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Comparison of five cardiac markers in the detection of reperfusion after thrombolysis in acute myocardial infarction

F Lavin, M Kane, A Forde, F Gannon, K Daly

Abstract

***Objective*—To investigate and compare the clinical usefulness of serial measurements of five cardiac marker proteins, namely creatine kinase (CK), CK-MB mass, myoglobin, troponin T, and myosin light chain 1, in the early detection of reperfusion after thrombolytic treatment.**

***Method*—Serial blood samples were taken from 26 patients presenting with acute myocardial infarction. Concentrations of the five markers were assayed in each sample. Thrombolytic treatment was given to the patients who were divided into those who reperfused (n = 17, group A) and those who failed to reperfuse (n = 9, group B) on the basis of clinical signs and angiography within 24 h.**

***Results*—The release profiles of CK, CK-MB mass, myoglobin, and troponin T for patients in group A differed from those of patients in group B. No difference was observed in the release profile of myosin light chain 1 between the two groups. The time to peak concentration of CK, CK-MB mass, myoglobin, and troponin T occurred significantly earlier in patients of group A than in those of group B, with myoglobin peaking earlier than the other markers. An index, defined as the ratio of the concentration of each marker immediately before and 2 h after the start of thrombolytic treatment, was calculated for each marker in groups A and B. The 2 h myoglobin and troponin T indices were significantly different between groups A and B. The diagnostic efficiency of the myoglobin index, however, was best at 85%.**

***Conclusions*—These studies suggest that myoglobin has greater potential than the other markers examined in the detection of reperfusion after thrombolytic treatment.**

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Keywords: cardiac marker proteins; reperfusion; thrombolysis

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The most important recent development in the treatment of patients with acute myocardial infarction is the ability to reperfuse the ischaemic heart muscle in the early hours after the onset of coronary occlusion. Intravenous thrombolytic treatment has now become the standard therapeutic approach for patients with acute myocardial infarction.[1–3] The reduction in short- and long-term mortality caused by thrombolytic treatment has been demonstrated in several large clinical trials.[4–6] The greatest therapeutic effect is seen during the early phase of acute myocardial infarction with improved left ventricular function occurring predominantly when reperfusion is established within 6 h.[7–9]

Despite early administration of thrombolytic agents recanalisation of the infarct related artery is not always achieved. Varying coronary patency rates of 60–70% have been reported.[10] The management of patients with patent infarct related arteries after thrombolytic treatment remains controversial. The literature is divided as to whether immediate coronary angioplasty has an advantage over delayed elective angioplasty in patients with patent but critically stenosed coronary arteries after thrombolytic treatment.[11 12] Conversely, patients with a persistently occluded infarct related artery may benefit from invasive interventions.[13 14] The aforementioned reasons indicate the importance of being able to determine whether or not successful reperfusion has occurred after thrombolysis.

To date, reliable determination of reperfusion status is only possible by coronary angiography. This technique is frequently either impractical or unavailable in an emergency setting. Standard non-invasive criteria, such as rapid relief of chest pain, rapid normalisation of ST segment elevation, and occurrence of reperfusion arrhythmia, have been accepted as non-invasive signs of reperfusion, but they are not sufficiently sensitive or specific criteria for an accurate evaluation of the reperfusion status. Predictability of reperfusion proved to be clearly insufficient in several trials using these criteria.[15 16]

A single non-invasive marker to evaluate reperfusion would be of significant clinical benefit. Various studies have assessed different cardiac marker proteins as indicators of reperfusion and the value of myoglobin[17] and creatine kinase (CK)[18] has been demonstrated in this setting. One study suggested that an early increase in myoglobin, 2 h after administration of thrombolytic treatment is indicative of reperfusion.[17] Until recently, however, assays of myoglobin were very time consuming and therefore of limited value in the acute clinical setting. Early peaking of CK has been demonstrated in successful reperfusion but occurs too late to be of value in the selection

of patients for further invasive treatment.

In recent years, a wide range of rapid assays for cardiac marker proteins have been developed. The aim of this study was to compare directly the release kinetics of five cardiac markers for which rapid assays are available: CK, CK-MB mass, myoglobin, troponin T, and myosin light chain 1 throughout the course of acute myocardial infarction and to determine which could provide the earliest and most reliable indication of reperfusion post-thrombolytic treatment.

Patients and methods

PATIENTS

The study group comprised twenty six patients (21 men and five women) admitted to our hospital with acute myocardial infarction and who were eligible for thrombolysis. All patients gave informed consent to the protocol which was approved by the hospital ethics committee. Patients were divided into two groups: those who reperfused after thrombolytic treatment (group A) and those who failed to reperfuse (group B). Thrombolytic treatment was given to any patient presenting within 12 h of the onset of symptoms with clinical and electrocardiographic evidence of acute myocardial infarction—that is, presenting with typical anginal chest pain for at least 30 min but not greater than 24 h and with ST segment elevation on electrocardiogram (ECG) of greater than or equal to 0·1 mV in two limb leads or 0·2 mV in two pericardial leads, and who did not have a contraindication to thrombolysis.

The thrombolytic agent used was streptokinase in 16 patients, tissue plasminogen activator in five, and combined streptokinase and tissue plasminogen activator in five. The standard doses of streptokinase 1·5 million U and tissue plasminogen activator 100 mg were given to all patients with acute myocardial infarction. The outcome was assumed to be independent of the type of thrombolytic agent used for the purposes of this study.

ECG RECORDINGS

ECGs were performed before and 2 h after the start of thrombolytic treatment. The lead showing the greatest ST segment elevation was used for the initial and subsequent measurements. The isoelectric line was defined as the level of the preceding PR segment and the ST segment was measured at the J point. The mean change in ST elevation at 2 h after the start of thrombolytic treatment was expressed as a percentage reduction from the initial value (fractional change).

CLINICAL ASSESSMENT OF INFARCT REPERFUSION

Reperfusion was assessed by standard non-invasive criteria. The first of these was rapid ST segment normalisation defined as fractional change greater than or equal to 50% at 2 h. A previous study suggested that a fractional change of 50% was useful for determining coronary patency.[19] The second criterion was the occurrence of reperfusion arrhythmia. Accelerated idioventricular rhythm and ventricular tachycardia were considered significant reperfusion arrhythmia. On the basis of these criteria, 17 of 26 patients who received thrombolytic treatment showed evidence of reperfusion (group A). The remaining nine patients were defined as group B.

Table 1 Patient data

	Group A	*Group B*
Sex ratio (M:F)	13:4	8:1
Mean (range) age (years)	61 (41–72)	61 (42–76)
Infarct site		
Inferior	9	2
Anterior	7	5
Posterior	1	2
Mean (range) time to thrombolysis (h)	3 (0–4)h	5·5 (1–10)h
Mean (range) percentage ST change	80 (50–100)%	4 (0–25)%
Arrythmia	16	3

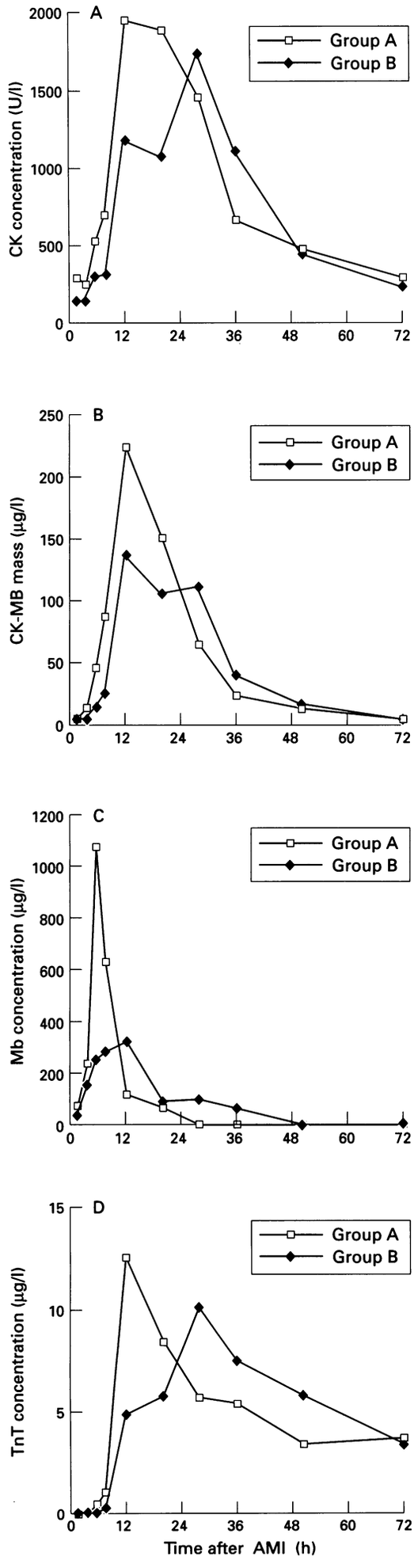
Classification into groups A and B was subsequently confirmed by angiography between 12 and 24 h, whereby 16 of the 17 patients in group A were shown clearly to have patent infarct related arteries. Early angiography could not be carried out on the remaining patient, but this patient showed almost complete normalisation of the ST segment and significant arrhythmia, which were considered adequate for inclusion in group A. The angiographic findings were assessed according to the thrombolysis in myocardial infarction (TIMI) criteria. TIMI grades II or III were defined as successful reperfusion. Angiography also confirmed the lack of reperfusion in the nine patients of group B. Table 1 gives the clinical details of the two groups.

BLOOD SAMPLING

Blood samples were taken on admission and hourly up to 8 h after the first onset of symptoms. A maximum of four samples was taken in the first 8 h. Samples were then taken at 8 hourly intervals up to 40 h after the onset of symptoms and a further two samples were taken over the next 48 h. Samples were collected without angicoagulant and then allowed to clot at room temperature for 15 min. The serum was stored at − 70°C in aliquots after centrifugation until assayed.

ANALYTICAL METHODS

Activity of CK was determined using an automated CK NAC-activated CK UV test kit (Human GmbH, Taunusstein, Germany) on a Technicon RA 1000 analyser. CK-MB mass was measured by the IMx CK-MB mass assay (Abbott GmbH Diagnostica, Wiesbaden, Germany) on the Abbott IMx analyser. This is a two step automated microparticle enzyme immunoassay which uses two different antibodies specific for the M and the B subunits of CK-MB. Myoglobin was determined by an immunoturbidimetric method (Turbiquant Myoglobin; Behringwerke AG, Marburg, Germany) using the Behring Turbitimer analyser. Cardiac troponin T was determined by the enzyme linked immunosorbent assay of Boehringer Mannheim, Germany on their



Serum concentration profiles of (A) creatine kinase (CK), (B) CK-MB mass, (C) myoglobin (Mb), and (D) troponin T (TnT) in patients who reperfused (group A), and those who did not (group B). Median values are plotted. AMI, acute myocardial infarction.

Enzymun-test system ES300 batch analyser. The concentration of cardiac myosin light chain 1 was also measured by a fully automated assay for the IMx immunoassay system.[20] Appropriate control samples were analysed for quality control of each assay system.

STATISTICAL ANALYSIS

Variables are given as mean (SE) but in all further analysis non-parametric (distribution-free) statistics were used. Differences between groups were analysed by the Kruskal-Wallis test and the Mann-Whitney U test. The Friedman rank test was used to compare variables within each group. Significance was taken at the 5% level. Sensitivity, specificity, efficiency, and positive and negative predictive values were calculated to describe the performance of CK, CK-MB mass, myoglobin, troponin T, and myosin light chain 1 index in the detection of successful reperfusion.

Results

CLINICAL DATA

Reliable and accurate determination of reperfusion can be difficult with standard non-invasive clinical criteria. The predictive accuracy of these standard markers when used in combination is high only when they are concordant.[21] Biochemical markers offer an objective alternative to these criteria. The aim of this study was to identify the most appropriate biochemical marker which could be used to predict accurately and rapidly the reperfusion status of the patient after thrombolytic treatment and so allow further interventive action to be taken if appropriate.

The mean (range) percentage change in ST segment normalisation in patients who reperfused after thrombolytic treatment (group A) was 80 (50–100)%, while in those who failed to reperfuse (group B) the mean (range) percentage change was only 4 (0–25)% (table 1). There was considerable variation in arrhythmia that occurred early after myocardial infarction. Sixteen of the 17 patients in group A had significant reperfusion arrhythmia. Eight patients had prolonged episodes of slow ventricular tachycardia and eight had accelerated idioventricular rhythm. The remaining patient showed very rapid near normalisation of all ST segments, which was considered sufficiently diagnostic for inclusion in group A. Angiography confirmed that this classification was correct. Three of the nine patients in group B had short runs of non-sustained ventricular tachycardia (six to 10 beats maximum) and these arrhythmia were not considered significant.

EFFECT OF EARLY REPERFUSION ON RELEASE PROFILES OF CARDIAC MARKER PROTEINS

The serum concentrations of the five markers, namely CK, CK-MB mass, myoglobin, troponin T, and myosin light chain 1, were traced for approximately 3 days after the onset of symptoms in each group. The figure shows the resulting profiles. The profiles of all

Table 2 Peak concentration, time from first onset of symptoms to peak value, and 2_h indices of cardiac marker proteins

	Creatine kinase	*CK-MB mass*	*Myoglobin*	*Troponin T*	*Myosin light chain 1*
*Peak concentration**					
Group A	2334 (335)	218 (22)	1400 (345)	10·0 (0·9)	6·8 (0·9)
Group B	1776 (271)	222 (36)	735 (280)	10·2 (1·3)	9·0 (3·8)
Peak time (h)					
Group A	18·9** (2·4)	14·6** (1·1)	5·1*** (0·4)	17·0** (1·0)	50·4 (6·3)
Group B	23·4 (2·4)	20·1 (2·1)	10·4 (1·5)	29·8 (8·4)	48·3 (4·7)
2 h index					
Group A	3·0 (0·6)	19·3 (13·9)	9·8** (4·1)	9·8 ** (6·8)	24·0 (20·4)
Group B	1·3 (0·3)	2·5 (0·9)	2·0 (0·3)	1·0 (0·3)	2·0 (0·9)

Values are mean (SE). * Peak concentration units are U/l for creatine kinase, and μg/l for CK-MB mass, myoglobin, troponin T, and myosin light chain 1. ** Significantly different from values in group B (Mann-Whitney U test). *** Significantly different from values in group B (Mann-Whitney U test) and significantly different from the other values in group A (Friedman test). CK-MB, creatine kinase-MB.

markers, except myosin light chain 1, in patients of group A are shifted to the left of the corresponding profiles of patients in group B, indicating that reperfusion was associated with an earlier, more rapid increase in the concentration of four of the markers. The myosin light chain 1 profiles of the two groups were similar, indicating that release of myosin light chain 1 after acute myocardial infarction is independent of reperfusion.

EFFECT OF EARLY REPERFUSION ON PEAK VALUES AND TIMES TO PEAK

Table 2 gives the peak concentrations and times from the onset of symptoms to peak values of CK, CK-MB mass, myoglobin, troponin T, and myosin light chain 1. There was wide variation in the peak concentrations of all markers among each group. The peak concentrations therefore were not significantly different from each other and were of no predictive value. The times at which the concentrations of four of the markers, namely CK, CK-MB mass, myoglobin, and troponin T, peaked were significantly earlier in patients of group A than in those of group B. These results emphasise the earlier release of these markers when reperfusion is established. Peak levels of myoglobin in patients of group A occur significantly earlier than the other markers ($P < 0·01$).

PREDICTION OF INFARCT REPERFUSION BY USE OF AN INDEX CALCULATED FOR EACH MARKER

An index, defined as the ratio of the concentration of each marker immediately before and 2 h after the start of thrombolytic treatment was calculated for each marker in groups A and B. The indices calculated at 2 h (table 2) for myoglobin and troponin T were statistically different in patients of group A, in whom early reperfusion occurred, compared with those of patients in group B who did not reperfuse. These two markers, therefore, have potential as indicators of reperfusion status within 2 h of administration of thrombolytic treatment. The difference between the 2 h indices for CK and CK-MB was slightly short of significance. The mean 2 h index of myosin light chain 1 in patients of group A was much greater than in those of group B but there was wide variation in the results. This was because of the low or undetectable levels of this marker at the stage when thrombolytic treatment was administered.

The diagnostic performance of t h index of all markers to detect reperfusi as assessed (table 3). The discriminator lue was taken as the mean plus twice the standard deviation of the indices for group B. The specificity and positive predictive value of all indices were excellent with this cut-off point. The sensitivity and diagnostic efficiency of the myoglobin index, however, was much better than the other indices.

Discussion

Thrombolysis is now standard treatment for patients with acute myocardial infarction and is widely used even in centres lacking cardiac catheterisation facilities. There is consequently an increasing need for a reliable, rapid, non-invasive marker of reperfusion to permit identification of those patients who might benefit from further interventional procedures such as rescue coronary angiography. Clinical and electrocardiographic indices of reperfusion, either alone or in combination, are not sufficiently reliable to predict reperfusion with a high degree of accuracy.[15 16] It is well established that the pattern of several cardiac markers is altered in the blood when reperfusion occurs. We decided therefore to

Table 3 Comparison of 2 h indices of creatinine kinase, CK-MB mass, myoglobin, troponin T, and myosin light chain 1

	Creatine kinase	*CK-MB mass*	*Myoglobin*	*Troponin T*	*Myosin light chain 1*
Diagnostic sensitivity (%)	33	40	80	57	33
Diagnostic specificity (%)	100	100	100	100	100
Positive predictive value (%)	100	100	100	100	100
Negative predictive value (%)	33	36	63	45	33
Diagnostic efficiency (%)	50	55	85	68	50

CK-MB, creatine kinase-MB.

examine and compare the performance of five cardiac markers to predict reperfusion after thrombolytic treatment.

Our studies confirmed previous observations that peak times of the four markers, namely CK, CK-MB mass, myoglobin, and troponin T, were significantly earlier when reperfusion occurred.[22 23] We have also confirmed that the time to peak myosin light chain 1 activity is not affected by reperfusion.[24] Several studies have assessed the clinical usefulness of the time to peak concentration of these markers as indicators of reperfusion.[11 14 25] For example, Katus *et al*[11] showed that the time of peak serum concentration of myoglobin, CK, and CK-MB activity predicted reperfusion with diagnostic efficiencies of 93, 89, and 88%, respectively. Hohnloser *et al*,[21] found that the time to peak CK activity in combination with two clinical markers, resolution of ST segment elevation, and occurrence of arrhythmia could predict the occurrence of reperfusion with 100% sensitivity 90% specificity.

Determination of the time to peak concentration of any marker, however, involves measurement of the concentration of the marker by serial blood sampling until the decline in plasma concentration is observed. Such a procedure does not lend itself to early indication of the reperfusion status of the patient. As an alternative, the rate of change in the serum concentration of some markers shortly after administration of thrombolytic agent has been examined. Ellis *et al*[17] reported that a myoglobin index, defined as the ratio of myoglobin concentration immediately before and 2 h after the start of thrombolytic treatment could give useful information about coronary patency. Increases in CK-MB mass of 2·2-fold over baseline within 90 min or increases in CK-MB activity (mean (SE)) of 48 (36) U/l in the first hour after treatment were indicative of reperfusion in other studies.[26 27] The ratio of troponin T concentration on day 1 to that on day 4 was shown to discriminate between patients who reperfused and those who failed to reperfuse.[23] This would, however, have no practical use in the selection of patients for coronary angiography.

The present study allows direct comparison of how the early rate of increase in the concentration of five cardiac markers can predict reperfusion after thrombolytic treatment. Because all the markers were analysed in the same patient group, we were able to compare directly the diagnostic performance of each of these indices in the prediction of reperfusion. The myoglobin index is clearly the best biochemical discriminator in this study, with an overall diagnostic efficiency of 85%. We have also identified troponin T as a promising biochemical marker of reperfusion. The increase in concentration of troponin T occurs too late, however, to be of clinical benefit. The diagnostic sensitivity and specificity of the myoglobin index obtained in this study are comparable to those reported by Ellis *et al*,[17] although higher sensitivities have been reported.[28]

The ideal non-invasive marker of reperfusion must indicate as early as possible whether reperfusion has occurred to permit maximum benefit to be derived from further interventional procedures. In addition to the presence of the marker in concentrations related to the reperfusion status of the patient, it is essential that rapid assay methods are available for the marker. Otherwise, the benefits of early detection will not be realised.

In this study, myoglobin was measured by an immunoturbidimetric method carried out on a specialised analyser, which can give results in less than 10 min[29] and is thus ideally suited to act as an early marker of reperfusion. We chose to measure CK-MB mass in this study because of its reported higher sensitivity than the traditional activity measurements.[30] A sensitive immunometric assay[31] was performed by the use of automated analyser. The turnaround time of this assay for one to 24 samples is approximately 40 min, which is still reasonably acceptable. Several alternative assays for CK-MB mass have been described, many giving results in less time. The troponin T assay used here takes 90 min for results to be made available. Therefore, troponin T falls behind myoglobin and CK-MB as a non-invasive marker of reperfusion in terms of clinical performance and speed of availability of results.

In conclusion, this study has shown that myoglobin allows the earliest prediction of infarct reperfusion. The diagnostic sensitivity and efficiency of myoglobin were significantly better than the other markers tested and therefore should be the marker of choice for the prediction of reperfusion.

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