Original Research

Creatine Kinase-MB Assessed in Patients with Acute Myocardial Infarction Correlates with Cardiac Magnetic Resonance Infarct Size at 6-Month Follow Up

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Introduction: There are still only limited data concerning the use of creatine kinase-MB (CKMB) values for predicting infarct size in long-term follow up in patients with ST-segment elevation myocardial infarction (STEMI) who have undergone primary percutaneous coronary intervention (PCI). The aim of this study was to analyze the correlation between CKMB and both infarct size and left ventricular function during a 6-month follow up.

Methods: In a cohort of 68 patients with STEMI treated with PCI, serial CKMB assessment was performed at baseline and at 6, 12, 18, 24 and 48 hours after PCI. The area under the curve (AUC) of CKMB was calculated. Cardiac magnetic resonance (CMR) parameters were assessed at 6 months.

Results: All CKMB single time-point values, AUC CKMB, and CKMB maximal value after primary PCI were correlated with CMR infarct size and left ventricular function, but a high correlation (r>0.7) was found only for CKMB at 6 hours, CKMB at 12 hours, CKMB AUC, CKMB maximal value, and CMR infarct size (r=0.71, r=0.73, r=0.72, r=0.75, respectively, p<0.001 for all).

Conclusions: CKMB assessment is a good predictor of infarct size at 6 months in patients with STEMI treated with PCI. The CKMB value at a single time point 12 hours after PCI is a good predictor of infarct size at 6 months, comparable to serial assessment parameters such as AUC CKMB and CKMB maximal value.

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The extent of myocardial injury is an important predictor of outcome in patients with ST-segment elevation myocardial infarction (STEMI).[1] Cardiac necrosis markers are routinely assessed in STEMI patients in clinical practice, but the results are mainly used for confirmation of infarct diagnosis, rather than the estimation of infarct size.[2] Usually, a larger release of cardiac necrosis markers is correlated with a larger extent of myocardial injury, and a faster release (wash-out) has been considered as a indicator of successful reperfusion. However, such a method is not very popular in clinical practice, mainly because of the relatively high number of blood samples that have to be drawn in order to calculate the area under the curve or to avoid missing the actual peak level. The optimal method of enzymatic infarct size assessment (area under time-concentration curve, peak concentration or single time-point measurements) remains unclear. Similarly the choice of optimal biomarker method, between traditional cardiac

markers and modern, more cardio-specific markers (troponin I and T), is still under evaluation. Cardiac magnetic resonance (CMR) imaging is the most accurate technique for infarct size assessment and allows the identification of even a small subendocardial injury.[3,4] The aim of this study was to evaluate creatine kinase MB fraction values (CKMB) in the prediction of infarct size and left ventricular function assessed by CMR 6 months after STEMI.

Methods

Patient population

The study was approved by the Institutional Review Board. All patients gave informed consent and the study conformed to applicable institutional and national guidelines for research on human subjects, as well as to the Declaration of Helsinki. The inclusion criteria were: age >18 years and acute STEMI (chest pain >30 min, ST-segment elevation >0.2 mV in at least two contiguous leads), presenting within six hours from chest pain onset. The exclusion criteria were: previous myocardial infarction, contraindications for lytics or abciximab, contraindications for percutaneous coronary intervention (PCI), previous PCI or coronary artery bypass grafting, cardiogenic shock, left bundle branch block or pacemaker rhythm in the electrocardiogram, participation in another clinical study, neoplastic diseases, pregnancy, low-molecular-weight heparin usage during previous 24 hours.

All patients received aspirin (300-500 mg), a loading dose of clopidogrel (≥300 mg), and a bolus of unfractionated heparin (60-100 U/kg). Tenecteplase was given in a weight-adjusted standard dose in patients with a long anticipated delay before PCI. Abciximab was given in a standard dose as intravenous bolus (0.25 mg/kg) and continuous infusion (0.125 μg/kg/min). Before PCI, activated clotting time was monitored in all patients and unfractionated heparin boluses were added, if necessary, to maintain optimal anticoagulation. Bare metal stents were used during PCI. In patients with multivessel coronary artery disease PCI was performed only in the infarct-related artery.

Enzymatic infarct size analysis

Enzymatic infarct size was analyzed based on serial CKMB assessment. CKMB was measured using an automated immunoassay method on a Roche/Hitachi Cobas Systems device (Roche Diagnostics, Basel, Switzerland). Blood samples were collected at baseline and at 6, 12, 18, 24 and 48 hours. The area under the curve (AUC) of CKMB was calculated by the trapezoidal rule.

Cardiac magnetic resonance

The CMR study was performed using a 1.5 T scanner (GE Signa EXCITE) with a TORSOPA coil. Dedicated software was used for post-processing (MASS, Medis). Analyses were performed by an observer who was blinded to the patients' clinical data. Left ventricular volumes, ejection fraction and infarct size were analyzed in one study per patient, a minimum of 6 months after the index myocardial infarction. The end-diastolic and end-systolic volume indices were obtained after dividing volume by body surface area, according to the DuBois formula.[5] Left ventricular volumes and ejection fraction were assessed with cine-CMR using a steady-state free-precession technique (FIESTA) with the following imaging parameters: 20 phases per slice location, FOV 32×32 cm, TR 1.6 ms, TE 2.8 ms, FA 20-30°, matrix 256×160, NEX 1. Ten to 14 consecutive 8 mm slices were planned in short-axis view. In addition, one horizontal long-axis view (four-chamber) was obtained. Delayed enhancement images were acquired 15-20 min after a double bolus of gadolinium (0.2 mmol/kg), using an inversion recovery gradient-echo sequence with the following imaging parameters: FOV 42×42 cm, TR 8 ms, TE 3.8 ms, FA 40-50°, NEX 2, slice thickness 8 mm. The inversion time was adjusted individually to null normal myocardium. Slice locations of the delayed enhancement images were copied from the cine images to ensure registration between cine-CMR and infarct measurements. The volume of delayed enhancement was quantified manually from consecutive short axis slices and was multiplied by 1.05 g/ml to obtain myocardial infarct mass (1 ml = 1.05 g). Papillary muscles were not included in the delineations of hyperenhanced area. Infarct size was expressed as a percentage of total left ventricular mass.

Statistical analysis

Results were expressed as medians with interquartile range (IQR), or as percentages of patients. Correlations were calculated using the Spearman method. Differences between continuous variables were assessed by the Mann–Whitney U-test. Receiver-op-

erating characteristic (ROC) curve analysis was performed to calculate the sensitivity and specificity of CKMB values in predicting a large CMR residual infarct size (≥10%), and left ventricular dysfunction with ejection fraction ≤40% after 6 months. A p-value <0.05 was considered statistically significant.

Results

A total of 68 patients with STEMI treated with PCI entered the study. Baseline characteristics and angiographic characteristics are shown in Table 1. In 26 patients (38.2%), lytic therapy was administered before transfer to the catheterization laboratory because of a long anticipated delay before PCI. The values of AUC CKMB, CKMB maximal value (CKMB max), and CKMB at baseline, 6, 12, 18, 24 and 48 hours are presented in Table 2. The CMR study showed an infarct size of 8.5 (4-16.7)%, a left ventricular ejection fraction (LVEF) of 42.4 (38-50)%, a left ventricular end-diastolic volume index of 80.6 (64.7-97.6) ml/m^2, and a left ventricular end-systolic volume index of 43.3 (31.2-57) ml/m^2 (all medians with IQR). There was a significant correlation between enzymatic parameters and CMR parameters after 6 months (Table 2). However, a high correlation (r>0.7) was found only for CKMB at 6 hours, CKMB at 12 hours, CKMB AUC, CKMB max, and CMR infarct size. Patients with a CKMB value at 12 hours >179 UI/L (median value) had a larger infarct size, larger left ventricular volumes, and lower LVEF by CMR at 6 months (Table 3).

Table 1. Characteristics of the study population. Angiographic and PCI findings (n=68).

Age (years, median + IQR)	58 (54-67)
Male (%)	79.4
Diabetes (%)	6
Hypertension (%)	50
Dyslipidemia (%)	36.8
History of smoking (%)	58.8
Killip class >1 (%)	13.2
Time from chest pain onset to PCI (minutes, median + IQR)	234 (184-300)
Infarct-related artery (%):	
LAD	54.4
Cx	5.9
RCA	39.7
Multivessel disease (%)	35.3
Tenecteplase (%)	38.2
Abciximab (%)	55.9
Stent implantation (%)	94.1
TIMI 3 after PCI (%)	91.2
TMPG 3 after PCI (%)	64.7

Cx – circumflex artery; IQR – interquartile range; LAD – left anterior descending artery; PCI – percutaneous coronary intervention; RCA – right coronary artery; TIMI – thrombolysis in myocardial infarction; TMPG – TIMI myocardial perfusion grade.

In ROC curve analysis the AUC values for predicting a large residual infarct size (≥10%) on CMR at 6 months were:

Table 2. Spearman correlation between CKMB values and 6-month CMR findings. Data presented as r-value (p-value).

	CMR infarct size	CMR LVEF	CMR EDVI	CMR ESVI
CKMB baseline	-0.04	-0.02	-0.22	-0.13
27.5 (14-62) UI/L (median, IQR)	(p=0.8)	(p=0.87)	(p=0.1)	(p=0.32)
CKMB 6 hours	0.71*	-0.5	0.42	0.53
239 (121-373) UI/L (median, IQR)	(p<0.001)	(p<0.001)	(p<0.001)	(p<0.001)
CKMB 12 hours	0.73*	-0.47	0.41	0.51
179 (101-320) UI/L (median, IQR)	(p<0.001)	(p<0.001)	(p<0.001)	(p<0.001)
CKMB 18 hours	0.7	-0.50	0.35	0.47
120 (61-249) UI/L (median, IQR)	(p<0.001)	(p<0.001)	(p<0.001)	(p<0.001)
CKMB 24 hours	0.60	-0.46	0.38	0.5
80 (40-158) UI/L (median, IQR)	(p<0.001)	(p<0.001)	(p<0.001)	(p<0.001)
CKMB 48 hours	0.44	-0.4	0.39	0.47
29 (18-48) UI/L (median, IQR)	(p<0.001)	(p<0.001)	(p<0.001)	(p<0.001)
CKMB AUC	0.72*	-0.54	0.46	0.57
5053.5 (2862-9186) UI/L (median, IQR)	(p<0.001)	(p<0.001)	(p<0.001)	(p<0.001)
CKMB max	0.75*	-0.53	0.49	0.58
254 (147-418) UI/L (median, IQR)	(p<0.001)	(p<0.001)	(p<0.001)	(p<0.001)

* Correlation with r>0.7

AUC – area under the curve; CKMB – creatine kinase-MB fraction; CMR – cardiac magnetic resonance; EDVI – end-diastolic volume index; ESVI – end-systolic volume index; LVEF – left ventricular ejection fraction; IQR – interquartile range.

Table 3. CMR left ventricular function according to CKMB median value at 12 hours (median, interquartile range).

CKMB at 12 hours (IU/L) median Proportions of patients	≤179 50%	>179 50%	p
CMR infarct size (%)	5.1 (2.4-9.5)	16.1 (10.9-23.1)	<0.001
CMR ejection fraction (%)	46.5 (41.2-55.5)	39.2 (34.8-43.8)	0.004
CMR end-diastolic volume index (mL/m^2)	70.8 (61.6-83.4)	91 (78.4-102.1)	0.001
CMR end-systolic volume index (mL/m^2)	36.1 (27.1-43.2)	55.7 (45.3-63.4)	<0.001

CKMB – creatine kinase-MB fraction; CMR – cardiac magnetic resonance.

– 0.854 (95% CI: 0.76 to 0.95; p<0.001) for CKMB at 12 hours with an optimal cutoff value of 207.5 IU/L; 75% sensitivity and 84.6% specificity.
– 0.853 (95% CI: 0.76 to 0.95; p<0.001) for AUC CKMB with an optimal cutoff value of 5596.5 UI/L; 74.1% sensitivity and 84.6% specificity.
– 0.875 (95% CI: 0.79 to 0.99; p<0.001) for CKMB max at 12 hours with an optimal cutoff value of 330 IU/L; 65.5% sensitivity and 93.8% specificity.

The AUC values for predicting LVEF ≤40% in CMR at 6 month were:

– 0.783 (95% CI: 0.66 to 0.9; p<0.001) for CKMB at 12 hours with an optimal cutoff value of 207.5 IU/L; 75% sensitivity and 72.5% specificity.
– 0.823 (95% CI: 0.71 to 0.93; p<0.001) for AUC CKMB with an optimal cutoff value of 6241.5 IU/L; 80% sensitivity and 79.5% specificity.
– 0.821 (95% CI: 0.71 to 0.93; p<0.001) for CKMB max at 12 hours with an optimal cutoff value of 335.5 IU/L; 70% sensitivity and 85.4% specificity.

Discussion

In the present study, CKMB assessment (both serial and single time-point) was a good predictor of infarct size and left ventricular function at 6-month follow up in patients with STEMI. Single time-point assessment predicts infarct size as accurately as AUC CKMB and CKMB max, which makes it important in everyday practice. These results emphasize the value of the assessment of cardiac markers after PCI for STEMI.

Cardiac markers are good predictors of clinical outcome in patients with STEMI treated with primary PCI.[5,7] Additionally, previous studies have shown a correlation between cardiac markers and infarct size. However, infarct size was usually assessed over short-term follow up, while in most studies the extent of myocardial injury was quantified using single-photon emission computed tomography (SPECT) but not CMR.[8-10] Both SPECT and CMR detect transmural myocardial infarcts at similar rates. However, subendocardial infarcts detected with CMR are systematically missed by SPECT.[3,4] CKMB enzymatic infarct size is usually calculated based on serial blood sample analysis, which is a relatively complicated method to apply in daily practice. For this reason, we decided to analyze the role, not only of serial, but also single time-point CKMB assessment in the prediction of infarct size on CMR over a long-term follow up.

Similarly to our results, Tzivoni et al showed that both peak value and the AUC of CKMB, as well as CK and troponin T, are good predictors of infarct size assessed by SPECT at days 7 and 30 after myocardial infarction. The value of single time-point results was not analyzed.[8] Byrne et al analyzed a large cohort of more than 1200 patients who underwent primary PCI for STEMI, based on a SPECT study before hospital discharge and a 1-year clinical follow up. Both peak CKMB value and troponin T showed a moderate but significant correlation with SPECT infarct size. SPECT infarct size itself was a better predictor of 1-year mortality than biomarkers.[9] In the study of Chia et al, serial blood samples of CK, CK-MB mass, and troponin T and I were collected and SPECT was performed at days 5 and 30. Detailed data on single time-point values, AUC and peak values were analyzed. All single time-point and peak values, and the AUC of CK, CK-MB, and troponins T and I after PCI were significantly correlated with infarct size and LVEF. Single time-point CKMB mass at 12 hours showed a significant correlation with infarct size, though weaker than in our study. The highest single time-point correlation with 5-day and 30-day infarct size was found for troponin I at 72 hours.[10] However, in clinical practice the value of assessment at 72 hours is diminished because some patients may be discharged before this point. Also, since enzymatic infarct size may be helpful in identifying high-risk patients, it is important to perform such evaluation as early as possible. In our study, one single CKMB assessment at 12 hours, with a threshold of 207.5 IU/L, was a good predictor of a large residual infarct and

LV dysfunction after primary PCI for first STEMI. A high value of a single time-point assessment is very important in clinical practice, because serial blood sampling may be avoided. Single time-point assessment represents a simple, effective, and inexpensive tool for determining infarct size and allows the identification of high-risk patients who need early implementation of therapeutic strategies. This may include additional early aggressive prevention of left ventricular remodeling, including an optimal dosage of β-blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and aldosterone antagonists. In our study, LVEF and LV volumes were also analyzed. However, the Spearman correlation of cardiac markers was higher for infarct size than for other LV parameters. These results are consistent with previously published reports.[8,10]

Limitations

The main limitation of the present study is the relatively small number of patients enrolled. This allowed us to analyze only surrogate endpoints, but not the correlation between CKMB assessment and clinical endpoints. Troponin was not assessed at the given time points, so it was impossible to analyze the importance of this cardio-specific marker in relation to the CMR results, as well as the relative value of both markers. Only one CMR study was performed for each patient 6 months after the event, so it was impossible to observe the changes in LV parameters over time or to analyze early myocardial injury and microvascular obstruction.

Conclusions

CKMB assessment is a good predictor of infarct size at 6 months in patients with STEMI who are treated with PCI. The CKMB value at a single time point 12 hours after PCI is a good predictor of infarct size at 6 months, comparable to serial assessment parameters such as AUC CKMB and CKMB max.

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