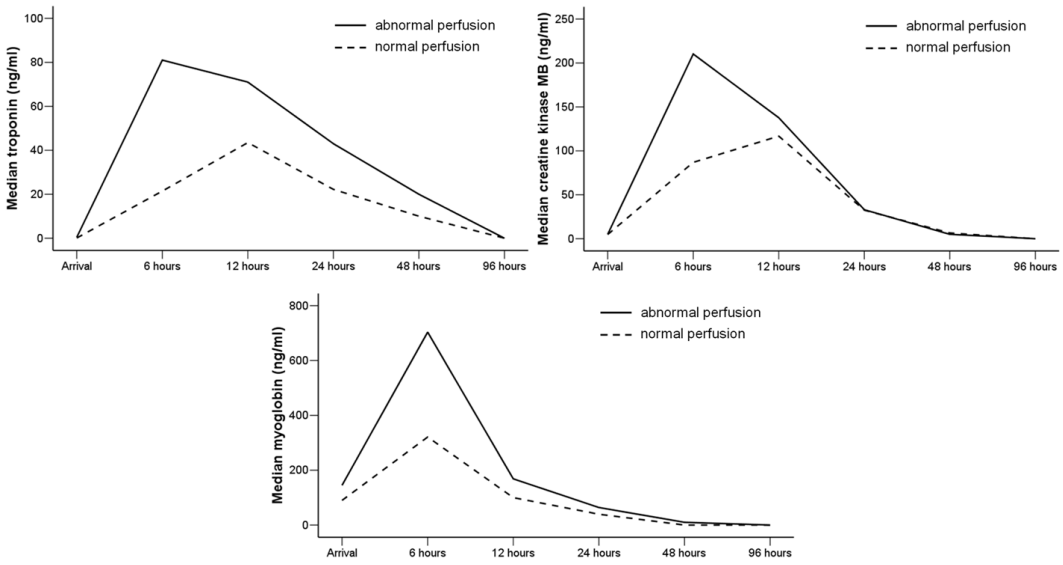


Fig. 5 - Evolution of necrosis marker release depending on the presence of abnormal perfusion.

In a comprehensive multivariate analysis, adjusted for clinical, angiographic, cardiovascular magnetic resonance parameters and all necrosis markers, high troponin levels at 6 hours after reperfusion (>median) independently predicted abnormal microvascular perfusion (OR 2.6 95%CI [1.2 - 5.5], p=.012).

Patients with elevated troponin at 6 hours after reperfusion showed larger infarctions. To verify that the association between troponin release and abnormal perfusion was not a mere consequence of a larger infarct size or delayed presentation the following analyses were performed:

The whole group was categorized according to the median of infarct size (small infarct: ≤34% of left ventricular mass vs. large infarct: >34% of left ventricular mass). Abnormal perfusion was more frequent in patients with high troponin at 6 hours after reperfusion regardless of infarct size: small infarct, 13/31 (42%) vs. 9/50 (18%), p=.019; large infarct, 37/50 (74%) vs. 16/32 (50%), p=.027.

Upon arrival, 72 patients (44%) displayed normal troponin values (<.1 ng/ml). As in the whole group, abnormal perfusion was more frequent in the case of high troponin at 6 hours after reperfusion: 19/35 (54%) vs. 11/37 (30%), p=.035.

A multivariate analysis to identify predictors of high troponin levels at 6 hours after reperfusion was performed including variables showing a p-value <.1 in the univariate analysis: heart rate, anterior infarction, ST-segment resolution ≥70%, rescue angioplasty, proximal left anterior descending lesion and all CMR variables. Time to reperfusion was also included. Abnormal perfusion (OR 1.23, 95%CI [1.03-1.48], per segment, p=.021), ejection fraction (OR .96, 95%CI [.93-.1] per 1% increase, p=.009) and ST-segment resolution ≥70% (OR 0.44 95%CI [.19-.99], p=.048) were predictors of high troponin levels at 6 hours after reperfusion.

6.3 Predictors of Cardiovascular Magnetic Resonance-derived Microvascular Obstruction on Patient Admission in STEMI (Appendix 3)

Aim: We hypothesized that characteristics available on admission would be useful for very early prediction MVO-infarction. For this purpose we analyzed the value of clinical and electrocardiographic, laboratory and angiographic characteristics, available on patient admission in STEMI in the order as the information is available to the clinician, for determination of the best and earliest predictors of MVO in patients with STEMI referred for primary PCI.

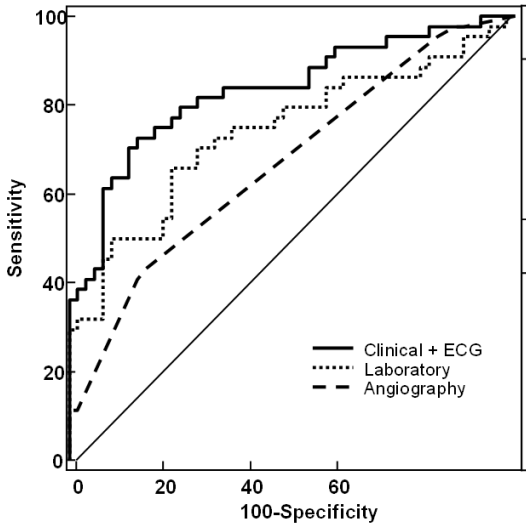
Methods: Characteristics available on admission were documented in 97 STEMI patients referred for primary PCI and their association with CMR-derived MVO was assessed.

Results: CMR was performed 8±5 days after PCI. MVO was present in 44 patients (45%). Patients with MVO-infarctions had a lower left ventricular ejection fraction (43%±12 vs. 59±11, p<.0001), a larger infarct size (37%±22 vs. 11±10, p<.0001) and more dilated left ventricular volumes and masses.

First the individual value of parameters on patient admission for predicting MVO was assessed. Clinical variables on admission associated with MVO were: younger age (56±13 vs. 60±13, p=.008), lower systolic blood pressure (120mmHg±25 vs. 132±25, p=.02), diabetes (25% vs. 9%, p=.04) and Killip class>1 (23% vs. 2%, p=.002). There was a trend towards a higher rate of delayed presentation (>3 hours from pain onset) in patients with MVO-infarctions (39% vs. 21%, p=.05) The ECG on admission revealed a higher percentage of anterior infarctions (68% vs. 34%, p<.0001) and a larger median sumSTE (12mm[7-17] vs. 6[4.5-10], p<.0001) in patients with MVO infarctions. The C-statistic for predicting MVO of clinical and ECG variables on admission was .832 [.742-.901].

Laboratory findings on admission associated with MVO were: higher myoglobin serum levels (95ng/ml [45-899] vs. 55 [23-99], p=.003) and higher neutrophil count (10.1 (x1000cells/ml) ±3.7 vs. 8.4±3.7, p=.03). The C-statistic for predicting MVO of laboratory findings on admission was .743 [.643-.826].

The only angiographic parameter significantly associated with MVO was involvement of the proximal left anterior descending artery (43% vs. 17%, p=.005). The C-statistic for predicting MVO of angiographic variables was .669 [.566-.762]. Clinical, ECG, laboratory and angiographic variables according to the presence of MVO are displayed in table 1. The C-statistics are displayed in figure 6.

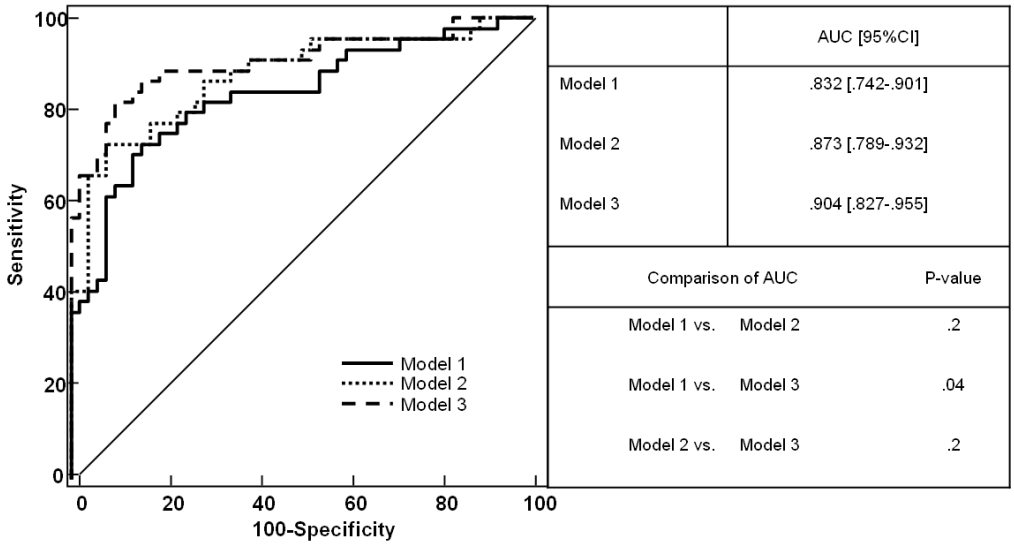


	AUC [95%CI]
Clinical + ECG data	.832 [.742-.901]
Laboratory data	.743 [.643-.826]
Angiographic data	.669 [.566-.762]

Comparison of AUC		P-value
Clinical + ECG data vs.	Laboratory data	.1
Clinical + ECG data vs.	Angiographic data	.006
Laboratory data vs.	Angiographic data	.3

Fig. 6 - Individual diagnostic value of parameters for predicting MVO

The incremental value of parameters for predicting MVO in the order of temporal availability was analyzed. The C-statistic of clinical and ECG characteristics (model 1) did not improve significantly after adding laboratory information (model 2) (.873 [.789-.932] vs. .832 [.742-.901], p=.2). Further addition of angiographic findings (model 3: 904 [.827-



	AUC [95%CI]
Model 1	.832 [.742-.901]
Model 2	.873 [.789-.932]
Model 3	.904 [.827-.955]

Comparison of AUC		P-value
Model 1 vs.	Model 2	.2
Model 1 vs.	Model 3	.04
Model 2 vs.	Model 3	.2

Fig. 7 - Incremental diagnostic value for predicting MVO

.955]) significantly improved the C-statistic compared to model 1 (p=.04) but not compared to model 2 (p=.2) (see figure 7).

Clinical and ECG characteristics, the parameters most timely available on patient admission, displayed a high predictive value for MVO, which was only significantly improved by the addition of both laboratory and angiographic data. Owing to this finding, a multivariate analysis to identify predictors of MVO from clinical and ECG parameters was performed. Independent predictors of MVO were: Killip class>1 (OR 15.97 95%CI [1.37-186.76], p=.03), diabetes (OR 6.15 95%CI [1.49-25.39], p=.01), age <55 years (OR 4.70 95%CI [1.56-14.17], p=.006), sumSTE>10mm (OR 4.5 95%CI [1.58-12.69], p=.005) and delayed presentation (OR 3.80 95%CI [1.19-12.1], p=.02). Low blood pressure on admission was not included in this analysis since Killip class already accounts for cardiogenic shock. The C-statistic for predicting MVO of the model using these variables was .846 [.758-.912], which was not inferior to any of the 3 models (p-value between .2-.8).

In order to allow for our findings to be integrated into clinical practice a predictive score was developed. According to the ORs obtained we created a 4 level score depending on the presence of each index. Killip class>1 was assigned 2 points and the remaining indexes 1 point. The sum was calculated for each patient and patients were categorized into 4 groups (0 points, 1 point, 2 points and 3+ points). The C-statistic for predicting MVO using this score was 0.845 [0.756-0.911], which was not inferior to any of the 3 models (p-value between .1-.9). The incidence of MVO gradually increased as the score increased: 0 points: 2 of 23 (8.7%); 1 point: 9 of 32 (28.1%); 2 points: 20 of 28 (71.4%) and 3+ points: 13 of 14 (93%) (p<.0001 for the trend, figure 8). In parallel, the extent of MVO (number of segment with MVO) gradually increased with each step of the score (p for the trend <.0001, figure 9). Finally, in order to assess the value of the constructed score, we performed a comparison of the new predictive score with established markers of MVO.

Patients with MVO infarctions had a higher TIMI risk score than patients without MVO (3.3±2.2 vs. 2.2±1.9, p=.004), nevertheless the C-statistic of the TIMI risk score to predict MVO was significantly lower compared to the newly developed score (.658 vs. .839, p=.004).

The C-statistic of the newly developed score was compared with other, less timely available, markers of MVO, namely peak troponin and residual ST-segment elevation. Additionally, the score was compared to angiographic surrogates of MVO after PCI: TIMI flow grade, corrected TIMI frame count and myocardial blush grade (figure x). The newly developed score performed comparable to peak troponin (p=.6) and was superior to residual ST-elevation (p=.01) and any of the angiographic parameters (p<.01).

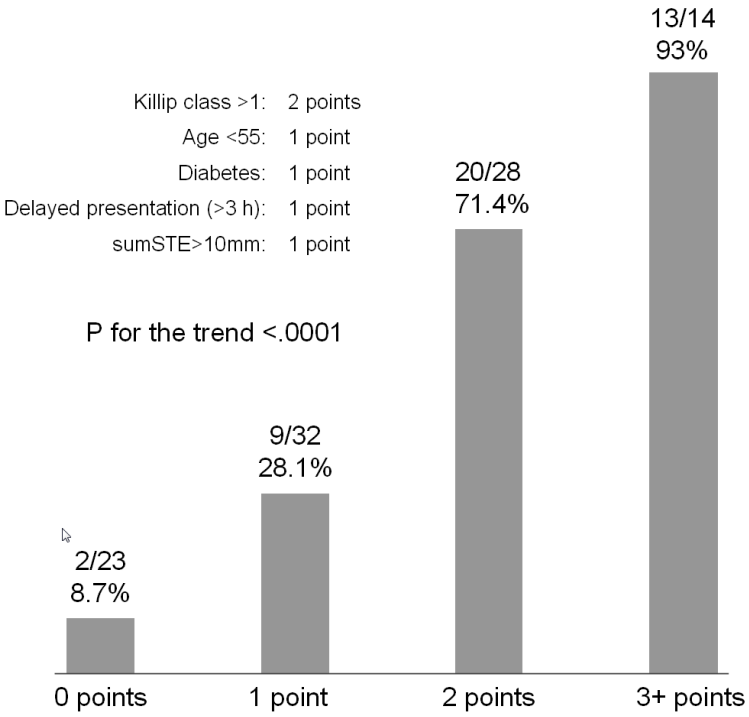


Fig. 8 - Prevalence of MVO at each step of the score

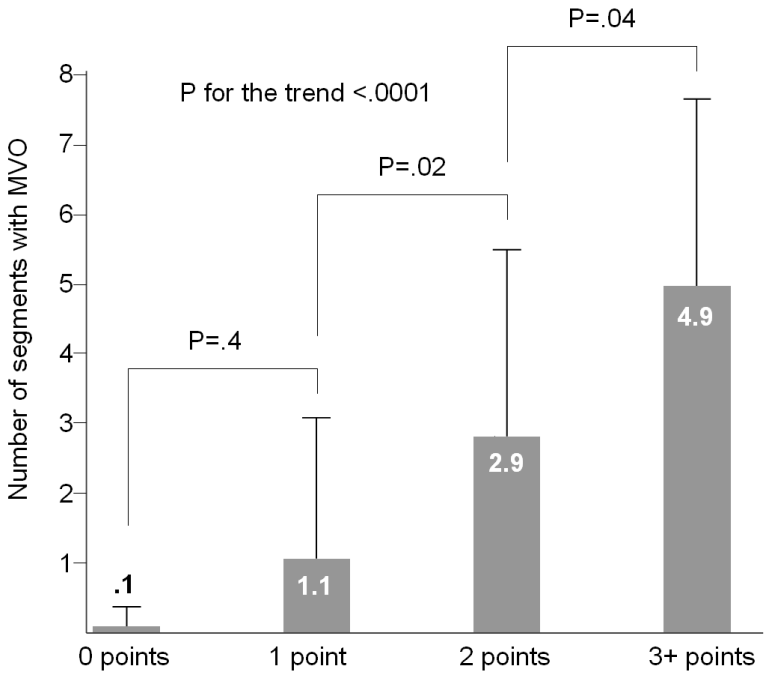


Fig. 9 - Extent of MVO at each step of the score

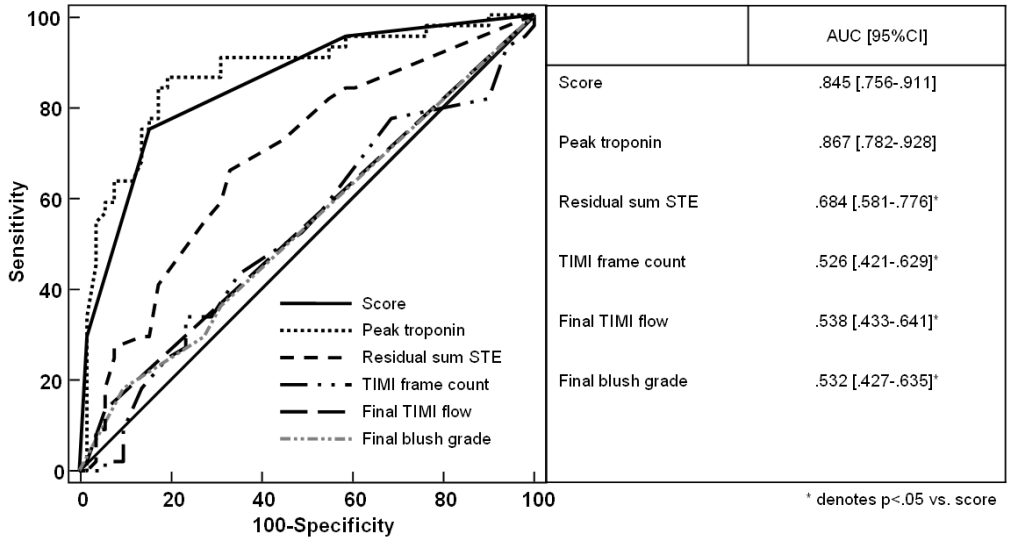


Fig. 10 - Comparison of the predictive score with established markers of MVO

7 Discussion

7.1 The Impact of MVO after STEMI

As exposed in the introduction of this work, the paramount importance of microcirculation after myocardial infarction has been known for over a decade (1; 2). Despite restored epicardial blood flow in STEMI, MVO occurs in about 40% of the cases (11; 12). It has been demonstrated that patients with MVO-infarctions have poor recovery of left ventricular function and are at high risk for the development of heart failure and death (12). Several non-invasive and invasive indexes such as angiographic parameters (31; 32), myocardial contrast echocardiography (12; 33) or scintigraphy (34) have been used for evaluation of MVO.

CMR has become the gold standard in cardiovascular imaging and allows for a comprehensive assessment of a wide range of parameters in patients with STEMI (5), including infarct size and MVO (4; 7). The presence of MVO on CMR imaging has been shown to predict less functional recovery (10)and post infarction complications independent of infarct size (11). Moreover the presence of MVO on CMR has been associated with worse outcome and left ventricular remodelling compared to non-MVO infarctions. (7; 12).

7.2 ST-Segment Analysis for the Assessment of MVO

7.2.1 Role of ST-Segment Resolution

The ECG, as a widely available, rapid and simple method, has been applied as a tool for assessing the success of reperfusion therapy in thrombolysis (35). STR has shown to be useful for predicting the patency of the infarct related artery. However, its relationship to perfusion at the microcirculatory level remains unclear. Several studies investigating microvascular perfusion assessed by means of myocardial contrast echocardiography or angiographic blush scores have shown that a lack of STR is indicative of MVO (36-38).

The relationship between STR and MVO, as derived by a state-of-the-art CMR study, has been barely explored in STEMI patients with a patent infarct related artery. Moreover, the existing data on the association of CMR-derived MVO with STR is conflicting (31; 32; 39). In the present series of patients, we only detected a weak association of STR with MVO. A possible explanation for this finding is that STR is a frequent observation after successful primary percutaneous coronary intervention and a progressive increase in the amount of STR occurred in all patients regardless of the presence of MVO.

7.2.2 Sum of ST-Segment Elevation and MVO

A persistence of sumSTE after successful primary percutaneous coronary intervention has been linked to microvascular damage assessed by myocardial contrast echocardiography (40). Further, it has been shown that a persistent ST-Segment deviation after revascularization yields prognostic information after STEMI (41; 42). To the extent of our knowledge, there is no study investigating the value of sumSTE for the detection of CMR-derived MVO. In the present study, SumSTE was significantly larger throughout all measurements in patients with MVO-infarction and the extent of sumSTE related to a larger extent of MVO. Additionally, SumSTE at 90 min after percutaneous coronary intervention was the only parameter that predicted the presence of MVO even after adjustment for clinical, angiographic and other electrocardiographic parameters. Each millimeter of remaining sumSTE at 90 min after primary PCI increased the probability of MVO by 30%.

One drawback for the usage of STR as a perfusion marker is that STR highly depends on preprocedural extent of sumSTE (43). As a relative measure, STR reflects resolution of the initial sumSTE and does not take into account the absolute extent of sumSTE neither on admission nor after primary percutaneous coronary intervention. Therefore STR does not incorporate the remaining microvascular injury after revascularization. In the present study we found a tendency towards a progressive STR in all patients and there was no significant

difference between MVO and non-MVO-infarctions, pointing to the low discriminative power of this index. For example, a patient who displays complete STR might still have a significant amount of sumSTE after percutaneous coronary intervention and thus have a higher probability of MVO.

The dynamic behavior of myocardial microcirculation within the first days and month after STEMI has been demonstrated (27). These dynamic changes in abnormal perfusion are likely reflected by the smooth normalization in the extent of sumSTE observed in our study. This advocates the ECG as the ideal non-invasive tool for assessing the status of the microcirculation in the first phase after STEMI and 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. The information about the status of the microcirculation after successful primary PCI yielded by the surface ECG was greatest shortly after the procedure at a time point when this information is most appreciated by the clinician.

7.3 The Role of Cardiac Necrosis Markers in MVO

7.3.1 Necrosis Markers and Abnormal Perfusion

Studies from the past two decades have demonstrated that successful epicardial reperfusion is related to a larger release of cardiac necrosis markers with a steeper increase and wash-out (23; 24; 44; 45). Currently, the conclusions of these works remain entirely valid, however in STEMI the attention has shifted from the macro- to the microcirculation (1; 2). At the time these previous studies were performed, the available imaging modalities for the assessment of the microcirculation had not been well developed. Today, with CMR, more accurate instruments are available, meriting further investigation of the association of cardiac necrosis marker release with microvascular perfusion.

In the present work, although each of the 3 necrosis markers showed a relationship with MVO, the association was strongest with troponin. In non-STEMI, adverse outcome of patients with elevated troponin levels seems to result from the presence of fissured plaques, coronary thrombi and micro-embolization (21; 22). On the basis of this data one could speculate that, at the microvascular level, high troponin elevations relate to impaired rather than successful reperfusion. We aimed to validate this hypothesis in the scenario of STEMI in which the amount of necrosis and microvascular damage is much larger than in non-STEMI.

Performing serial measurements of cardiac necrosis markers, we found that patients showing MVO on CMR imaging displayed a significantly larger release of necrosis markers with peak values at around 6 hours after reperfusion. These results were consistent in the whole group and separately in the thrombolysis and primary PCI subgroup.

Interestingly, the differences in necrosis marker release between patients with and without MVO were more pronounced in primary PCI. Contrary to thrombolysis, where timing and amount of epicardial flow restoration is less clear, primary PCI represents the perfect scenario to assess the relationship between necrosis marker release and microcirculatory damage since coronary blood flow was completely and rapidly restored in all patients. In the adjusted multivariate analysis, high troponin at 6 hours after successful PCI was a strong predictor of MVO.

These findings likely reflect that in some patients, despite of full recovery of TIMI 3 flow in the epicardial artery, massive downstream embolization provokes severe abnormal perfusion, large infarctions and consequently higher elevations of necrosis markers.

Of all cardiac necrosis markers, Troponin most closely related to MVO, consistently in the whole group, as well as in the subgroups treated with primary PCI and thrombolysis. Additionally, a larger CK-MB and myoglobin release also related to MVO. Both markers have been classically used for the detection of myocardial infarction (46). Myoglobin allows for a

very early detection of myocardial necrosis with limitations due to poor specificity. CK-MB, because of its faster kinetics, is a traditional marker of re-infarction (47). In the present study, CK-MB and myoglobin levels follow the same course as troponin values, but in the multivariate analysis did not enter as independent predictors of abnormal perfusion.

Elevated troponin and CK-MB after angioplasty yield prognostic information and predict adverse outcome (48; 49). Our present study, in the setting of reperfused STEMI, confirms the link between elevated biomarkers and MVO previously described in non-STEMI (50).

7.3.2 Independent Association of Troponin Release with MVO

The close relationship between troponin release and infarct size has been well established (25). Accordingly, we observed that patients with higher troponin values displayed larger infarctions. Nevertheless, MVO was more frequent in patients with higher troponin levels regardless of infarct size, indicating that the association of troponin release with MVO was not a mere consequence of infarct size. Moreover, in a multivariate analysis adjusted for infarct size, the extent of MVO persisted as an independent predictor of high serum troponin levels.

Delayed presentation and consequently delayed reperfusion might provoke larger infarcts and wider perfusion deficits (18). Thus, elevated troponin levels detected in patients with MVO might originate from delayed reperfusion. Nevertheless, the association of elevated troponin with MVO persisted in patients undergoing early reperfusion (with normal troponin values immediately before reperfusion) and was even stronger in patients with an early and complete coronary flow restoration via primary angioplasty, suggesting a direct connection of MVO with a larger troponin release.

7.4 Prediction of MVO on Patient Admission

7.4.1 Clinical Characteristics on Admission and MVO

Data on how patients with MVO-infarctions initially present is scarce since most studies have focused on prediction of MVO after reperfusion therapy and the prognostic impact of MVO. We determined the individual value of baseline characteristics in the order as they are available on patient admission for predicting the presence of MVO in CMR study performed at 1 week after STEMI in a large cohort of STEMI patients referred for primary PCI. An interesting finding is that clinical characteristics alone already exhibited a high predictive value for MVO. This predictive capability was only significantly improved using the combination of all diagnostic domains (i.e. electrocardiographic, laboratory and angiographic data). Of clinical parameters, Killip class was identified as the strongest predictor of MVO. Only one patient with Killip class >1 on admission did not develop MVO. High Killip class has been shown to be an independent predictor of failure to restore TIMI 3 flow in the epicardial coronary artery after STEMI (10). In our study we did not confirm this finding (TIMI 3 flow in patients with Killip >1: 82%), but there was a strong association with the development of MVO. This finding might partly explain the worse prognosis of patients with a high Killip class by linking it to the development of MVO, which in turn exhibits a strong negative impact on prognosis (7; 13).

In the present study patients with MVO-infarction were younger and there was a trend towards delayed presentation. The observation that young age associates with MVO has not been reported before. Smaller studies in that area did not show a significant age difference between patients with MVO and non-MVO-infarctions (51). A possible explanation for this finding might be that younger patients might have less ischemic preconditioning and less collateral circulation compared to older patients which potentially aggravates myocardial damage during coronary occlusion in STEMI.

Patients who developed MVO-infarctions had a trend towards a higher rate of delayed presentation. This is in line with previous studies demonstrating that MVO strongly depends on the duration of the ischemic time (52; 53).

7.4.2 Biomarkers of MVO on Admission

The association of CMR-derived MVO with biomarkers like the ECG, cardiac necrosis markers and leucocytes has been investigated in the past. Of ECG parameters, as shown in the present work, the amount of residual sumSTE after successful primary PCI is a strong predictor of MVO and also predicts myocardial salvage (54; 55). We confirmed this finding in the present study by demonstrating the high predictive value of ECG data for MVO already on admission.

As is also shown in the present work, a larger release of cardiac necrosis markers, especially troponin, after successfully reperfused STEMI is associated with MVO. Since troponin values can be normal or low on admission in STEMI, we did not find a significant association of troponin on admission with MVO in the present study. However, due to its faster kinetics, myoglobin was significantly higher in patients developing MVO. Nevertheless, the use of biomarkers for early risk stratification and decision making is somewhat limited due to the inherent time delay in their use.

Additionally, post-interventional lymphopenia has been linked to a larger amount of MVO in reperfused STEMI (56). The present study shows that on admission, there is only a trend towards a lower lymphocyte count in patients with MVO infarctions, but neutrophil count was significantly higher.

7.4.3 Angiographic Parameters and MVO

Angiographic parameters have been used in the past for the evaluation of microvascular reperfusion in STEMI.

In our study, the only angiographic parameter significantly associated with MVO was the involvement of the proximal left anterior descending artery. The lack of association of established angiographic parameters like TIMI flow grade, frame count or myocardial blush grade might be owed to several reasons. Firstly, the evaluation of the microcirculation by angiography is performed at a very early time point and it has been shown that the microcirculation display a dynamic behaviour in the first weeks after STEMI (27). Re-established epicardial blood flow, represented by TIMI 3 flow, is a very specific but not very sensitive marker for successful microvascular reperfusion. Accordingly, in our study TIMI 3 flow was achieved in 91% of patients and there was not a statistical association with MVO. Myocardial blush grade, as a good alternative for evaluating microvascular perfusion, displays a high interobserver variability. Lastly and a limitation of our study, the evaluation of angiographic parameters in a core laboratory might have yielded better results. The addition of both laboratory and angiographic parameters to clinical and ECG characteristics improved the predictive capacity of the model for MVO, nevertheless the usefulness of angiography for early prediction of MVO is limited because the information arrives relatively late for clinical decision-making.

7.4.4 Development of a Predictive Score of MVO on Admission

The present study is the first to address the problem of MVO in patients with STEMI before reperfusion therapy is initiated. A common trait of previous studies investigating predictors of MVO is, that they are focused on parameters obtained after the therapeutic intervention had been carried out. At that time point the microvascular damage cannot be influenced anymore as could be with the use of earlier tools. We identified, from a wide range of clinical and ECG, laboratory and angiographic variables available on patient admission independent predictors of MVO. We detected that clinical characteristics and ECG data, the two diagnostic domains most rapidly available to the clinician on patient admission, yielded a predictive value that was only

improved by the addition of both laboratory and angiographic parameters. In order to facilitate the integration of this finding into clinical practice we devised a simple predictive score according to the presence of 5 indexes (Killip class >1, age<55, diabetes, delayed presentation and sumSTE>10mm). This score allowed for the classification of patients according to the risk for developing MVO after STEMI. The prevalence, ranging from low (8.7%) to high risk (93%), as well as the extent of MVO increased with the increasing points of the score.

Potentially this simple universally available score allows for triage of patients according to the risk for developing MVO and might prove useful as a tool for assessing the efficacy of future early therapies aiming at the reduction of MVO.

8 Final Conclusions

In the present cumulative work we set out to investigate the relationship of several biomarkers with CMR-derived MVO in reperfused STEMI. Firstly, we demonstrate the value of ST-segment monitoring for the prediction of CMR-derived MVO. MVO was best predicted by the extent of sumSTE shortly after revascularization (90 minutes). Therefore, the assessment of ST-segment changes should not only involve the evaluation of STR after primary PCI but should focus on the remaining sumSTE providing information on the quality of microvascular reperfusion after primary PCI as a simple bedside measure.

Secondly MVO associates with a larger release of cardiac necrosis markers. Of these, troponin resulted as the best necrosis marker for predicting MVO, especially in primary PCI. The predictive capacity yielded by troponin is greatest at 6 hours after reperfusion, a time point when information on the microcirculatory status after reperfusion is most appreciated by the clinician. The assessment of troponin serum levels at that time point might serve as an additional diagnostic tool in our armamentarium to identify patients with MVO.

Finally, we transferred the results of these previous studies and demonstrated that the prevalence of MVO after STEMI can be predicted using parameters available on patient admission. Clinical characteristics and ECG parameters yielded a high predictive value, which was only improved by the addition of both laboratory and angiographic findings. We developed a simple score using clinical and ECG characteristics, which allowed for classification of patients according to the prevalence and extent of MVO. Given the timely availability this score might prove useful for early classification and risk stratification before reperfusion therapy is initiated and for assessing the value of future therapies aiming at the reduction of MVO in STEMI.

9 References

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10 Curriculum vitae

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11 Publications

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12 Appendix

Appendix 1

ORIGINAL ARTICLE

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 ($P \leq .001$ 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 ($P = .1$), though there was after 6 h ($P < .05$ at all times). The area under the receiver operating characteristic curve for detecting MVO was greater for sumSTE than STR ($P < .05$ 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 ≥70% was not (odds ratio=3.1; 95% confidence interval, 1.2-8.4; $P = .02$).

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.*

SEE EDITORIAL ON PAGES 1120-2

La suma de la elevación del segmento ST predice mejor la obstrucción microvascular en pacientes tratados con éxito con una intervención coronaria percutánea primaria. Un estudio de resonancia magnética cardiovascular

Introducción y objetivos. La utilidad de la resolución del segmento ST (RST) para la predicción de la reperfusión epicárdica está bien establecida. La asociación de los cambios del segmento ST con la obstrucción microvascular (OMV) observada en la resonancia magnética cardiovascular (RMC) tras una intervención coronaria percutánea primaria (ICPp) en el infarto de miocardio con elevación del ST (IMEST) no se ha aclarado todavía.

Métodos. Estudiamos a 85 pacientes consecutivos ingresados por un primer IMEST y tratados con una ICPp que tenían una arteria relacionada con el infarto permeable. Se registró un ECG al ingreso, tras 90 min y tras 6, 24, 48 y 96 h de la ICPp. Se calculó la RST y la suma de la elevación del ST (sumEST) en todas las derivaciones.

Resultados. La RMC reveló una OMV en 37 pacientes. En los infartos con OMV, el valor de la sumEST antes y después de la revascularización fue mayor que en los infartos sin OMV ($p \leq 0,001$ en todos los casos). En cambio, no hubo diferencias significativas en la cantidad de RST entre los infartos con y sin OMV a los 90 min de la revascularización ($p = 0,1$), sino sólo a partir de las 6 h ($p < 0,05$ en todos los casos). El área bajo la curva de características operativas del receptor para la detección de la OMV fue mayor para la sumEST que para la RST ($p < 0,05$ en todas las determinaciones). En el análisis multivariable, ajustado respecto a las características clí-

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ABBREVIATIONS

CMR: cardiovascular magnetic resonance
MVO: microvascular obstruction
pPCI: primary percutaneous intervention
STEMI: ST-segment elevation myocardial infarction
STR: ST-segment elevation resolution
sumSTE: sum of ST-segment elevation

nicas, angiográficas y electrocardiográficas, una sumEST > 3 mm a los 90 min de la ICPp, pero no una RST ≥ 70%, predijo de manera independiente la OMV observada en la RMC (*odds ratio* = 3,1; intervalo de confianza del 95%, 1,2-8,4; p = 0,02).

Conclusiones. La OMV se asoció a un valor significativamente superior de la sumEST en todos los momentos de valoración tras la revascularización. La diferencia en la cantidad de RST entre los infartos con OMV y sin OMV sólo fue significativa a partir de las 6 h tras la revascularización. La OMV se predijo mejor con una sumEST > 3 mm a los 90 min de la ICPp.

Palabras clave: *Resonancia magnética cardiovascular. Obstrucción microvascular. Resolución del segmento ST. Suma de la elevación del segmento ST. Infarto de miocardio con elevación del segmento ST.*

INTRODUCTION

In ST-segment elevation myocardial infarction (STEMI), the timely re-establishment of blood flow in the infarct related artery via primary percutaneous coronary intervention (pPCI) is crucial. However, in spite of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 in the epicardial coronary artery, perfusion at tissue level may be impaired; a phenomenon referred to as microvascular obstruction (MVO). Cardiovascular magnetic resonance (CMR) allows for a comprehensive assessment of STEMI patients[1] with accurate detection of MVO.[2,3]

Several studies have shown that the presence of MVO is associated with adverse outcome, unfavourable left ventricular remodelling and higher mortality.[4-6]

Monitoring of ST-segment changes, especially ST-segment resolution (STR), has been employed in the past as a simple measure of epicardial reperfusion quality in STEMI.[7] Furthermore, STR has been used as a surrogate end-point for MVO in the past[7,8] but the value of STR for detecting CMR-derived MVO is conflicting[9,10,11] and the relationship between ST-segment changes and MVO remains to be clarified.

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 ST-segment elevation in all leads using previously validated algorithms 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.[7,14,15] 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 model[18]. Left ventricular mass (g/m^2), ejection fraction (%), and volumes (mL/m^2) 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 enhancement[2] (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 χ^2 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

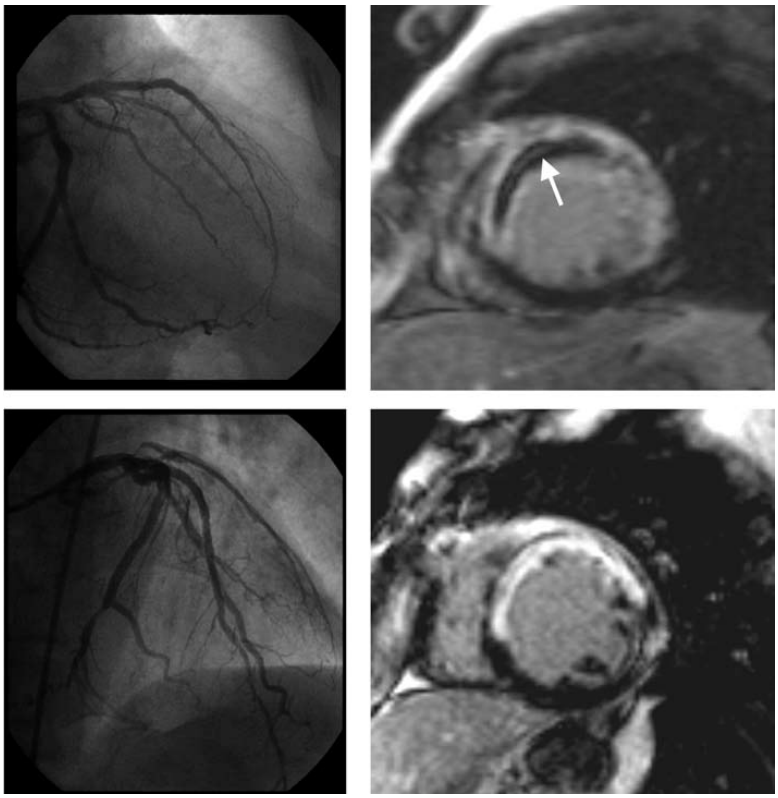

Figure 1. Coronary angiography and late gadolinium enhancement cardiovascular magnetic resonance imaging of two patients with an anterior myocardial infarction. After primary percutaneous intervention, TIMI flow grade 3 was established in the left anterior descending artery (left upper and lower panel). In one patient, on cardiovascular magnetic resonance imaging (right upper panel), late enhancement sequences show a large area of transmural necrosis along the anteroseptal wall with a lack of contrast arrival in the core of the infarcted area (arrow). While infarct size was comparable, no evidence of microvascular obstruction was present in the other patient (right lower panel).

min after pPCI was 71% [22-100] (Figure 2B). Both indexes showed a progressive normalization over time. The percentage of patients displaying complete STR (≥70%) steadily increased over time (53% at 90 min, 67% at 6h, 73% at 24h, 74% at 48h, and 77% at 96h).

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).

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/m^2 vs 29 [14]; *P*<.0001) and end-diastolic (93 [33] mL/m^2 vs 70 [18]; *P*<.0001) left ventricular volumes and mass (81 [19] g/m^2 vs 65 [15]; *P*<.0001).

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*≤.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

TABLE 1. **Baseline Characteristics and Angiographic Data**

	Total	Microvascular Obstruction		*P*-Value
		Absent	Present	
Patients	85	48	37	
Men (%)	69 (81)	40 (83)	29 (78)	.6
Age, mean (SD), y	60 (13)	63 (12)	56 (14)	.02
Median time to revascularization, min	210 [141-420]	190 [140-326]	240 [145-510]	.22
Median peak creatine kinase-MB, ng/mL	299 [62-408]	85 [44-197]	334 [162-503]	<.0001
Heart rate, bpm	79 (17)	78 (17)	79 (18)	.8
Systolic blood pressure, mm Hg	125 (26)	130 (25)	119 (26)	.05
Risk factors				
Active smoker (%)	44 (52)	21 (44)	23 (62)	.09
Hypertension (%)	40 (47)	22 (46)	18 (49)	.8
Diabetes mellitus (%)	12 (14)	4 (8)	8 (22)	.08
Dyslipidemia (%)	34 (40)	19 (40)	15 (41)	.9
Anterior infarction (%)	41 (48)	16 (33)	25 (68)	.002
TIMI flow grade 3 before PCI (%)	11 (13)	6 (13)	5 (14)	.9
Myocardial blush grade 2-3 after PCI (%)	65 (77)	36 (75)	29 (78)	.7
Affection of the proximal LAD (%)	22 (26)	9 (19)	13 (35)	.09
Glycoprotein IIb/IIIa inhibitors (%)	53 (62)	28 (58)	25 (68)	.4
Stent placement (%)	82 (96)	46 (96)	36 (97)	.9
Vessel occulusion prior to PCI (%)	66 (78)	35 (73)	31 (84)	.2

Bpm indicates beats per minute; PCI, primary percutaneous intervention; LAD, left anterior descending artery; TIMI, Thrombolysis in Myocardial Infarction.
Values are displayed as the mean (standard deviation) (compared with Student t test), absolute numbers with percentages in parenthesis (compared using χ^2 test) or the median with the interquartile range in square parenthesis (compared using the Mann-Whitney U test).

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

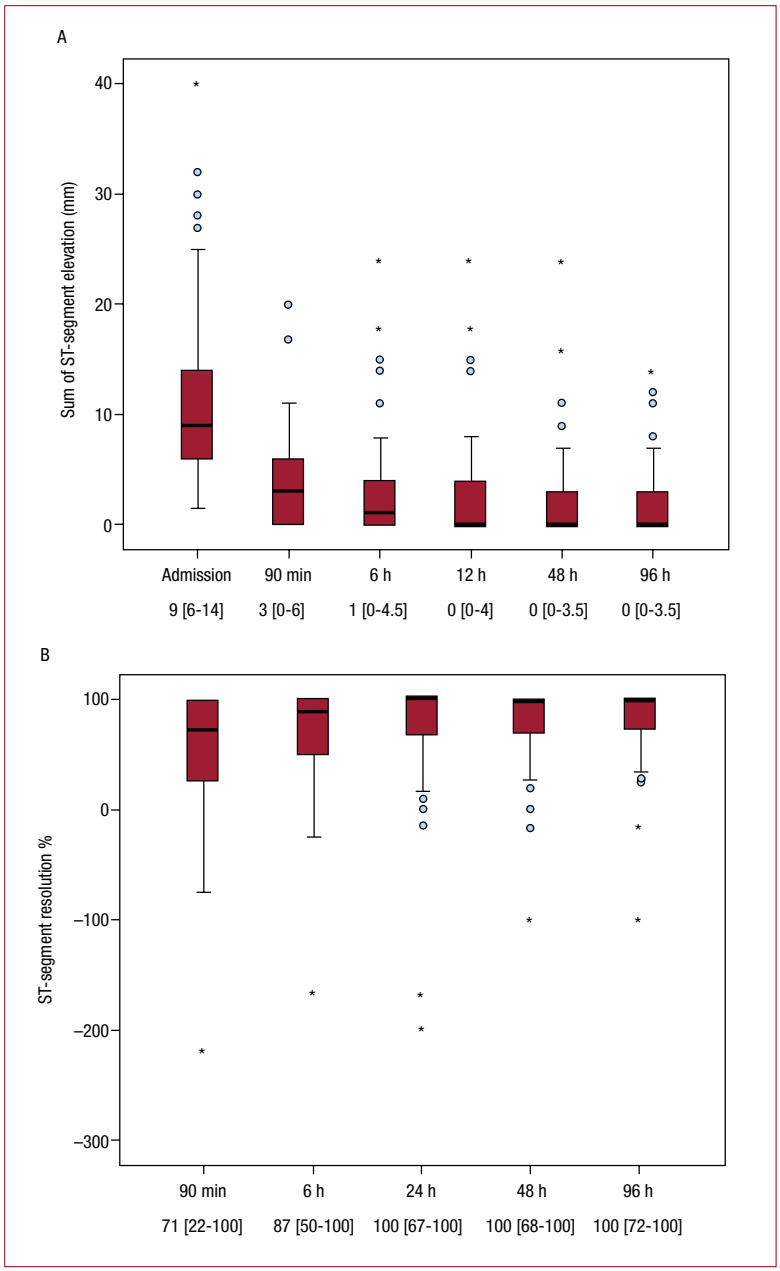

Figure 2. A: sum of ST-segment elevation (mm).B: extent ST-segment resolution (%) on admission and after revascularization in the entire group of patients. Data at the bottom of the graphs indicate the median with the interquartile range.

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.[20,21] 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.[20] Several non-invasive and invasive indexes such as angiographic parameters,[9,10]

TABLE 2. **Area Under the Receiver Operating Characteristic Curve of ST-Segment Elevation and ST-Segment Resolution at All Time Points for Predicting Microvascular Obstruction**

Time	Sum of ST-Segment Elevation	ST-Segment Resolution	
	AUC (95% Confidence Interval)	AUC (95% Confidence Interval)	*P*-Value
Admission	0.728 (0.621 to –0.819)	–	–
90 min	0.699 (0.59 to –0.794)	0.602 (0.49 to –0.707)	.006
6 h	0.706 (0.597 to –0.8)	0.647 (0.536 to –0.748)	.01
24 h	0.704 (0.596 to –0.798)	0.666 (0.555 to –0.764)	.048
48 h	0.708 (0.599 to –0.801)	0.665 (0.555 to –0.764)	.02
96 h	0.714 (0.605 to –0.807)	0.672 (0.562 to –0.77)	.03

AUC indicates area under the receiver operating characteristic curve.

TABLE 3. **Prevalence of Microvascular Obstruction According to Complete ST-Segment Resolution (≥70%) at Every Time Point**

Time	Prevalence of MVO		*P*-Value
	STR <70%	STR ≥70%	
90 min	52%	36%	.1
6 h	57%	37%	.08
24 h	65%	36%	.01
48 h	68%	35%	.007
96 h	70%	35%	.006

MVO indicates microvascular obstruction; STR, ST-segment resolution.

myocardial contrast echocardiography,[20,22] or scintigraphy[23] have been used for the evaluation of MVO.

CMR has become the gold standard in cardiovascular imaging and allows for a comprehensive assessment of a wide range of parameters in patients with STEMI,[1] including infarct size and MVO.[2,3] The presence of MVO on CMR imaging has been shown to predict less functional recovery[24] and post infarction complications independent of infarct size.[21]

ST-Segment Analysis for Assessing Microvascular Perfusion. Role of ST-Segment Resolution

The ECG, as a widely available, rapid and simple method, has been applied as a tool for assessing the success of reperfusion after thrombolysis.[25] STR is useful for predicting the patency of the infarct related artery and thus epicardial reperfusion but its relationship to perfusion on the microcirculatory level remains unclear. Several studies investigating microvascular perfusion assessed by myocardial contrast echocardiography or angiographic blush scores have shown that a lack of STR is indicative of MVO.[13,14,26]

So far, the relationship between STR and CMR-derived MVO has been barely explored in STEMI patients with a patent infarct related artery after pPCI and existing data on the association of CMR-derived MVO with STR is conflicting.[9,10,11]

Two studies in the past reported no significant relationship with STR and CMR-derived MVO.[9,10] While in another study CMR-derived MVO analyzed in first pass perfusion and late enhancement was related to incomplete STR, defined as ≥70%.[11]

In our series of patients, there was not a significant association of STR with MVO at 90 min after pPCI neither as a continuous nor as a binary variable. Nevertheless, in the following measurements patients with MVO-infarctions displayed a significant lower amount of STR that did patients without MVO-infarctions. Accordingly, after 24 hours after revascularization and onwards, patients with complete STR (≥70%) had a significantly lower prevalence of MVO.

Sum of ST-Segment Elevation and Microvascular Obstruction

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

TABLE 4. **Diagnostic Accuracy of Sum of ST-Segment Elevation (>3 mm) and Complete ST-Segment Resolution (≥70%) at 90 Minutes After Percutaneous Coronary Intervention for Detecting Microvascular Obstruction**

	Sensitivity	Specificity	PPV	NPV	Accuracy
sumSTE >3 mm	24/37 (65%)	34/48 (71%)	24/38 (63%)	34/47 (72%)	58/85 (68%)
STR ≥70%	21/37 (57%)	29/48 (60%)	21/40 (53%)	29/45 (64%)	50/85 (59%)

NPV, negative predictive value; PPV, positive predictive value; STR, ST-segment resolution; sumSTE indicates sum of ST-segment elevation.

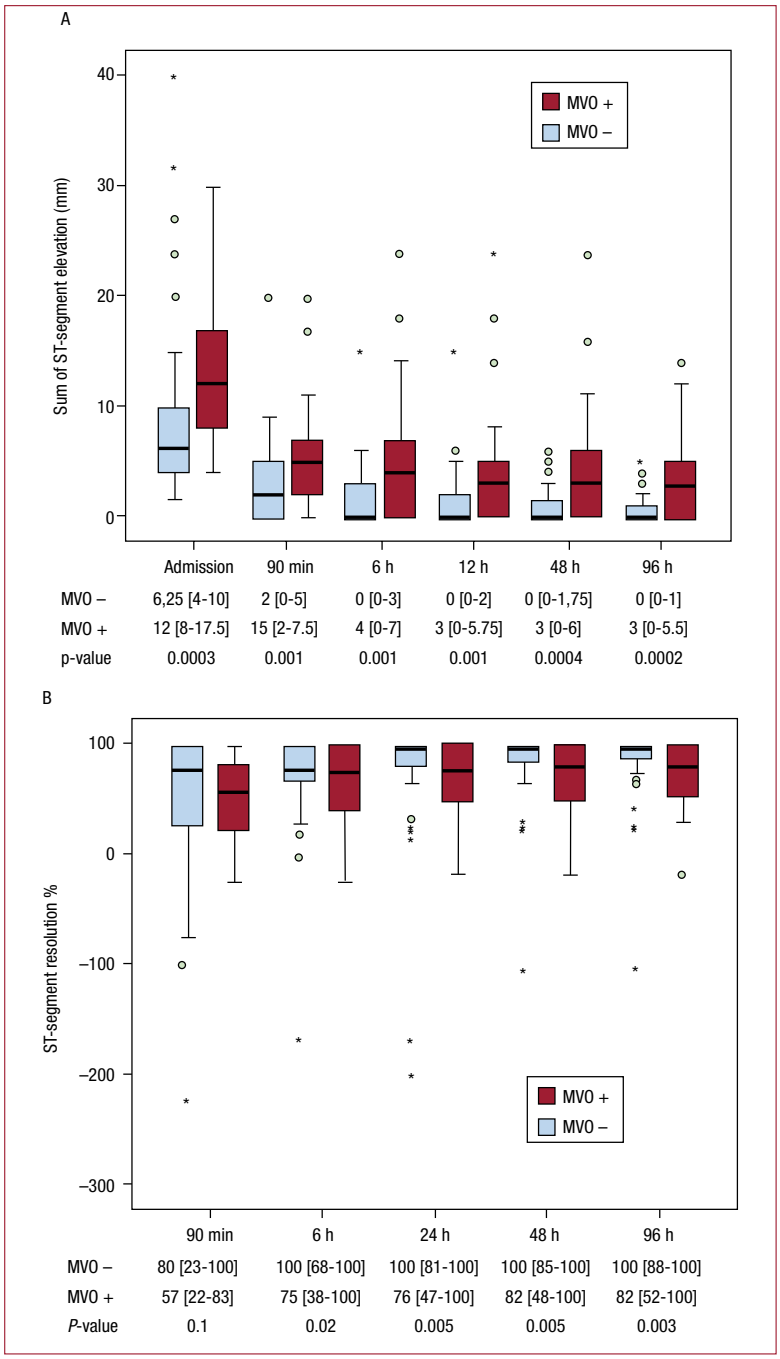

Figure 3. A: time course of the sum of ST-segment elevation (mm). B: ST-segment resolution (%) according to the presence of microvascular obstruction on cardiovascular magnetic resonance imaging. The sum of ST-segment elevation was significantly higher at all time points in patients with microvascular obstruction (MVO) compared to patients without MVO. For ST-segment resolution there was no statistically significant difference at the first measurement after revascularization between the 2 groups. During the following measurements patients without MVO displayed a significant larger amount of STR. Data at the bottom of the graphs indicate the median with the interquartile range and the P-value for comparison of patients with and without MVO.

(>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.

STR highly depends on pre-procedural extent of sumSTE.[27] As a relative measure, STR reflects

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.[16] 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.

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Appendix 2

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Regular Article

Release of necrosis markers and cardiovascular magnetic resonance-derived microvascular perfusion in reperfused ST-elevation myocardial infarction

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ABSTRACT

Introduction: The association of the temporal evolution of cardiac necrosis marker release with cardiovascular magnetic resonance-derived microvascular perfusion after ST-elevation myocardial infarction is unknown.
Methods: We analyzed 163 patients with a first ST-elevation myocardial infarction and a patent infarct-related artery treated with thrombolysis (67%) or primary angioplasty (33%). Using first-pass perfusion CMR, abnormal perfusion was defined as a lack of contrast arrival into the infarct area in >1 segment. Troponin I, creatine kinase MB and myoglobin were measured upon arrival and at 6, 12, 24, 48 and 96 hours after reperfusion.
Results: Abnormal perfusion was detected in 75 patients (46%) and was associated with a larger release of all 3 necrosis markers after reperfusion and higher peak values. This association was observed in the whole group and separately in patients treated with thrombolysis and primary angioplasty. Out of the 3 markers, troponin levels at 6 hours after reperfusion yielded the largest area under the receiver operating characteristic curve for prediction of abnormal perfusion (troponin: 0.69, creatine kinase MB: 0.65 and myoglobin: 0.58). In a comprehensive multivariate analysis, adjusted for clinical, angiographic, cardiovascular magnetic resonance parameters and all necrosis markers, high troponin levels at 6 hours after reperfusion (>median) independently predicted abnormal microvascular perfusion (OR 2.6 95%CI [1.2 - 5.5], p = .012).
Conclusions: In ST-elevation myocardial infarction, a larger release of cardiac necrosis markers soon after reperfusion therapy relates to abnormal perfusion. Troponin appears as the most reliable necrosis marker for an early detection of cardiovascular magnetic resonance-derived abnormal microvascular reperfusion.

Introduction

Cardiac necrosis markers, especially troponin quantification, have been incorporated into daily practice for diagnostic and risk stratification purposes [1–4]. In non-ST-elevation myocardial infarction, worse prognosis of troponin-positive patients seems to be related to the presence of coronary thrombi and microvascular embolization [5,6].

In ST-elevation myocardial infarction (STEMI), the primary therapeutic objective is the restoration of tissue perfusion [7,8]. In patients with an open infarct-related artery, a lack of reperfusion at the microvascular level is related to a worse outcome [7–11]. Classically, a larger and faster release of cardiac necrosis markers has been considered an indicator of successfully recovered epicardial coronary flow [12,13] and the close relationship between troponin release and infarct size has been well established [14]. Nevertheless, the relationship between the temporal evolution of cardiac necrosis marker release and reperfusion at the microvascular level is unknown. Moreover, a simultaneous assessment of the relationship of the 3 most widely used necrosis markers, namely troponin, creatine kinase MB mass (CK-MB) and myoglobin, with the state of microvasculature after reperfused STEMI has not been performed so far.

Cardiovascular magnetic resonance (CMR) allows for a state-of-the-art analysis of infarct size and microvascular perfusion after myocardial infarction [9,10,15]. We analyzed the association of troponin,

Abbreviations: STEMI, ST-elevation myocardial infarction; CMR, cardiovascular magnetic resonance; CK-MB, creatine kinase MB mass.

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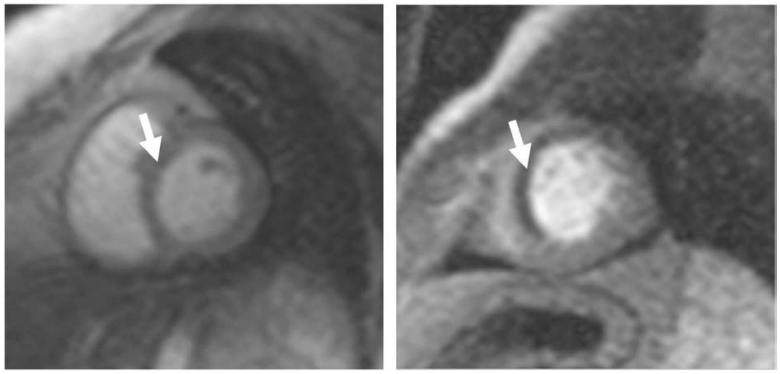


Fig. 1. Short-axis view of first-pass perfusion imaging in two patients with anterior infarction. Left: preserved perfusion in the infarcted area (arrow). Right: abnormal perfusion in the infarcted area (arrow).

CK-MB and myoglobin release with CMR-derived abnormal microvascular perfusion after STEMI.

Methods

Patients

We prospectively included 229 consecutive patients admitted for a first STEMI. Inclusion criteria were: Reperfusion therapy within the first 12 hours after chest pain onset, stable clinical course during the first week and no contraindications to CMR. Further, in order to investigate primary alterations in the microcirculation, only patients with TIMI 3 flow and no significant residual stenosis (<50%) in the infarct-related artery at the end of cardiac catheterization as well as TIMI 3 flow in non-related arteries were included. We excluded 66 patients due to: delayed presentation (8 cases), death (12 cases), re-infarction (8 cases), clinical instability precluding CMR (15 cases), TIMI flow ≤2 (10 cases), occlusion of non-related arteries (4 cases), angioplasty-related infarction in routine post-thrombolysis catheterization (defined as >10 ng/ml increase; twice upper limit of normal for CK-MB; 3 cases), claustrophobia (4 cases) and cardiac surgery (2 cases). Therefore, the final study group included 163 patients.

The local ethics committee approved the research protocol and informed consent was obtained from all subjects.

Blood samples and cardiac necrosis markers

Troponin I, CK-MB and myoglobin were measured upon arrival and at 6, 12, 24, 48 and 96 hours after reperfusion.

Troponin I was measured using a highly sensitive immunoassay (Dimension, Dade Behring Inc., Newark, USA). The coefficient of variation for troponin values between 0.1 and 1 ng/ml was <10% and for troponin values >1 ng/ml was <5%.

CK-MB mass and myoglobin (using immunometric assay; DPC; Los Angeles, CA, USA) were also determined. The coefficients of variation for CK-MB mass >5 ng/ml and for myoglobin >70 ng/ml were <10%.

Cardiac catheterization

The infarct-related artery was the left anterior descending artery in 89 patients (55%), the right coronary artery in 64 (39%) and the left circumflex artery in 10 (6%).

The reperfusion strategy was left to the discretion of the attending cardiologists: 109 patients (67%) were treated with thrombolysis and 54 (33%) were directly submitted to percutaneous revascularization. Time to reperfusion (from chest pain onset) was recorded.

In patients treated with thrombolysis, rescue angioplasty was carried out within the first 3 hours after thrombolytic administration in 20 patients (18%) with persistent chest pain and ST-segment resolution <50%. In the remaining 89 patients, cardiac catheterization was performed at least 24 hours after STEMI (at 3 ± 1 days, range 1-4 days).

A stent was placed in 147 patients (90%) when luminal narrowing in the infarct-related artery was >50%: 51 in primary angioplasty, 18 in rescue angioplasty and 78 in patients treated with thrombolysis in routine pre-discharge cardiac catheterization.

Table 1
Characteristics of the whole group and of patients with abnormal perfusion and normal perfusion.

	All patients (n = 163)	Normal Perfusion (n = 88)	Abnormal perfusion (n = 75)	p-value
Age (years)	58 ± 12	59 ± 11	58 ± 13	.8
Male sex (%)	141 (87)	75 (85)	66 (88)	.6
Diabetes (%)	23 (14)	14 (16)	9 (12)	.5
Hypertension (%)	72 (44)	38 (43)	34 (45)	.8
Hypercholesterolemia (%)	59 (36)	28 (32)	31 (41)	.2
Current smoker (%)	100 (61)	56 (64)	44 (59)	.5
Anterior infarction (%)	89 (55)	36 (41)	53 (71)	.0001
Heart rate (beats per minute)	80 ± 21	76 ± 19	85 ± 23	.004
Systolic blood pressure (mmHg)	123 ± 26	125 ± 24	121 ± 27	.3
Primary angioplasty (%)	54 (33)	23 (26)	31 (41)	.04
Rescue angioplasty (%)	20 (12)	4 (5)	16 (21)	.001
Time to reperfusion (minutes)	242 ± 178	218 ± 162	269 ± 194	.07
ST-segment resolution ≥70% (%)	40 (25)	25 (28)	15 (20)	.2
Median peak troponin (ng/ml)	78 (62)	56 (62)	91 (42)	<.0001
Median peak creatine kinase-MB (ng/ml)	210 (323)	170 (208)	276 (339)	.001
Median peak myoglobin (ng/ml)	655 (1174)	348 (923)	800 (1567)	.08
Cardiac catheterization				
Proximal left anterior descending (%)	44 (27)	21 (24)	23 (31)	.4
Stent (%)	147 (90)	81 (92)	66 (88)	.4
Occluded artery pre-angioplasty (%)	59 (36)	22 (25)	37 (49)	.001
TIMI 3 flow pre-angioplasty (%)	84 (52)	53 (60)	31 (41)	.02
TIMI 3 flow post-angioplasty (%)	163 (100)	88 (100)	75 (100)	-
Blush grade 2-3 post-angioplasty (%)	126 (77)	76 (86)	50 (67)	.003
Glycoprotein IIb/IIIa inhibitor use (%)	72 (44)	41 (47)	31 (41)	.5
Cardiovascular magnetic resonance				
Ejection fraction (%)	52 ± 14	57 ± 11	45 ± 13	<.0001
End-diastolic volume (ml/m^2)	80 ± 26	75 ± 23	86 ± 29	.01
End-systolic volume (ml/m^2)	40 ± 23	33 ± 16	49 ± 27	<.0001
Left ventricular mass (g/m^2)	71 ± 20	68 ± 17	75 ± 22	.01
Infarct size (% of left ventricular mass)	32 ± 15	25 ± 13	39 ± 15	<.0001
Abnormal perfusion (segments)	2.1 ± 2.5	.2 ± .4	4.5 ± 1.9	<.0001

Abbreviations: TIMI = thrombolysis in myocardial infarction.

TIMI flow grade in the initial and final angiographies and myocardial blush grade after angioplasty were determined offline by an experienced observer unaware of CMR results using the software Integris HM3000 (Philips, Best, The Netherlands). TIMI 3 flow and myocardial blush grade 2-3 were regarded as normal [16].

CMR

CMR (1.5-T scanner, Sonata Magnetom, Siemens, Erlangen, Germany) was performed 9 ± 6 days (at least 48 hours after cardiac catheterization) after myocardial infarction in accordance with our

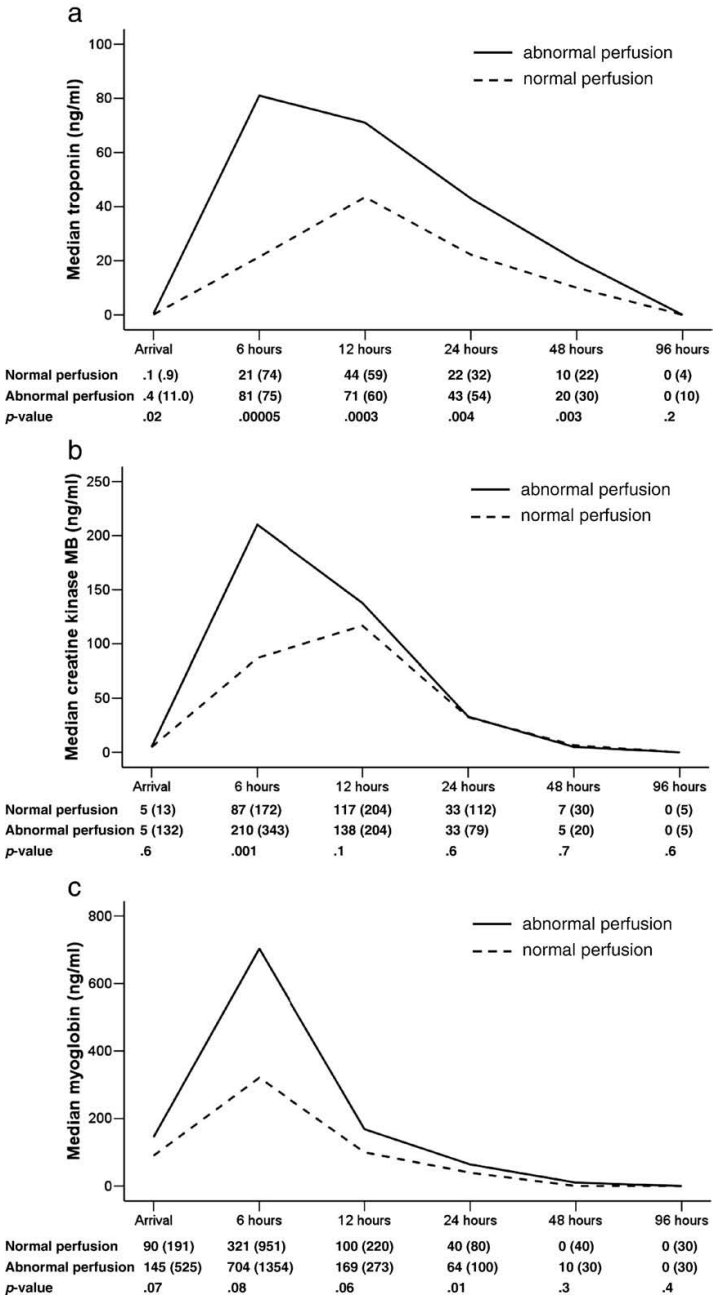


Fig. 2. Evolution of necrosis marker release depending on the presence of abnormal perfusion in the whole group. Data at the bottom indicate the median with the interquartile range of troponin over time according to normal or abnormal perfusion in all patients (a), CK-MB over time according to normal or abnormal perfusion in all patients (b) and myoglobin over time according to normal or abnormal perfusion in all patients (c).

laboratory protocol [9–11]. Images were acquired by a phased-array body surface coil during breath-holds and were electrocardiogram-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.

After cine images, 5 short-axis views and 2 long-axis views were acquired every other beat for rest first-pass perfusion imaging (steady-state free precession sequence, inversion time: 110 ms, repetition time / echo time: 190 / 1 ms, flip angle: 49 degrees, matrix 128×72, in-plane spatial resolution 2.7×3.6 mm) after administering 0.1 mmol/kg of gadolinium-diethylenetriaminepentaacetic acid (Magnograf, Juste S.A.Q.F., Madrid, Spain) at a flow rate of 3 ml/s.

Delayed enhancement imaging was performed in the same projections used for cine images at least 10 minutes after administering contrast. 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.

CMR data analysis

CMR studies were analyzed by two experienced observers blinded to all patient data using customized software (QMASS MR 6.1.5, Medis, Leiden, The Netherlands). Segments location was defined applying the 17-segment model [17].

Left ventricular end-diastolic and -systolic volumes (ml/m2), ejection fraction (%) and mass (g/m2) were quantified by manual definition of endocardial borders of all short-axis slices in cine-images.

Segmental abnormal perfusion was defined, based on visual assessment, as regions showing hypoenhancement both in short- and long-axis views compared with remote non-infarcted segments in the same slice at the end of first-pass perfusion imaging [10,11]. A patient was considered to have abnormal perfusion if >1 segment displayed abnormal perfusion (Fig. 1).

Delayed enhancement was considered in case of signal intensity >2 standard deviations with respect to a remote non-infarcted area in delayed enhancement imaging. Infarct size was defined as the percentage of left ventricular mass showing delayed enhancement [10].

Disagreement concerning abnormal perfusion occurred in 8 patients (5%) and was solved by consensus.

Statistical analysis

All data were tested for normal distribution using the one-sample Kolmogorov-Smirnov test. Continuous data were expressed as the mean ± standard deviation and compared using Student's t-test. Group percentages were compared using the chi-square test or Fisher's exact test as appropriate. Nonparametric data were expressed as the median with the interquartile range and were compared using the Mann-Whitney U-test.

Receiver operating characteristic (ROC) curve analysis was used to determine the accuracy of cardiac necrosis marker for predicting abnormal perfusion.

Cardiac necrosis marker levels in the first measurement after reperfusion (at 6 hours) were most closely related to abnormal perfusion. Attending to this finding as well as to the fact that, from a clinical point of view, it is at this time point (soon after reperfusion) when information on the microcirculatory status is most needed (e.g. for assessment of the effect of therapies on microcirculation), our analyses focused on necrosis markers at that time point.

The value of cardiac necrosis marker levels for predicting abnormal perfusion was determined in the whole group and separately in the thrombolysis and primary angioplasty group using a forward logistic regression model, adjusted for variables yielding a p-value <.1 in univariate analyses. Odds ratios and their 95% confidence intervals (OR [95% CI]) were computed.

Statistical significance was considered for a two-tailed p-value <.05. SPSS 13.0 (SPSS Inc, Chicago, Illinois, USA) was used.

Results

Temporal evolution of cardiac necrosis marker release and abnormal perfusion

Out of 163 patients, 75 (46%) showed abnormal perfusion. Baseline characteristics of the whole group and of patients with normal and abnormal perfusion are displayed in Table 1. Patients with abnormal perfusion had a higher heart rate, more anterior infarctions and on angiography displayed a higher percentage of an occluded infarct-related artery, abnormal TIMI flow pre- angioplasty and abnormal blush grade post-angioplasty. Patients treated with primary and rescue angioplasty were more likely to have abnormal perfusion.

Abnormal perfusion related to a larger release of all three cardiac necrosis markers after reperfusion and higher peak values (Table 1, Fig. 2). The most significant differences were detected in all cases at 6 hours post-reperfusion. ROC curve analysis for detection of abnormal perfusion of the 3 necrosis markers at 6 hours are displayed in Table 2. Troponin was the necrosis marker most strongly associated with abnormal perfusion (Table 2, Figs. 2–4).

Patients were categorized according to the median troponin level at 6 hours after reperfusion (lower troponin 0-42 ng/ml and high troponin >42 ng/ml). Abnormal perfusion was more frequent in patients with high troponin levels (50/81 (62%) vs. 25/82 (31%), p<.0001).

On CMR imaging, patients with high troponin levels at 6 hours had larger left ventricular volumes, a larger infarct size, poorer systolic function and a wider perfusion deficit (Table 3).

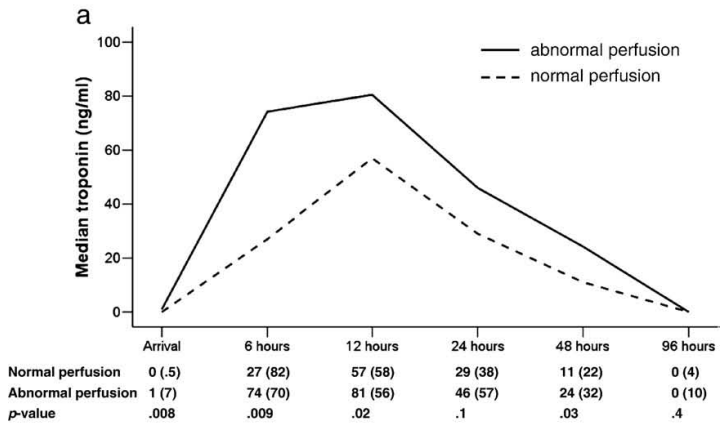
Patients treated with thrombolysis and primary angioplasty

In thrombolysis, abnormal perfusion was detected in 44 of 109 patients (40%) and was associated with a larger release of troponin and CK-MB at 6-12 hours after thrombolysis and higher peak values. There was a trend to a larger myoglobin release in patients with abnormal perfusion (Fig. 3). In ROC curve analysis, troponin at 6 hours yielded the largest area under the curve (Table 2). Abnormal perfusion was more frequent in patients with high troponin levels after reperfusion (29/57 (51%) vs. 15/52 (31%), p = .019).

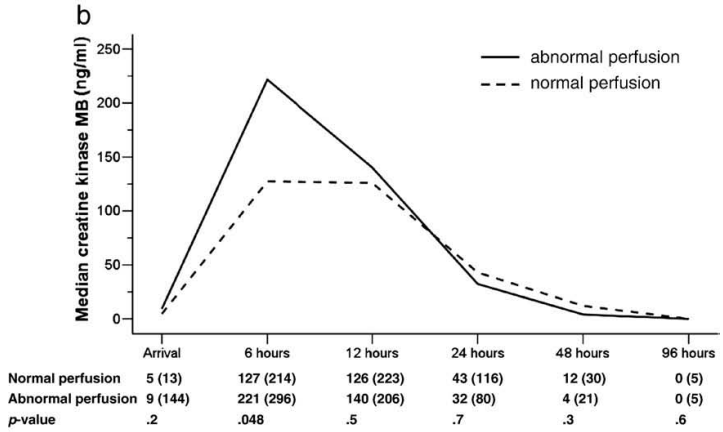
The relationship between abnormal perfusion and necrosis marker release was even stronger in patients treated with primary

Table 2
Receiver operating characteristics curve analysis of cardiac necrosis markers for detecting abnormal perfusion at 6 hours after revascularization in the whole group and in the primary angioplasty and thrombolysis subgroup.

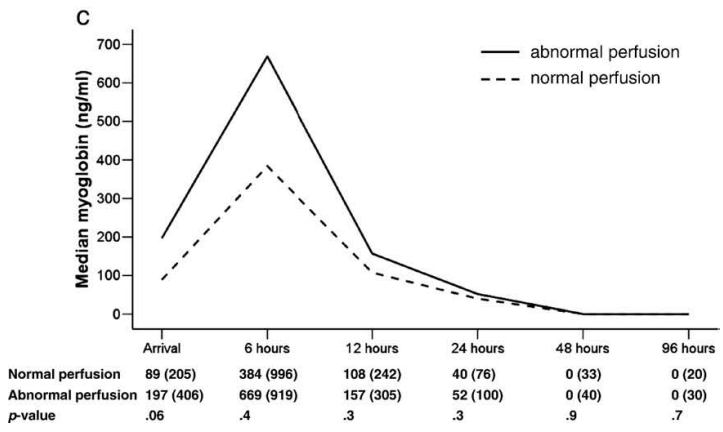
	Area under the curve	p-value	95% confidence interval
Whole Group			
Troponin	.685	.00005	.603 - .767
Creatine kinase-MB	.648	.001	.563 - .734
Myoglobin	.580	.08	.490 - .669
Primary angioplasty			
Troponin	.787	.0003	.661 - .913
Creatine kinase-MB	.764	.001	.632 - .897
Myoglobin	.698	.01	.553 - .843
Thrombolysis			
Troponin	.647	.01	.543 - .750
Creatine Kinase-MB	.612	.048	.501 - .723
Myoglobin	.543	.4	.429 - .657



	Arrival	6 hours	12 hours	24 hours	48 hours	96 hours
Normal perfusion	0 (.5)	27 (82)	57 (58)	29 (38)	11 (22)	0 (4)
Abnormal perfusion	1 (7)	74 (70)	81 (56)	46 (57)	24 (32)	0 (10)
p-value	.008	.009	.02	.1	.03	.4



	Arrival	6 hours	12 hours	24 hours	48 hours	96 hours
Normal perfusion	5 (13)	127 (214)	126 (223)	43 (116)	12 (30)	0 (5)
Abnormal perfusion	9 (144)	221 (296)	140 (206)	32 (80)	4 (21)	0 (5)
p-value	.2	.048	.5	.7	.3	.6



	Arrival	6 hours	12 hours	24 hours	48 hours	96 hours
Normal perfusion	89 (205)	384 (996)	108 (242)	40 (76)	0 (33)	0 (20)
Abnormal perfusion	197 (406)	669 (919)	157 (305)	52 (100)	0 (40)	0 (30)
p-value	.06	.4	.3	.3	.9	.7

Fig. 3. Evolution of necrosis marker release depending on the presence of abnormal perfusion in patients treated with thrombolysis. Data at the bottom indicate the median with the interquartile range of troponin over time according to normal or abnormal perfusion in patients treated with thrombolysis (a), CK-MB over time according to normal or abnormal perfusion in patients treated with thrombolysis (b) and myoglobin over time according to normal or abnormal perfusion in patients treated with thrombolysis (c).

angioplasty. Abnormal perfusion was detected in 31 of 54 patients (57%) and was associated with a larger release of cardiac necrosis markers after revascularization and higher peak values (Fig. 4). In ROC curve analysis, troponin at 6 hours yielded the largest area under the curve (Table 2). Abnormal perfusion was more frequent in patients with high troponin levels at 6 hours after primary angioplasty (21/24 (88%) vs. 10/30 (33%), $p<.0001$). The time from revascularization to CMR study did not differ between patients treated with primary angioplasty and thrombolysis (9 ± 5 days vs. 9 ± 6, $p=.9$).

Multivariate analyses

For the whole group and separately for the primary angioplasty and thrombolysis subgroup, a multivariate analysis to identify predictors of

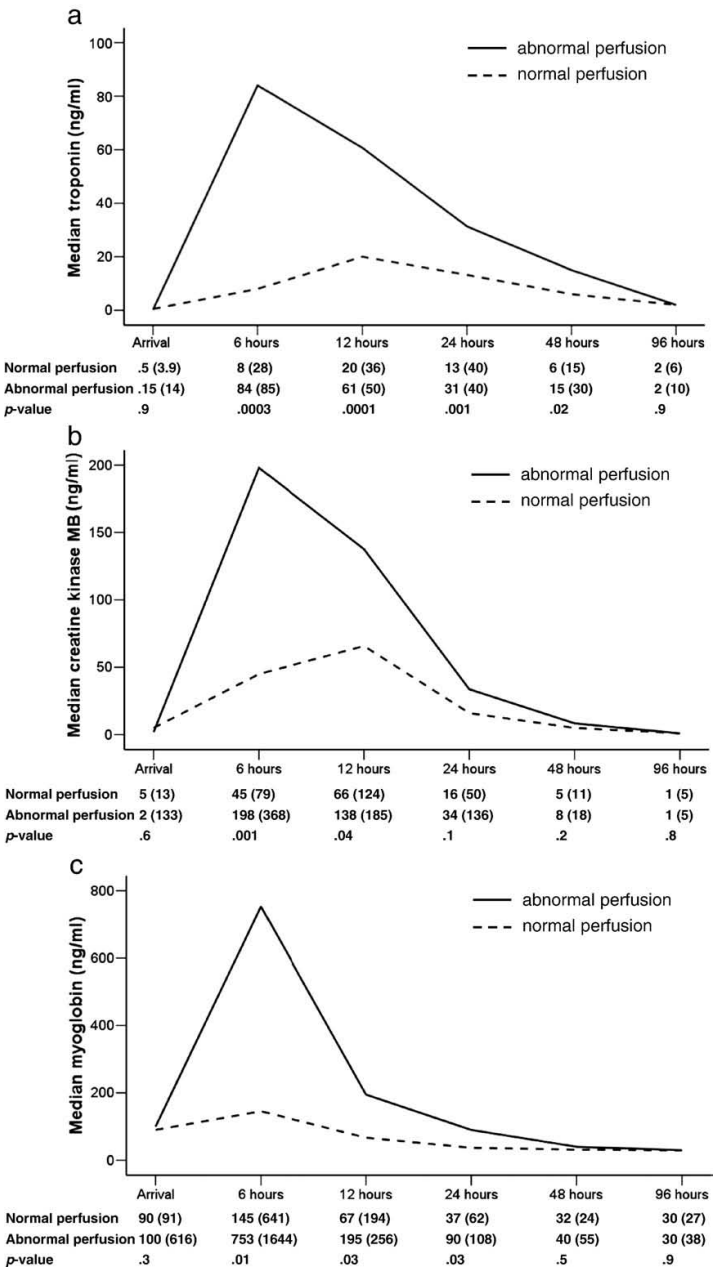


Fig. 4. Evolution of necrosis marker release depending on the presence of abnormal perfusion in patients treated with primary angioplasty. Data at the bottom indicate the median with the interquartile range of troponin over time according to normal or abnormal perfusion in patients treated with primary angioplasty (a), CK-MB over time according to normal or abnormal perfusion in patients treated with primary angioplasty (b) and myoglobin over time according to normal or abnormal perfusion in patients treated with primary angioplasty (c).

abnormal perfusion, adjusted for variables showing a p-value<.1 in the univariate analysis, was performed (Table 4).

In the whole study group, high troponin levels at 6 hours after reperfusion related to abnormal perfusion. Infarct size and vessel occlusion prior to angioplasty were also associated with abnormal perfusion. In patients treated with primary angioplasty, high troponin levels at 6 hours were related to abnormal perfusion. Infarct size and hypertension were also associated with abnormal perfusion. In thrombolysis the predictors of abnormal perfusion were infarct size and rescue angioplasty.

Independent association of troponin release with abnormal perfusion regardless of infarct size or delayed presentation

Patients with elevated troponin at 6 hours after reperfusion showed larger infarctions (Table 3). To verify that the association

Table 3
Cardiovascular magnetic resonance parameters according to the median troponin level at 6 hours after reperfusion (lower troponin 0-42 ng/ml and high troponin >42 ng/ml).

	Troponin		
	Lower n = 82	High n = 81	p-value
Ejection fraction (%)	57 ± 12	46 ± 13	<.0001
End-diastolic volume (ml/m^2)	73 ± 21	87 ± 29	.001
End-systolic volume (ml/m^2)	32 ± 15	49 ± 27	<.0001
Left ventricular mass (g/m^2)	68 ± 18	74 ± 21	.06
Infarct size (% of left ventricular mass)	27 ± 15	37 ± 14	<.0001
Abnormal perfusion (segments)	1.2 ± 1.7	3.1 ± 2.8	<.0001

between troponin release and abnormal perfusion was not a mere consequence of a larger infarct size or delayed presentation the following analyses were performed:

(a) The whole group was categorized according to the median of infarct size (small infarct: ≤34% of left ventricular mass vs. large infarct: >34% of left ventricular mass). Abnormal perfusion was more frequent in patients with high troponin at 6 hours after reperfusion regardless of infarct size: small infarct, 13/31 (42%) vs. 9/50 (18%), p = .019; large infarct, 37/50 (74%) vs. 16/32 (50%), p = .027.
(b) Upon arrival, 72 patients (44%) displayed normal troponin values (<.1 ng/ml). As in the whole group, abnormal perfusion was more frequent in the case of high troponin at 6 hours after reperfusion: 19/35 (54%) vs. 11/37 (30%), p = .035.
(c) A multivariate analysis to identify predictors of high troponin levels at 6 hours after reperfusion was performed including variables showing a p-value<.1 in the univariate analysis: heart rate, anterior infarction, ST-segment resolution ≥70%, rescue angioplasty, proximal left anterior descending lesion and all CMR variables. Time to reperfusion was also included. Abnormal perfusion (OR 1.23, 95%CI [1.03-1.48], per segment, p = .021), ejection fraction (OR .96, 95%CI [.93-.1] per 1% increase, p = .009) and ST-segment resolution ≥70% (OR 0.44 95%CI [.19-.99], p = .048) were predictors of high troponin levels at 6 hours after reperfusion.

Discussion

The present study shows that in patients with reperfused STEMI, (1) abnormal microvascular perfusion is associated with a larger release of troponin, CK-MB and myoglobin. (2) In primary angioplasty this relationship is more pronounced than in thrombolysis. (3) Serum levels at 6 hours after reperfusion were most closely related to abnormal perfusion. (4) Of the 3 necrosis markers, troponin best predicted abnormal perfusion independent of infarct size and delayed presentation.

Abnormal perfusion after infarction

The paramount importance of microcirculation after myocardial infarction has been known for over a decade [7,8]. CMR allows for a complete non-invasive evaluation of patients after STEMI with simultaneous and reliable assessment of heart chambers, infarct size and microcirculation [9–11,14,15,18–20].

Using first-pass perfusion CMR, we detected abnormal perfusion in 46% of patients. This figure is in agreement with recent reports [19] and reflects the magnitude of the problem even in an ideal scenario represented by patients with TIMI 3 flow in the infarct-related artery prior to the CMR study. Abnormal perfusion was not an incidental finding, indeed it related to larger infarct sizes and left ventricular volumes and to a more depressed systolic function. Furthermore, several studies have shown that abnormal perfusion is associated with a worse outcome [7,8,16].

Necrosis markers and abnormal perfusion

Studies from the past two decades demonstrated that successful epicardial reperfusion relates to a larger release of cardiac necrosis markers with a faster increase and wash-out [12,13,21,22]. Currently, the conclusions of these works remain entirely valid, but in STEMI attention has shifted from the macro- to the microcirculation [7,8]. At the time of these studies, imaging modalities for assessment of microvascular perfusion had not been well developed. Today, more accurate instruments are available, meriting further investigation of the association of cardiac necrosis marker release with microvascular perfusion.

In this study, although each of the 3 necrosis markers showed a relationship with abnormal perfusion, the association was strongest with troponin.

In non-STEMI, adverse outcome of patients with elevated troponin levels seems to result from the presence of fissured plaques, coronary thrombi and micro-embolization [5,6]. On the basis of this data one could speculate that, at the microvascular level, high troponin elevations relate to impaired rather than successful reperfusion. We aimed to validate this hypothesis in the scenario of STEMI in which the amount of necrosis and microvascular damage is much larger than in non-STEMI.

Performing serial measurements of cardiac necrosis markers, we found that patients showing abnormal perfusion on CMR imaging displayed a significantly larger release of necrosis markers with peak values at around 6 hours after reperfusion. These results were consistent in the whole group and separately in the thrombolysis and primary angioplasty subgroup.

Interestingly, the differences in necrosis marker release between patients with normal and abnormal perfusion were more pronounced in primary angioplasty. Contrary to thrombolysis, where timing and amount of epicardial flow restoration is less clear, primary angioplasty represents the perfect scenario to assess the relationship between necrosis marker release and microcirculatory damage since TIMI 3 flow was completely and rapidly restored in all patients. In the adjusted multivariate analysis, high troponin at 6 hours after successful angioplasty was a strong predictor of abnormal microvascular perfusion.

These findings likely reflect that in some patients, despite of full recovery of TIMI 3 flow in the epicardial artery, massive downstream embolization provokes severe abnormal perfusion, large infarctions and consequently higher elevations of necrosis markers.

Table 4
Multivariate analysis for predictors of abnormal perfusion in the whole group and in the primary angioplasty and thrombolysis subgroup.

	Odds ratio	95% confidence interval	p-value
Whole group*			
Troponin at 6 hours (>median)	2.6	1.2 – 5.5	.012
Infarct size, per 1% of left ventricular mass	1.07	1.04 – 1.1	<.0001
Vessel occlusion prior to angioplasty	3.2	1.5 – 6.9	.003
Primary angioplasty†			
Troponin at 6 hours (>median)	13.9	2.4 – 78.8	.003
Infarct size, per 1% of left ventricular mass	1.1	1.03 – 1.2	<.0001
Hypertension	9.7	1.5 – 64.1	.02
Thrombolysis‡			
Infarct size, per 1% of left ventricular mass	1.1	1.03 - 1.1	.001
Rescue angioplasty	6.7	1.8 - 24.5	.004

Adjusted for variables showing a p-value<.1 in the univariate analysis.
*Heart rate, anterior infarction, primary and rescue angioplasty, time to reperfusion, ST-segment resolution ≥70%, occluded infarct related artery pre-angioplasty, TIMI 3 flow pre-angioplasty, blush grade 2-3 post angioplasty, all 3 cardiac necrosis markers at 6 hours after reperfusion and all CMR parameters.
† Hypertension, anterior infarction, all 3 cardiac necrosis markers at 6 hours after reperfusion and all CMR parameters.
‡ Anterior infarction, heart rate, rescue angioplasty, occluded artery pre-angioplasty TIMI 3 flow pre-angioplasty,blush grade 2-3 post-angioplasty , all 3 cardiac necrosis markers at 6 hours after reperfusion and all CMR parameters.

Troponin most closely related to abnormal perfusion, consistently in the whole group, as well as in the subgroups treated with primary angioplasty and thrombolysis. Additionally, a larger CK-MB and myoglobin release also related to abnormal perfusion. Both markers have been classically used for the detection of myocardial infarction [23]. Myoglobin allows for a very early detection of myocardial necrosis with limitations due to poor specificity. CK-MB, because of its faster kinetics, is a traditional marker of reinfarction [24]. In the present study, CK-MB and myoglobin levels follow the same course as troponin values but in the multivariate analysis did not enter as independent predictors of abnormal perfusion.

Elevated troponin and CK-MB after angioplasty yield prognostic information and predict adverse outcome [25,26]. Our present study, in the setting of reperfused STEMI, confirms the link between elevated biomarkers and abnormal perfusion previously described in non-STEMI [27].

Independent association of troponin release with abnormal perfusion

The close relationship between troponin release and infarct size has been well established [14]. Accordingly, we observed that patients with higher troponin values displayed larger infarctions. Nevertheless, abnormal perfusion was more frequent in patients with higher troponin levels in smaller as well as in large infarctions, indicating that the association of troponin release with abnormal perfusion was not a mere consequence of infarct size. Moreover, in a multivariate analysis adjusted for infarct size, the extent of abnormal perfusion on CMR imaging persisted as an independent predictor of high serum troponin levels.

Delayed presentation and consequently delayed reperfusion might provoke larger infarcts and wider perfusion deficits [2]. Thus, elevated troponin levels detected in patients with abnormal perfusion might originate from delayed reperfusion. Nevertheless, the association of elevated troponin with abnormal perfusion persisted in patients undergoing early reperfusion (with normal troponin values immediately before reperfusion) and was even stronger in patients with an early and complete coronary flow restoration via primary angioplasty, suggesting a direct connection of abnormal perfusion with a larger troponin release.

Limitations

The optimal time point to visualize microvascular obstruction has not been defined yet. Nevertheless, data derived from an experimental dog model indicate that the extent of microvascular obstruction is unchanged at 2 and 9 days after reperfused myocardial infarction [28]. Accordingly, several studies assessing the implications of microvascular obstruction after STEMI have used the first week (6-10 days) after STEMI as the ideal moment for post-infarct imaging [19,29–31]. The mean delay to CMR in our study was 9 ± 6 days (median 8; IQR 6-10). A sooner time point for assessing the extent of infarcted myocardium and microvascular obstruction might overestimate these indices partly due to extensive edema. On the other hand, CMR performed at a later time point, might underestimate myocardial and microcirculatory damage. Nonetheless, we cannot exclude changes in the extent of microvascular obstruction during the days from STEMI to CMR imaging.

Conclusions

In reperfused STEMI, abnormal microvascular perfusion associates with a larger release of cardiac necrosis markers. Troponin is the best necrosis marker for predicting abnormal perfusion, especially in primary angioplasty. Information yielded by troponin is greatest at 6 hours after reperfusion, a time point when information on the microcirculatory status after reperfusion is most appreciated by the clinician. The assessment of troponin serum levels at that time point might serve as an additional diagnostic tool in our armamentarium to identify patients with impaired microvascular perfusion.

Conflict of interest statement

No conflict of interest exists in the present study.

Acknowledgments

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Appendix 3

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Predictors of cardiovascular magnetic resonance-derived microvascular obstruction on patient admission in STEMI ☆

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ABSTRACT

Background: Early stratification of patients according to the risk for developing microvascular obstruction (MVO) after ST-segment elevation myocardial infarction (STEMI) is desirable. We aimed to identify predictors of cardiovascular magnetic resonance (CMR)-derived MVO from clinical + ECG, laboratory and angiographic parameters available on admission.

Methods: Characteristics available on admission were documented in 97 STEMI patients referred for primary angioplasty. MVO was determined using contrast-enhanced CMR.

Results: MVO was present in 44 patients (45%). The C-statistic for predicting MVO was: clinical + ECG (.832), laboratory (.743), and angiographic parameters (.669). Adding laboratory to clinical + ECG information did not improve the C-statistic (.873 vs. .832, p = .2). Further addition of angiographic data (.904) improved the C-statistic of clinical + ECG (p = .04) but not of clinical + ECG and laboratory (p = .2). Independent predictors of MVO using clinical and ECG parameters were: Killip class >1 (OR 15.97 95%CI [1.37–186.76], p = .03), diabetes (OR 6.15 95%CI [1.49–25.39], p = .01), age <55 years (OR 4.70 95%CI [1.56–14.17], p = .006), sum of ST-segment elevation >10 mm (OR 4.5 95%CI [1.58–12.69], p = .005) and delayed presentation >3 h (OR 3.80 95%CI [1.19–12.1], p = .02). A score was constructed assigning Killip class >1 2 points and the remaining indexes 1 point. The incidence of MVO increased with the score: 0 point: 8.7%; 1 point: 28.1%; 2 points: 71.4%; and 3+ points: 93% (p<.0001).

Conclusions: MVO can be predicted using parameters already available on patient admission. We developed a clinical-ECG score allowing for early and reliable classification of STEMI patients according to the risk of MVO.

1. Introduction

In ST-segment elevation myocardial infarction (STEMI), despite re-established epicardial blood flow, perfusion at the microvascular level may be impaired; a phenomenon referred to as microvascular obstruction (MVO).

The capability of clinical parameters and biomarkers already available on patient admission for prediction of MVO has been barely investigated so far. The prediction of MVO at such a pivotal time point for therapeutic decision making has not been attempted before and is desirable since it bears the potential of early risk stratification and might have therapeutic implications for therapies aiming at the reduction of MVO before reperfusion therapy is initiated.

Cardiovascular magnetic resonance (CMR) allows for a comprehensive assessment of STEMI patients [1,2] with accurate detection of MVO [3,4]. Several studies have shown that the presence of MVO is associated with adverse outcome, unfavorable left ventricular remodeling and higher mortality [5–7].

We hypothesized that characteristics available on admission would be useful for early prediction of MVO-infarctions. For this purpose we analyzed clinical, electrocardiographic, laboratory and angiographic characteristics available on patient admission for determination of the best and earliest predictors of MVO in patients with STEMI.

2. Materials and methods

2.1. Patients

We prospectively included 110 consecutive patients referred for primary percutaneous coronary intervention (PCI) for a first STEMI within 12 h of chest pain onset.

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ST-elevation myocardial infarction was defined following current definitions [8]. Patients with a history of prior myocardial infarction or new onset bundle branch block were not considered for participation. The inclusion criteria were: stable clinical course without complications during hospitalization and no contraindications to CMR. We excluded 13 patients because of death (n = 5), reinfarction (n = 2), clinical instability (n = 3) and claustrophobia (n = 3). Therefore, the final study group comprised 97 patients. All patients gave written informed consent and the study protocol was approved by the institutional committee on human research and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2. Clinical and ECG characteristics

Clinical characteristics were recorded in all cases on patient admission. Time from pain onset to presentation was recorded. Delayed presentation was considered as >3 h [9]. Killip class was determined [10]. The TIMI risk score for each patient was calculated [11].

A standard 12 lead ECG was recorded upon admission at a paper speed of 25 mm/s and an amplification of 10 mm/mV. The isoelectric line was defined as the level of the TP-segment. Extent of ST-elevation was measured 20 ms after the J-point in every lead and the sum of ST-elevation (sumSTE) was calculated in leads V1–6, I, and aVL for anterior infarction and in leads II, III, aVF, V5, and V6 for non-anterior infarction using previously validated algorithms [12–14]. Infarct location was assigned as anterior versus non-anterior infarction. Residual sum of ST-segment elevation 90 min after PCI was determined.

2.3. Laboratory test

Troponin I (using a highly sensitive immunoassay, Dimension, Dade Behring Inc., Newark, USA) CK-MB mass and myoglobin (using immunometric assay; DPC; Los Angeles, CA, USA) were determined. Troponin I was serially measured at 6, 12, 24, 48 and 96 h after reperfusion. Peak troponin I was determined.

The coefficient of variation for troponin values between 0.1 and 1 ng/ml was <10% and for troponin values >1 ng/ml was <5%. The coefficients of variation for CK-MB mass >5 ng/ml and for myoglobin >70 ng/ml were <10%.

Total leucocyte count and separately neutrophil, lymphocyte and monocyte count (all as ×1000 cells/ml) were determined by an automated blood cell counter.

2.4. Coronary angiography and PCI

PCI was performed within 12 h of symptom onset in all patients. Door to balloon time was recorded. TIMI flow grade [15] before and after PCI was assessed. Myocardial blush grade [16] and corrected TIMI frame count [17] were evaluated after PCI. Patients were treated with double anti-platelet therapy except of 9 patients who received mono-therapy with aspirin after balloon angioplasty only with good angiographic result. Patients with contraindication to dual antiplatelet therapy (chronic or active bleeding (n = 5), aspirin intolerance, (n = 2) or oral anticoagulation due to paroxysmal atrial fibrillation (n = 1)) treated with stenting received indefinite clopidogrel and low-molecular weight heparin for up to 1 month. Angiographic data was analyzed by an experienced investigator using standard software blinded to CMR results (HM3000, Philipps, Best, The Netherlands).

2.5. Cardiovascular magnetic resonance imaging

CMR (1.5-T scanner, Sonata Magnetom, Siemens, Erlangen, Germany) was performed at least 48 h after PCI in accordance with our laboratory protocol [18,19]. Images were acquired by a phased-array body surface coil during breath-holds and were ECG-triggered. Cine images (true fast imaging with steady state precession, repetition time/echo time: 3.2/1.6 ms, flip angle: 61°, matrix: 256 × 128, slice thickness: 6 mm, temporal resolution: 26 ms) were acquired in 2-, 3-, and 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 min after administering 0.1 mmol/kg of gadolinium-diethylenetriaminepentaacetic acid (Magnograf, Juste S.A.Q.F., Madrid, Spain). A segmented inversion recovery true fast imaging with steady state precession sequence was used (repetition time/echo time: 2.5/1.1 ms, slice thickness: 6 mm, flip angle: 50°, matrix: 195 × 192) nullifying myocardial signal.

2.6. CMR data analysis

CMR studies were analyzed by an experienced observer blinded to all clinical, ECG, laboratory and angiographic data using customized software (QMASS MR 6.1.5, Medis, Leiden, The Netherlands).

Segment location was defined according to the 17-segment model [20]. Left ventricular mass (g/m^2), ejection fraction (%) and volumes (ml/m^2) were quantified by manual definition of endocardial borders of all short-axis slices in cine-images. Late enhancement was considered in the case of signal intensity >2 standard deviations with respect to a remote non-infarcted area in late enhancement imaging [18,21]. Infarct size was calculated as the percentage of left ventricular mass showing late enhancement [19].

According to our laboratory protocol [22], the presence of MVO was semi-quantitatively defined as a lack of contrast uptake in the core of at least one segment surrounded by tissue showing late enhancement [3] (see Fig. 1). In our laboratory, intra-observer variability for the detection of MVO using this criterion is less than 5% [23].

2.7. 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 the Student's *t*-test. Non-parametric data were expressed as the median with the interquartile range and were compared with the Mann–Whitney *U*-test. Group percentages were compared using the chi-square test or Fisher's exact test where appropriate.

The individual predictive capability of clinical and ECG, laboratory and angiographic parameters was assessed by calculating the C-statistic derived from logistic regression analysis including all variables yielding a p<.2 in univariate analysis. In detail the variables included were: for clinical and ECG characteristics age, diabetes, systolic blood pressure, current smoker, delayed presentation, Killip class>1, sumSTE and infarct location. For laboratory parameters: CK-MB, myoglobin, leucocytes, neutrophils and lymphocytes. For angiographic parameters: involvement of the proximal left anterior descending artery, vessel occlusion prior to angioplasty and TIMI 3 flow post-angioplasty yielded a p-value<.2 and were included. Moreover, from a pathophysiological point of view, TIMI 3 flow pre-angioplasty was also included.

In order to assess the incremental predictive capability of parameters in the order of temporal availability to the clinician on patient admission, the C-statistics of 3 multivariable models (model 1: only clinical and ECG variables; model 2: clinical and ECG + laboratory variables; model 3: clinical and ECG + laboratory + angiographic variables) were calculated and compared using Rocomp module (STATA 11.0). Briefly, for each curve, Roccomp reports summary statistics and provides a test for the equality of the area under the curves, using an algorithm suggested by DeLong, DeLong, and Clarke-Pearson.

In order to identify independent predictors of MVO, a logistic regression analysis was performed including variables yielding a p-value<.2 in univariate analysis. Continuous variables were dichotomized according to cut-off values established on the basis of their area under the receiver operating characteristic curves for predicting MVO by maximizing the observed overall diagnostic accuracy (minimizing the number of false positives plus the number of false negatives). Odds ratios (OR) and their respective 95% confidence intervals (95%CI) were computed.

Statistical significance was considered for two-tailed p-value<.05. SPSS 13.0 (SPSS Inc, Chicago, Illinois, USA) and STATA 11.0 (StataCorp, College Station, Texas, USA) were used.

3. Results

The baseline clinical, ECG, laboratory and angiographic characteristics of all patients are displayed in Table 1. The majority of the patients was male (79%) with a mean age of 60 ± 14 years. The median time from pain onset to presentation was 115 [61–240] min. Median door to balloon time was 79 [44–123] min. All patients underwent primary PCI with stent placement or balloon angioplasty in 92% of the cases. In 8 patients, revascularization was not performed due to failed angioplasty (n = 5) or because of TIMI 3 flow on angiography

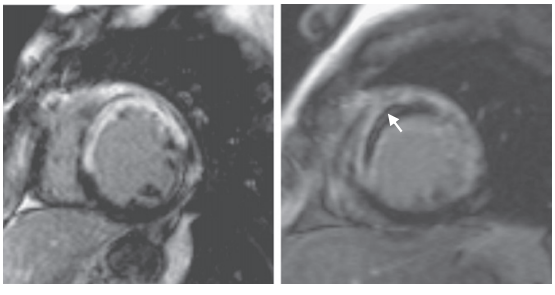


Fig. 1. Example of late enhancement imaging of MVO. Short-axis view of late enhancement imaging in two patients with anterior infarction of comparable size. Left: Normal contrast uptake in the infarcted zone. Right: Lack of contrast uptake in the core of the infarcted area indicating microvascular obstruction (arrow).

Table 1
Baseline, electrocardiographic, laboratory and angiographic characteristics of all patients and of patients with and without MVO.

	All patients n = 97	MVO − n = 53	MVO + n = 44	p-value
Clinical				
Age (years)	60 ± 14	60 ± 13	56 ± 13	.008
Male sex (%)	77 (79)	41 (77)	36 (82)	.6
Diabetes (%)	16 (17)	5 (9)	11 (25)	.04
Hypertension (%)	47 (49)	26 (49)	21 (48)	.9
Hypercholesterolemia (%)	40 (41)	20 (38)	20 (46)	.4
Previous coronary artery disease (%)	10 (10)	5 (9)	5 (11)	.8
Current smoker (%)	52 (54)	24 (45)	28 (64)	.07
Heart rate (bpm)	80 ± 17	79 ± 16	81 ± 18	.6
Systolic blood pressure (mm Hg)	126 ± 25	132 ± 25	120 ± 25	.02
Delayed presentation (>3 h)	28 (29)	11 (21)	17 (39)	.05
Killip class >1	11 (12)	1 (2)	10 (23)	.002
ECG				
Anterior infarction (%)	48 (50)	18 (34)	30 (68)	<.0001
Median sum of ST-segment elevation on admission (mm)	9 [6–14]	6 [4.5–10]	12 [7–17]	<.0001
Median sum of ST-segment elevation 90 min post PCI (mm)	3 [0–7]	2 [0–6]	6 [2–9]	.001
Laboratory				
Median troponin on admission (ng/ml)	.14 [.04–3.19]	.13 [.05–.59]	.18 [.01–20.0]	.4
Median creatine kinase MB on admission (ng/ml)	2.4 [1.0–55.0]	2 [1.1–6.0]	6 [1.0–187]	.1
Median myoglobin on admission (ng/ml)	69 [31–162]	55 [23–99]	95 [45–899]	.003
White blood cell count on admission (×1000 cells/ml)	12.3 ± 3.9	11.7 ± 4.0	13.0 ± 3.8	.1
Neutrophil count on admission (×1000 cells/ml)	9.1 ± 3.8	8.4 ± 3.7	10.1 ± 3.7	.03
Lymphocyte count on admission (×1000 cells/ml)	2.2 ± 1.4	2.4 ± 1.2	2.0 ± 1.2	.1
Monocyte count on admission (×1000 cells/ml)	.55 ± .22	.52 ± .19	.58 ± .26	.2
Median peak troponin (ng/ml)	56 [23–95]	31 [17–54]	95 [77–124]	<.0001
Angiography				
Median door to balloon time (min)	79 [44–123]	77 [45–118]	80 [43–134]	.7
Proximal left anterior descending artery (%)	28 (29)	9 (17)	19 (43)	.005
Vessel occlusion prior to angioplasty (%)	74 (76)	37 (70)	37 (84)	.1
Stent/balloon angioplasty (%)	89 (92)	48 (91)	41 (93)	.6
TIMI 3 flow pre-angioplasty (%)	12 (12)	7 (13)	5 (11)	.8
TIMI 3 flow post-angioplasty (%)	88 (91)	50 (94)	38 (86)	.2
Final myocardial blush grade 2–3 (%)	68 (72)	37 (73)	31 (71)	.8
Median corrected TIMI frame count	14 [11–19]	13 [11–17]	14 [12–20]	.7

MVO = microvascular obstruction, TIMI = thrombolysis in myocardial infarction.

in the absence of a significant stenosis (n = 3). The in-hospital medication of the patient population is displayed in Table 2. Patients with MVO received less beta-blocker therapy (34% vs. 60%, p = .01).

3.1. Cardiovascular magnetic resonance imaging results

CMR was performed 8 ± 5 days after PCI. MVO was present in 44 patients (45%). Patients with MVO-infarctions had a lower left ventricular ejection fraction (43% ± 12 vs. 59 ± 11, p<.0001), a larger infarct size (37% ± 22 vs. 11 ± 10, p<.0001) and more dilated left ventricular volumes and masses. CMR results are displayed in Table 3.

3.2. Individual value of parameters on patient admission for predicting MVO

Clinical and ECG characteristics on admission and MVO. Clinical variables on admission associated with MVO were: younger age (56 ± 13 vs. 60 ± 13, p = .008), lower systolic blood pressure (120 mm Hg ± 25 vs. 132 ± 25, p = .02), diabetes (25% vs. 9%, p = .04) and Killip class>1 (23% vs. 2%, p = .002). There was a trend towards a higher rate of delayed presentation (>3 h from pain onset) in patients with MVO-infarctions (39% vs. 21%, p = .05) The ECG on admission revealed a higher percentage of anterior infarctions (68% vs. 34%, p<.0001) and a larger median sumSTE (12 mm [7–17] vs. 6 [4.5–10], p<.0001) in patients with MVO infarctions. The C-statistic for predicting MVO of clinical and ECG variables on admission was .832 [.742–.901].

Table 2
Inhospital medication of all patients and according to the presence of MVO.

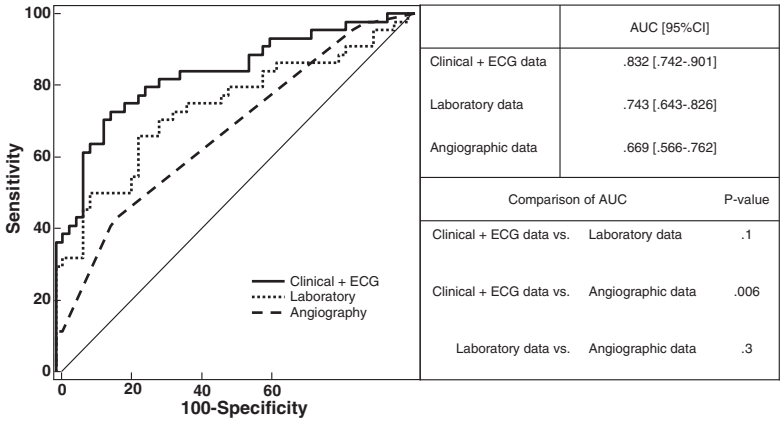
	All patients n = 97	MVO − n = 53	MVO + n = 44	p-value
Mono antiplatelet therapy (%)	97 (100)	53 (100)	44 (100)	.9
Dual antiplatelet therapy (%)	72 (74)	39 (74)	33 (75)	.9
ACE inhibitors (%)	37 (38)	16 (30)	21 (48)	.08
AT-II receptor blockers (%)	21 (22)	15 (28)	6 (14)	.08
Beta blockers (%)	47 (49)	32 (60)	15 (34)	.01
Statins (%)	66 (68)	37 (70)	29 (66)	.7
Diuretics (%)	14 (13)	7 (13)	7 (16)	.7

MVO = microvascular obstruction, ACE = angiotensin converting enzyme, AT = angiotensin.

Table 3
CMR characteristics of all patients and according to the presence of MVO.

	All patients n = 97	MVO − n = 53	MVO + n = 44	p-value
Ejection fraction (%)	52 ± 14	59 ± 11	43 ± 12	<.0001
End-diastolic volume index (ml/m^2)	81 ± 28	71 ± 19	94 ± 32	<.0001
End-systolic volume index (ml/m^2)	41 ± 26	27 ± 14	55 ± 29	<.0001
Left ventricular mass (g/m^2)	73 ± 18	66 ± 14	81 ± 19	<.0001
Infarct size (%)	23 ± 21	11 ± 10	37 ± 22	<.0001

MVO = microvascular obstruction.



	AUC [95%CI]
Clinical + ECG data	.832 [.742-.901]
Laboratory data	.743 [.643-.826]
Angiographic data	.669 [.566-.762]

Comparison of AUC		P-value
Clinical + ECG data vs.	Laboratory data	.1
Clinical + ECG data vs.	Angiographic data	.006
Laboratory data vs.	Angiographic data	.3

Fig. 2. Individual diagnostic value of each domain for predicting MVO. The C-statistic of clinical and ECG data includes: age, diabetes, hypercholesterolemia, smoker, delayed presentation, Killip class>1, sum of ST-segment elevation and infarct location. The C-statistic of laboratory data includes: CK-MB, myoglobin, leucocytes, neutrophils and lymphocytes. C-statistic of angiographic variables includes: involvement of the proximal left anterior descending artery, vessel occlusion prior to angioplasty and TIMI 3 flow post-angioplasty. Moreover, from a pathophysiological point of view, TIMI 3 flow pre-angioplasty was also included.

Laboratory findings on admission and MVO. Laboratory findings on admission associated with MVO were: higher myoglobin serum levels (95 ng/ml [45–899] vs. 55 [23–99], p = .003) and higher neutrophil count (10.1 (×1000 cells/ml) ±3.7 vs. 8.4 ± 3.7, p = .03). The C-statistic for predicting MVO of laboratory findings on admission was .743 [.643–.826].

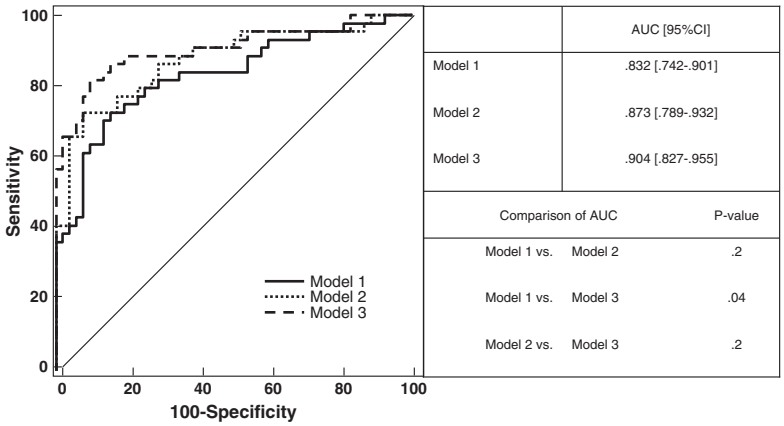
Angiographic parameters and MVO. The only angiographic parameter significantly associated with MVO was involvement of the proximal left anterior descending artery (43% vs. 17%, p = .005). The C-statistic for predicting MVO of angiographic variables was .669 [.566–.762]. Clinical, ECG, laboratory and angiographic variables according to the presence of MVO are displayed in Table 1. The C-statistics are displayed in Fig. 2.

3.3. Incremental value of parameters on patient admission for predicting MVO

The incremental value of parameters for predicting MVO in the order of temporal availability was analyzed. The C-statistic of clinical and ECG characteristics (model 1) did not improve significantly after adding laboratory information (model 2) (.873 [.789–.932] vs. .832 [.742–.901], p = .2). Further addition of angiographic findings (model 3: 904 [.827–.955]) significantly improved the C-statistic compared to model 1 (p = .04) but not compared to model 2 (p = .2) (Fig. 3).

3.4. Predictors of MVO on admission

Clinical and ECG characteristics, the parameters most timely available on patient admission, displayed a high predictive value for MVO which was only significantly improved by the addition of both laboratory and angiographic data. Owing to this finding, a multivariate analysis to identify predictors of MVO from clinical and ECG parameters was performed. Independent predictors of MVO were: Killip class>1 (OR 15.97 95%CI [1.37–186.76], p = .03), diabetes (OR 6.15 95%CI [1.49–25.39], p = .01), age <55 years (OR 4.70 95%CI [1.56–14.17], p = .006), sumSTE>10 mm (OR 4.5 95%CI [1.58–12.69], p = .005) and delayed presentation (OR 3.80 95%CI [1.19–12.1], p = .02). Low blood pressure on admission was not included in this analysis since Killip class already accounts for cardiogenic shock. The C-statistic for predicting MVO of the model using these variables was .846



	AUC [95%CI]
Model 1	.832 [.742-.901]
Model 2	.873 [.789-.932]
Model 3	.904 [.827-.955]

Comparison of AUC		P-value
Model 1 vs.	Model 2	.2
Model 1 vs.	Model 3	.04
Model 2 vs.	Model 3	.2

Fig. 3. Incremental diagnostic value of combined domains for predicting MVO. Model 1 = clinical and ECG characteristics. Model 2 = clinical and ECG characteristics + laboratory data. Model 3 = clinical and ECG characteristics + laboratory + angiographic data.

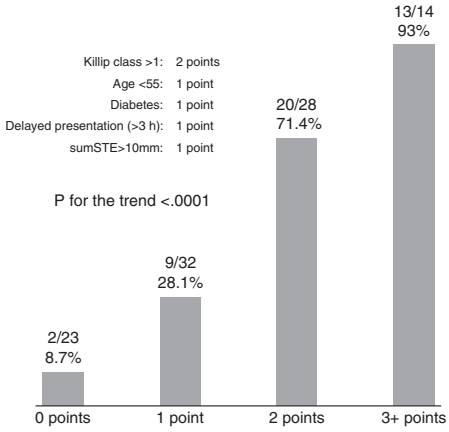


Fig. 4. Prevalence of MVO at each step of the score. Abbreviations: MVO = microvascular obstruction, sumSTE = sum of ST-segment elevation.

[.758–.912] which was not inferior to any of the 3 models (p-value between .2 and .8).

3.5. Development of a predictive score

According to the ORs obtained we created a 4 level score depending on the presence of each index. Killip class>1 was assigned 2 points and the remaining indexes 1 point. The sum was calculated for each patient and patients were categorized into 4 groups (0 points, 1 point, 2 points and 3+ points). The C-statistic for predicting MVO using this score was 0.845 [0.756–0.911] which was not inferior to any of the 3 models (p-value between .1 and .9). The incidence of MVO gradually increased as the score increased: 0 points: 2 of 23 (8.7%); 1 point: 9 of 32 (28.1%); 2 points: 20 of 28 (71.4%) and 3+ points: 13 of 14 (93%) ($p<.0001$ for the trend, Fig. 4). In parallel, the extent of MVO (number of segment with MVO) gradually increased with each step of the score (p for the trend<.0001, Fig. 5).

3.6. Comparison of the predictive score with other markers of MVO

Patients with MVO infarctions had a higher TIMI risk score than patients without MVO (3.3 ± 2.2 vs. 2.2 ± 1.9, $p=.004$), nevertheless the C-statistic of the TIMI risk score to predict MVO was significantly lower compared to the newly developed score (.658 vs. .839, $p=.004$).

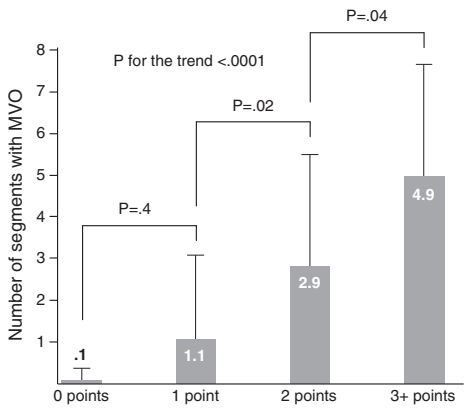


Fig. 5. Extent (number of segments) of MVO at each step of the score. Abbreviations: MVO = microvascular obstruction.

The C-statistic of the newly developed score was compared with other, less timely available, markers of MVO, namely peak troponin and residual ST-segment elevation. Additionally, the score was compared to angiographic surrogates of MVO after PCI: TIMI flow grade, corrected TIMI frame count and myocardial blush grade (Fig. 6). The newly developed score performed comparable to peak troponin ($p=.6$) and was superior to residual ST-elevation ($p=.01$) and any of the angioghraphic parameters ($p<.01$).

4. Discussion

This study analyzes the individual and incremental value of parameters available on patient admission, namely clinical and ECG, laboratory and angiographic characteristics, in the order of availability for predicting CMR derived-MVO in STEMI. It shows that clinical and ECG characteristics, the two diagnostic domains most rapidly available on patient admission, yield a high predictive value for MVO which is only significantly improved by the addition of both laboratory and angiographic findings. We created a stepwise score using independent predictors from clinical and ECG characteristics. Using this score it was possible to classify patients according to the prevalence and extent of MVO after STEMI.

4.1. Microvascular obstruction

Despite restored epicardial blood flow in STEMI, MVO occurs in about 40% of the cases [24,25]. CMR has become the gold standard in cardiovascular imaging allowing for a comprehensive assessment of a wide range of parameters in patients with STEMI [1], including infarct size and MVO [3,4]. Several studies have shown that the presence of MVO is associated with worse outcome and left ventricular remodeling compared to non-MVO infarctions. [3,24–26]. Timely detection of MVO is desirable since it potentially allows for early risk stratification and bears potential therapeutic implication for future therapies aiming at the reduction of MVO.

4.1. Clinical characteristics on admission and MVO

Data on how patients with MVO-infarctions initially present is scarce since most studies have focused on prediction of MVO after reperfusion therapy and the prognostic impact of MVO. We determined the individual value of baseline characteristics in the order as they are available on patient admission and the incremental value for predicting CMR-derived MVO in a large cohort of STEMI patients referred for primary PCI. An interesting finding is that clinical characteristics alone exhibited a high predictive value. This predictive capability was only significantly improved using the combination of all diagnostic domains. Of these clinical parameters, Killip class was identified as strongest predictor of MVO. In our cohort only one patient with Killip class >1 on admission did not develop MVO. High Killip class has been shown to be an independent predictor of failure to restore TIMI 3 flow in the epicardial coronary artery after STEMI [27]. In our study we did not confirm this finding (TIMI 3 flow in patients with Killip >1: 82%), but there was a strong association with the development of MVO. This finding might partly explain the worse prognosis of patients with a high Killip class by linking it to the development of MVO which in turn exhibits a strong negative impact on prognosis [3,22].

Patients with MVO-infarction were younger and there was a trend towards delayed presentation. The observation that young age associates with MVO has not been reported before. Smaller studies did not show a significant age difference between patients with MVO and non-MVO-infarctions [7]. A possible explanation for this finding is that younger patients might have less ischemic preconditioning and less collaterals than older patients aggravating myocardial damage by a total coronary occlusion.

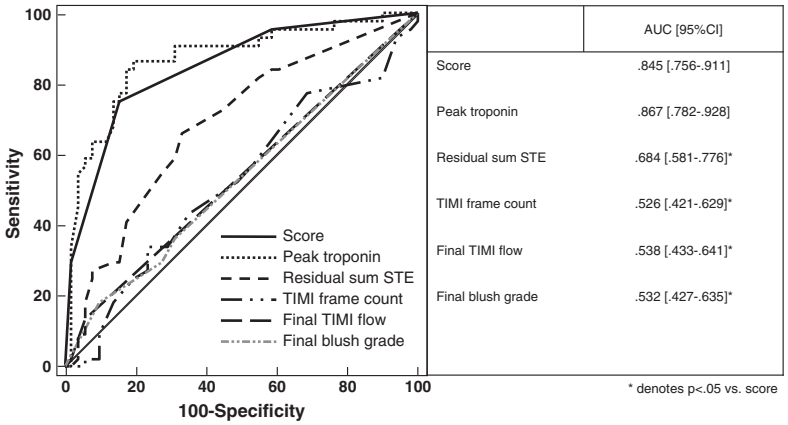


Fig. 6. Comparison of the predictive score with other markers of MVO. Abbreviations: MVO = microvascular obstruction, sumSTE = sum of ST-segment elevation, TIMI = thrombolysis in myocardial infarction.

Patients who developed MVO-infarctions had a trend to a higher rate of delayed presentation. This finding is in line with previous studies demonstrating that MVO strongly depends on the duration of the ischemic time [28,29].

There was a significant lower percentage of beta-blocker use in patients with MVO. Additionally there was a trend to more ACE-Inhibitor and less AT-II receptor blocker use in patients with MVO. Data on in-hospital medication is difficult to interpret because these data might be subject to several confounders. Whether this observation is linked to the pathophysiology of MVO or merely an epiphenomenon (cause or consequence) cannot be determined. Patients with MVO tended to have larger myocardial infarctions leading to more hemodynamic compromise which might have precluded the use of beta blockers. The present data is observational, not randomized and subject to confounding factors and should be interpreted with care.

4.2. Biomarkers of MVO

The association of CMR-derived MVO with biomarkers like the ECG, cardiac necrosis markers and leucocytes has been investigated in the past. Of ECG parameters, the amount of residual sumSTE after successful primary PCI is a strong predictor of MVO and also predicts myocardial salvage [30–32]. The present study demonstrates a high predictive value of ECG data for MVO already on admission.

After successfully reperfused STEMI a larger release of cardiac necrosis markers, especially troponin, is associated with MVO [33–35]. Since troponin values can be normal or low on admission in STEMI, there was no significant association with MVO in the present study. Due to its faster kinetics, myoglobin was significantly higher in patients developing MVO-infarctions. Nevertheless, the use of biomarkers for early risk stratification and decision making can be limited due to the time delay implied in their use.

Finally, post-interventional lymphopenia has been linked to a larger amount of MVO in reperfused STEMI [36]. The present study shows that on admission, there is only a trend towards a lower lymphocyte count in patients with MVO infarctions, but neutrophil count was significantly higher.

4.3. Angiographic parameters and MVO

Angiographic parameters have been used in the past for the evaluation of microvascular reperfusion in STEMI.

In our study, the only angiographic parameter significantly associated with MVO was involvement of the proximal left anterior descending artery. The lack of association of established angiographic parameters like TIMI flow grade, frame count or myocardial blush grade might be owed to several reasons. Firstly, the evaluation of the microcirculation by angiography is performed at a very early time point and it has been shown that the microcirculation displays a dynamic behavior in the first week after STEMI [18]. Re-established epicardial blood flow, represented by TIMI 3 flow, is a very specific but not very sensitive marker for successful microvascular reperfusion. Accordingly, in our study TIMI 3 flow was achieved in 91% of patients and there was not a statistical association with MVO. Myocardial blush grade is a good alternative for evaluating microvascular perfusion, nevertheless this index displays a high interobserver variability. Lastly and a limitation of our study, the evaluation of angiographic parameters in a core laboratory might have yielded better results. The addition of both laboratory and angiographic parameters to clinical and ECG characteristics improved the predictive capacity of the model, nevertheless the usefulness of angiography for early prediction of MVO is limited because the information arrives relatively late for clinical decision making.

4.4. Prediction of MVO on admission

The present study is the first to address the problem of MVO in patients with STEMI before reperfusion therapy is initiated. A common trait of previous studies investigating predictors of MVO is, that they were focused on parameters obtained after the therapeutic intervention had been carried out. At that time point the microvascular damage might not be influenceable to the same degree as it could be with the use of earlier predictors. We identified, from a wide range of clinical and ECG, laboratory and angiographic data available on patient admission independent predictors of MVO. We detected that clinical characteristics and ECG data, the two diagnostic domains most rapidly available to the clinician on patient admission, yielded a predictive value that was only improved by the addition of both laboratory and angiographic parameters. In order to facilitate integration of this finding into clinical practice we devised a simple predictive score according to the presence of 5 indexes (Killip class >1, age<55, diabetes, delayed presentation and sumSTE>10 mm). This score allowed for classification of patients according to the risk for developing MVO after reperfusion therapy. The prevalence, ranging from low (8.7%) to high risk (93%), as well as the extent of MVO gradually increased as the score increased.

Potentially this score, using simple, early and universally available parameters, allows for triage of patients according to the risk of MVO

and might prove useful as a tool for assessing the efficacy of future early therapies aiming at the reduction of MVO.

4.5. Limitations

This study represents the discovery group for this predictive score, and although derived from a large population of STEMI patients treated with primary PCI, further prospective validation in order to determine the true value of the clinical and therapeutic implications of these results is warranted.

ECGs were recorded at a paper speed of 25 mm/s. We cannot exclude that using a speed of 50 mm/s would yield a higher diagnostic accuracy for MVO.

The optimal time point to visualize MVO has not been defined yet. Nevertheless, data derived from an experimental dog model indicate that the extent of microvascular obstruction is unchanged at 2 and 9 days after reperfused myocardial infarction [37]. Accordingly, several studies assessing the implications of MVO after STEMI have used the first week (6–10 days) after STEMI as the ideal moment for post-infarct imaging [3,7,24,38]. The mean delay to CMR in our study was 8 ± 5 days. A sooner time point for assessing the extent of infarcted myocardium and MVO might overestimate these indices partly due to extensive edema. On the other hand, CMR performed at a later time point, might underestimate myocardial and microcirculatory damage. In our cohort, there was no significant difference in the mean delay (days) to CMR and the presence of MVO (MVO absent: 7 days [5–9.5] vs. MVO present 6 [5–9], $p = .1$). Nonetheless, we cannot exclude changes in the extent of MVO during the days from STEMI to CMR imaging.

In the present study, we did not routinely record pre-hospital medication and the occurrence of pre-infarct angina accounting for a possible ischemic preconditioning. Also the use of GpIIb/IIIa inhibitors was left at the discretion of the interventional cardiologist. In total GpIIb/IIIa inhibitors were used in 59 patients (61%). There was no statistical difference in the occurrence of MVO according to the use of GpIIb/IIIa inhibitors (MVO + 71% vs. MVO − 53%, $p = .08$), albeit with a contraintuitive trend towards a higher occurrence of MVO using GpIIb/IIIa inhibitors. Since this study was not designed to address the impact of prehospital and/or adjunctive pharmacotherapy on the incidence of MVO, further investigation on this issue is clearly warranted.

5. Conclusions

The prevalence of MVO after STEMI can be predicted using parameters available on patient admission. Clinical characteristics and ECG parameters yield a high predictive value which was only improved by the addition of both laboratory and angiographic findings. We developed a score using clinical and ECG characteristics allowing for classification of STEMI patients according to the prevalence and extent of MVO. Given the timely availability this score might prove useful for early classification and risk stratification before reperfusion therapy is initiated and for assessing the value of future therapies aiming at the reduction of MVO in STEMI.

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