ORIGINAL ARTICLE

Effect of serum creatine kinase-MBmass on the early and hierarchical diagnosis of related artery reperfusion in acute myocardial infarction

Shan-Shan Xing, Qi-Chong Xing, Yun Zhang, Wei Zhang

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See end of article for authors' affiliations

Correspondence to:
Professor Wei Zhang,
Department of Cardiology,
Shandong University Qilu
Hospital, 250012, 107#
West Wenhua Road, Jinan,
China;
professor-zhangwei@163.
com

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Aim: To evaluate creatine kinase-MBmass (CK-MBmass) for the early diagnosis of infarct-related artery (IRA) patency after thrombolysis and the hierarchical diagnosis of related artery reperfusion (RAR).

Patients and methods: CK-MBmass and creatine kinase-MBactivity (CK-MBactivity) were measured kinetically in 48 patients treated with thrombolysis and 96 patients treated with routine drugs.

Results: In the continuous-RAR (CRAR) group, the peak values of CK-MBmass and CK-MBactivity appeared at ≤ 12 h, the peak durations were maintained for ≤ 8 h before decreasing to normal at ≤ 42 h, which occurred more quickly than those values in the non-RAR (NRAR) group. In the temporary-RAR (TRAR) group, the peak values appeared at ≤ 12 h, but no significant differences were found between the TRAR and NRAR groups in the time that the peak durations lasted before decreasing to normal values. In the reoblationation group after RAR, the peak values appeared at ≤ 12 h, and the peak durations were maintained for ≤ 8 h. After returning to the normal, a second peak appeared, and the time required for the values to return to normal was prolonged significantly.

Conclusions: CK-MBmass could be used as an indicator of RAR after thrombolysis; and the kinetic changes of serum CK-MBmass could be used for the hierarchical diagnosis of RAR in acute myocardial infarction.

Early thrombolysis in patients with acute myocardial infarction (AMI) has a strong beneficial influence on short- and long-term outcome. The therapeutic goal of infarct-related artery (IRA) patency may be achieved with novel thrombolytic agents or percutaneous coronary interventions. Thrombolytic treatment is critical in the management of patients with AMI in order to reopen the infarct-related artery and improve the survival of heart muscle. The availability of a reliable biomarker for the status of IRA patency status may permit early identification of patients with patent IRA, for whom repeat thrombolysis or rescue percutaneous transluminal coronary angioplasty (PTCA) may not be necessary. Although coronary angiography has been considered the gold standard for this purpose, it is costly and often unavailable for routine care of most patients. Because the currently used non-invasive clinical and electrocardiographic indices of IRA patency status are neither sufficiently sensitive nor specific, several serum myocardium markers have been investigated and proposed as alternatives. The serum markers that have been investigated include creatine kinase-MB (CK-MB), total creatine kinase (CK), myoglobin, cardiac troponin T (cTnT) and cardiac troponin I (cTnI), which are either measured alone or in combination.¹

CK is found in a variety of striated and smooth muscles, and the brain. CK has three isozymes (CK-MM, CK-MB and CK-BB) in cytoplasm and two isozymes (non-sarcomeric and sarcomeric) in mitochondria. CK isozymes could potentially provide more specific information about injured tissue because of their tissue distribution. CK-MM is useful in skeletal muscle diseases, such as muscle dystrophy, whereas CK-MB is used as an indicator for AMI, and CK-BB has been tested in cases of brain damage and malignant tumour of the gastrointestinal tract. Mitochondrial CK, on the other hand, is a useful indicator for the severity of muscle injuries.²

Although cTnT or cTnI have been shown to have a higher sensitivity than CK-MB or myoglobin (and current guidelines

recommend the use of troponins rather than CK-MB or myoglobin for the diagnosis of AMI), CK-MB and myoglobin are more efficient for the early diagnosis (within 6 h) of AMI, whereas cTnI and cTnT are highly cardiac specific and are particularly efficient for the late diagnosis of AMI.³

CK-MB is measured either by enzyme activity or protein concentration. Activity measurements of cardiac enzymes, and especially the isoenzymes of CK, have become the gold standard by which myocardial damage is diagnosed or excluded. However, they are not fully cardiospecific and have a low sensitivity. Improved immunoassays have therefore been developed to measure the protein concentrations of CK-MB—that is, CK-MBmass rather than the enzymatic activity. In the current study, CK-MBmass was measured dynamically to investigate the role of serum CK-MBmass in early and hierarchical diagnosis of related artery reperfusion (RAR) in AMI. We also compared CK-MBmass with the established markers for diagnostic values.

MATERIALS AND METHODS

Patient recruitment

From October 2001 to October 2005, a total of 144 patients with AMI—48 treated with thrombolysis and 96 with routine drugs—were enrolled in this study. AMI was defined by a combination of two of three characteristics: typical symptoms (that is, chest discomfort), increase in myocardium enzymes, and inverted Q waves in the electrocardiogram (ECG).⁴ Eligibility for thrombolytic treatment was based on the

Abbreviations: AMI, acute myocardial infarction; CK, creatine kinase; CK-MB, creatine kinase-MB; CK-MBactivity, creatine kinase-MBactivity; CK-MBmass, creatine kinase-MBmass; CRAR, continuous-RAR; cTnI, cardiac troponin I; cTnT, cardiac troponin T; ECG, electrocardiogram; IRA, infarct-related artery; MEIA, microparticle enzyme immunoassay; NRAR, non-RAR; PTCA, percutaneous transluminal coronary angioplasty; RAR, related artery reperfusion; TIMI, Thrombolysis in Myocardial Infarction; t-PA, tissue plasminogen activator; TRAR, temporary-RAR

following criteria: prolonged chest pain (>30 min) resistant to nitrates that was accompanied by an ST-segment elevation ≥ 0.1 mV in two limb leads or ≥ 0.2 mV in two contiguous precordial leads. Forty-eight patients who were eligible for thrombolytic therapy received tissue plasminogen activator (t-PA) when they were admitted to hospital. This was followed by routine drugs (aspirin, β -blockers, angiotensin-converting enzyme inhibitors, nitrates, glycoprotein IIb/IIIa inhibitors, low molecular weight heparin and clopidogrel). Ninety-six patients who were not eligible for thrombolytic treatment (AMI without ST-segment elevation, history of chest pain lasting >12 h, and other contraindications for thrombolytic treatment) only received routine drugs. The study was approved by the ethics committee of Qianfoshan Hospital, Shandong University, Jinan. Signed consents were obtained from all patients who participated in this study.

Biochemical assays

Blood samples (2 ml) were obtained at 6 and 8 h following the occurrence of the chest pain. Venous blood was drawn for serum collection. Blood samples of 48 patients treated with thrombolysis were obtained every 2–4 h in the first 24 h following the onset of the AMI symptoms, and every 4–8 h thereafter until CK-MBmass and CK-MBactivity returned to normal. Blood samples of 96 patients treated with routine drugs were obtained every 4–8 h until CK-MBmass and CK-MBactivity returned to normal.

CK-MB enzyme activity was measured using an immunoinhibition assay (Roche Company, Basle, Switzerland). The normal range was 0.2–2.4 IU/l.⁵ Levels of CK-MBmass were measured by the microparticle enzyme immunoassay (MEIA) method using AxSYM kit (Abbott Company, USA). The normal range was 0–49.4 ng/ml and the time required to process a single specimen was 18 min.

Coronary angiography was performed in all 144 cases of AMI after 5–7 days of thrombolytic treatment. We regarded the Thrombolysis in Myocardial Infarction (TIMI) flow grade ≥ 2 in coronary angiography as coronary reperfusion and compared the relationship between CK-MBmass and coronary angiogram to predict reperfusion status after thrombolysis in AMI.

Statistical analysis

All data are expressed as mean (SD). Student's *t* test was used to compare the differences between the groups, and one way analysis of variance (ANOVA) was used for comparisons among three or more groups. Two-tailed $p < 0.05$ was considered significant. Data analyses were performed using SPSS version 10.0.

RESULTS

Patient characteristics

We enrolled 144 patients in this study: 107 men (median age 52.7 years) and 37 women (median age 54.8 years). Forty-eight

Figure 1 The dynamic changes of CK-MBmass in patients in groups A, B, C and D. Group A = related artery continuous reperfusion (CRAR); Group B = related artery temporary reperfusion (TRAR); Group C = reobilitation after related artery reperfusion; Group D = related artery non-reperfusion (NRAR). CK-MBmass = creatine kinase-MBmass.

patients were treated with thrombolysis and 96 were treated with routine drugs. The patients' characteristics in this study are summarised in table 1.

Using CK-MBmass to define the coronary reperfusion after thrombolytic treatment, we determined 33 cases of continuous reperfusion, five cases of temporary reperfusion, two cases of reobilitation after reperfusion, and eight cases of non-reperfusion. On the other hand, according to coronary angiography, there were 35 cases with reperfusion and 13 cases with non-reperfusion.

In patients receiving routine treatment, we identified five cases of continuous reperfusion, eight cases of temporary reperfusion, nine cases of reobilitation after reperfusion, and 74 cases of non-reperfusion according to the biochemical markers. With coronary angiography, six cases were defined with reperfusion and 90 cases with non-reperfusion.

Kinetic changes in biochemical markers

We divided all the patients into four groups (A, B, C, and D) according to the patency status of the IRA, which was graded according to the dynamic changes of serum CK-MBmass and CK-MBactivity levels. Group A (CRAR group) had the maximal values of CK-MBmass and CK-MBactivity appear at ≤ 12 h, and the peak durations were maintained for ≤ 8 h before decreasing to normal at ≤ 42 h. Group B (TRAR group) had the maximal values of CK-MBmass and CK-MBactivity appear at ≤ 12 h, and the peak durations were maintained for > 12 h before reducing to normal at ≥ 48 h. Group C (reobilitation group after RAR) had the maximal values of CK-MBmass and CK-MB activity appear at ≤ 12 h, and the peak durations were maintained for ≤ 8 h. After returning to the baseline level, a second peak appeared. In group D (NRAR group) the CK-MBmass and CK-MBactivity did not change significantly.

As shown in table 2, the average maximal values of CK-MBmass and CK-MBactivity appeared at 9.2 h and 9.4 h in group A, which were 11.2 h and 11.8 h earlier ($p < 0.01$) than those in group D. The peak durations of CK-MBmass and CK-MBactivity were maintained for 6.8 h and 7.2 h before returning to baseline at 34.8 h and 39.2 h. Compared with those in group D, group A had their durations reduced by 9.0 h, 10 h ($p < 0.01$) and 25.6 h, 29.2 h, respectively ($p < 0.01$). In group B, the maximal values of CK-MBmass and CK-MBactivity appeared at 9.4 h and 9.6 h, which were 11.0 h and 11.6 h earlier ($p < 0.01$) than those in group D. No significant differences were found between groups B and D

Table 1 Patients' characteristics

Groups	n	Thrombolytic treatment n (%)	Routine treatment n (%)
A	38	33 (68.8)	5 (5.2)
B	13	5 (10.4)	8 (8.3)
C	11	2 (4.2)	9 (9.4)
D	82	8 (16.7)	74 (77.1)

One-way ANOVA was used to compare the group differences and post-hoc Bonferroni correction was applied for between group differences in the statistical model.

Group A = related artery continuous reperfusion (CRAR); Group B = related artery temporary reperfusion (TRAR); Group C = reobilitation after related artery reperfusion; Group D = related artery non-reperfusion (NRAR).

Table 2 Mean (SD) changes in CK-MBmass and CK-MBactivity

Groups	n	CK-MBmass			CK-MBactivity		
		Up to peak	Duration	Down to normal	Up to peak	Duration	Down to normal
A	38	9.2 (1.6)**	6.8 (1.2)**	34.8 (5.4)**	9.4 (1.8)**	7.2 (1.1)**	39.2 (6.2)**
B	13	9.4 (1.7)**	15.2 (3.2)*	56.5 (9.4)*	9.6 (1.9)**	16.2 (3.4)*	63.6 (8.6)*
C	11	9.6 (1.8)**	7.0 (1.6)**	62.8 (10.8)	9.8 (2.0)**	7.5 (1.4)**	70.6 (11.2)
D	82	20.4 (3.8)	15.8 (3.4)	60.4 (9.8)	21.2 (4.1)	17.2 (3.6)	68.4 (10.8)

CK-MBmass, creatine kinase-MBmass; CK-MBactivity, creatine kinase-MBactivity.

One-way ANOVA was used to compare the group differences and post-hoc Bonferroni correction was applied for between group differences in the statistical model.

*p>0.05 compared with group D; **p>0.01 compared with group D.

Group A = related artery continuous reperfusion (CRAR); Group B = related artery temporary reperfusion (TRAR); Group C = reoblation after related artery reperfusion; Group D = related artery non-reperfusion (NRAR).

(p>0.05) in the time that the peak durations lasted before decreasing to normal values. In group C, the maximal values of CK-MBmass and CK-MBactivity appeared at 9.6 h and 9.8 h; the peak levels lasted for 7.0 h and 7.5 h, which reduced at 10.8 h, 11.4 h (p<0.01) and 8.8 h, 9.7 h, respectively (p<0.01) compared with those in group D. After returning to normal, a second peak appeared, and the time required to return to normal levels was significantly prolonged. As shown in table 3, the maximal values of CK-MBmass and CK-MBactivity were lowest in group A patients, whereas the highest values were observed in group D patients.

The kinetic changes of CK-MBmass are shown in fig1. The peak value of CK-MBmass was significantly higher in group D patients than in patients in groups A, B and C. The peak values of CK-MBmass appeared earlier in groups A, B and C than in group D. In group C, after the peak value of CK-MBmass reduced to normal, a second peak appeared.

DISCUSSION

The aim of the current study was to assess the diagnostic value of serum CK-MBmass after thrombolytic treatment in predicting the status of myocardial IRA patency—the most important aspect of early AMI care.⁶ IRA patency early after thrombolysis has a strong beneficial impact on short- and long-term outcome.^{7,8} Early identification of patients with persistent occlusion after thrombolysis during AMI is also important because it can pave the way for interventional rescue, such as percutaneous transluminal coronary angioplasty or repeated thrombolysis. Although coronary angiography is the gold standard for assessing reperfusion, it has several limitations that are related primarily to the frequent fluctuations in coronary patency early after thrombolysis, absence of assess-

ment of patency between 0–90 min, protective role of collateral circulation (which cannot be routinely quantified by angiography), no-reflow phenomenon, and invasiveness. Therefore, establishment of a reliable biomarker has a great value for assessing the effectiveness of the thrombolytic treatment. While the coronary angiogram is the gold standard in defining the patency of coronary arteries, it has limited use in reflecting myocardial reperfusion. Even when coronary angiography may show the re-opening of the stenosed coronary artery, it cannot indicate the degree of myocardial reperfusion. In particular, multiple coronary angiograms are not recommended in the acute stage post-myocardial infarction. Therefore, coronary angiography cannot be used for the hierarchical diagnosis of IRA after thrombolytic treatment in patients with AMI. On the other hand, biochemical measurements can be carried out dynamically to estimate quantitatively the status of IRA and the amount of infarcted myocardium.

In this study we found that CK-MBmass can be used as a reliable indicator for coronary patency post-thrombolytic treatment. Compared with CK-MBactivity, CK-MBmass increased to a peak and returned to baseline more quickly. The peak value of CK-MBmass was maintained for a shorter period. Thus, CK-MBmass was a more sensitive and more predictive cardiac marker than CK-MBactivity in assessing the status of IRA after thrombolysis.

During the treatment for AMI with routine drugs, the peak values of CK-MBmass and CK-MB activity appeared earlier, which were maintained for a short period before quickly returning to the baseline level. This indicates that the obturated infarct-related arteries have been spontaneously reperfused, which was approximately 5–24.9% according to recent publications.^{9–11} In our study, however, continuous reperfusion was found in five patients (5.2%) treated with routine drugs.

In conclusion, continuous reperfusion, as indicated by the dynamic changes of serum CK-MBmass, occurred in 33 of 48 patients who were treated with thrombolysis, and in five of 96 patients who were treated with routine drugs. The findings indicate that early identification of patients with patent IRA after thrombolysis is possible with CK-MBmass; and we can assess the status of RAR according to the dynamic changes of serum CK-MBmass, which has important implications for clinical practice.

Authors' affiliations

Shan-Shan Xing, Yun Zhang, Wei Zhang, Key Laboratory of Cardiovascular Remodeling and Function Research, Chinese Ministry of Education and Chinese Ministry of Public Health; Department of Cardiology Qilu Hospital Shandong University, Jinan 250012, China
 Qi-Chong Xing, Department of Cardiology, Qianfoshan Hospital of Shandong Province, Jinan 250014, China

Competing interests: none declared.

Table 3 Mean (SD) peak elevations of CK-MBmass and CK-MBactivity

Groups	n	CK-MBmass (ng/ml)	CK-MBactivity (IU/l)
A	38	377.8 (56.4)**	199.6 (35.1)**
B	13	416.5 (68.4)*	220.2 (46.3)*
C	11	430.4 (82.5)*	231.4 (41.7)*
D	82	457.0 (88.4)	252.6 (73.4)

CK-MBmass = creatine kinase-MBmass; CK-MBactivity = creatine kinase-MBactivity.

One-way ANOVA was used to compare the group differences and post-hoc Bonferroni correction was applied for between group differences in the statistical model.

*p>0.05 compared with group D; **p>0.01 compared with group D.

Group A = related artery continuous reperfusion (CRAR); Group B = related artery temporary reperfusion (TRAR); Group C = reoblation after related artery reperfusion; Group D = related artery non-reperfusion (NRAR).

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