Contribution of creatine kinase MB mass concentration at admission to early diagnosis of acute myocardial infarction

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Abstract

Objective—To assess the diagnostic value at admission of creatine kinase MB mass concentration, alone or in combination with electrocardiographic changes, in suspected myocardial infarction.

Design—Prospective study of all consecutive patients admitted within 12 hours after onset of chest pain to a coronary care unit for evaluation of suspected myocardial infarction.

Setting—Large regional hospital.

Patients—In 297 patients creatine kinase and creatine kinase MB activities and creatine kinase MB mass concentration were determined. Myocardial infarction according to the criteria of the World Health Organisation was diagnosed in 154 patients and excluded in 143 patients (including 70 with unstable angina pectoris).

Results—Sensitivity/specificity for creatine kinase MB mass concentration in patients admitted within 4 hours and 4–12 hours after onset of chest pain were 45%/94% and 76%/79% respectively. Corresponding values for creatine kinase activity were 20%/89% and 59%/83%, and for creatine kinase MB activity 16%/87% and 53%/87%. Raised creatine kinase MB mass concentration was seen in 17% of patients with unstable angina pectoris. Stepwise logistic regression analysis showed that independent predictors of acute myocardial infarction in patients admitted within 4 hours after onset of chest pain were electrocardiographic changes and creatine kinase MB mass concentration on admission; in patients admitted 4–12 hours after the onset of pain independent predictors were electrocardiographic changes and creatine kinase MB mass concentration and activity.

Conclusion—Creatine kinase MB mass concentration is a more sensitive marker for myocardial infarction than the activity of creatine kinase and its MB isoenzyme. Electrocardiographic changes on admission in combination with creatine kinase MB mass concentration (instead of creatine kinase and creatine kinase MB activities) are best in diagnosing myocardial infarction.

The diagnosis of acute myocardial infarction is generally based on a history of chest pain, specific electrocardiographic changes, and the typical rise and fall in the activity of cardiac enzymes. At hospital admission the diagnostic value of chest pain,¹ single electrocardiographic recordings,^{2,3} and single determinations of the activity of creatine kinase and its MB isoenzyme^{4–9} is limited. Serial measurement of creatine kinase and creatine kinase MB activities, as a reflection of myocardial cell damage, however, plays the most important part in establishing the definitive as well as the early diagnosis of myocardial infarction,¹⁰ because these enzymes are easily and rapidly measured with automated analysers. The immunological determination of the mass concentration of creatine kinase MB is a recent advance towards greater sensitivity and specificity.^{11–15} Creatine kinase MB mass concentration is often raised in the early phase of myocardial infarction.^{13,16} Therefore, measuring creatine kinase MB mass concentration might be advantageous as it can be measured rapidly¹⁷ like creatine kinase and creatine kinase MB activity.

In this study we assessed the validity of the reference ranges for a sensitive assay for creatine kinase MB mass concentration and creatine kinase and creatine kinase MB activities. We then evaluated the diagnostic properties of creatine kinase MB mass concentration at admission and compared them with those of the currently used methods for measuring creatine kinase and creatine kinase MB activities and electrocardiographic changes on admission. Finally, we evaluated the predictive power of combining these electrocardiographic changes with each of these biochemical markers at the time of admission.

Patients and methods

The study population consisted of all consecutive patients admitted over nine months to the coronary care unit of the Medisch Centrum Leeuwarden, a large regional hospital, for evaluation of suspected myocardial infarction within 12 hours after the onset of chest pain. Patients were not included when they had been resuscitated or received defibrillation. Standard 12 lead electrocardiograms obtained at admission, 24 hours after admission, and at discharge were used for establishing the final diagnosis. Blood samples for the determination of activities of creatine kinase, its MB

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isoenzyme, lactate dehydrogenase, aspartate aminotransferase, and alanine aminotransferase and the mass concentration of creatine kinase MB were taken at admission, three times in a fixed time schedule for the first 24 hours, and once daily until discharge.

DIAGNOSTIC CRITERIA

Electrocardiographic findings on admission were classified as normal, ischaemic, or non-conclusive. Normal findings were defined according to the criteria of the New York Heart Association.¹⁸ Electrocardiographic results were classified as ischaemic if the ST segment was depressed by more than 1 mm 0.08 s after the J point or the ST segment was elevated by more than 1 mm (in at least two contiguous leads) and provided that QRS complexes were normal and there was right bundle branch block. All other findings in electrocardiograms on admission were classified as non-conclusive.

Patients were classed as having myocardial infarction, unstable angina pectoris, or other cardiac disease or as having no acute ischaemic heart disease. The final diagnosis was established by an independent cardiologist who did not know the initial creatine kinase MB mass concentration. The diagnosis of myocardial infarction was established if a patient had at least two of the three classic findings. The first was a clinical history of ischaemic chest discomfort of more than 30 minutes' duration. The second was the development of typical changes in at least two leads of the electrocardiogram. Q waves greater than 0.04 s or an R/S ratio greater than 1 in leads V1 and V2 was termed Q wave infarction; ST segment depression of more than 1 mm 0.08 s after the J point or ST segment elevation of more than 1 mm persisting for at least 24 hours was termed non-Q wave infarction. The third was a time dependent change in serum creatine kinase and creatine kinase MB activities, showing an initial rise (with a peak value of creatine kinase MB activity exceeding twice the upper limit of normal values) and subsequent fall.

Unstable angina pectoris was defined as typical anginal pain at rest in combination with reversible or persistent electrocardiographic changes but without a peak value in activity of creatine kinase MB that exceeded twice the upper limit of normal values.

Patients were classed as having no acute ischaemic heart disease when there was a definite alternative source of the chest pain or an atypical history with a negative result on stress electrocardiography, myocardial scintigraphy, or coronary angiography.

ANALYTICAL METHODS

Catalytic activity of creatine kinase was measured at 30°C with a Hitachi 717 analyser by the method proposed by the International Federation of Clinical Chemistry⁶ using commercial reagents (product numbers 475742 and 475769) supplied by Boehringer Mannheim (Mannheim, Germany). The upper limit of normal values in this assay

was 130 U/l for men and 90 U/l for women.

Catalytic activity of creatine kinase MB was measured by immunoinhibition using an appropriate antibody (product number 418234; Boehringer Mannheim) and the creatine kinase assay method.¹⁹ Like creatine kinase activity, creatine kinase MB activity was measured with the Hitachi 717 analyser at 30°C. The upper limit of normal values in this assay was 15 U/l.

Creatine kinase MB mass concentration in serum was measured according to the manufacturer's instructions by a microparticle capture enzyme immunoassay with the IMx analyser from Abbott Laboratories (Abbott Park, Illinois; product number 2207-20). The sensitivity of this assay was reported to be 0.2 µg/l.²⁰ The measuring range covers concentrations from 0.2 to 300 µg/l. The upper limit of normal values in this assay was established in this study using serum samples from 77 male and 45 female apparently healthy blood donors. The upper limit of normal (97.5th percentile) was estimated at 5.0 µg/l according to the proposed guidelines of the International Federation of Clinical Chemistry.²¹

STATISTICAL ANALYSIS

Sensitivity, specificity, positive and negative predictive values, relative risk, and likelihood ratios were calculated to determine the diagnostic properties of electrocardiographic findings and the biochemical markers. The likelihood ratio of a positive test is the probability of a positive test in the presence of disease divided by the probability of a positive test in the absence of disease.

Differences in baseline characteristics (age, sex, clinical history, and risk factors) between patients with and without myocardial infarction were determined by a χ^2 test or by Fisher's exact test for categorical variables and by Student's *t* test for continuous variables (a *P* value <0.05 was considered to be significant).

A stepwise logistic regression analysis (PROC LOGISTIC²²) was performed to identify the variables that contributed significant independent information to distinguish patients with myocardial infarction from those without. At each step of the logistic regression analysis the variable that was most significantly associated with the presence of myocardial infarction was selected until no variables meeting the 0.05 significance level (χ^2 test) for entering the model were left. The probability of myocardial infarction in each patient given electrocardiographic information alone and in combination with the biochemical markers was calculated by using the coefficients obtained in the logistic regression analysis.

Results

Our study included 297 patients (148 of them admitted within 4 hours after the onset of anginal chest pain). Acute myocardial infarction was confirmed in 154 patients (75 Q wave); 50 of them (32%) received thrombolysis. In 143 patients acute myocardial

Table 1 Baseline characteristics of patients admitted within 12 hours after onset of chest pain. Values are numbers (percentages) of patients unless stated otherwise

	Patients with acute myocardial infarction (n=154)	Patients without acute myocardial infarction (n=143)
Men	111 (72)	96 (67)
Mean (SD) age (years)	65 (11.9)	62 (12.2)
History of angina	60 (39)	76 (53)*
Previous:		
Acute myocardial infarction	39 (25)	50 (35)
Percutaneous transluminal coronary angioplasty	3 (2)	10 (7)
Coronary artery bypass grafting	7 (5)	7 (5)
Diabetes	20 (13)	11 (8)
Hypertension	46 (30)	48 (34)
Hyperlipidaemia	70 (46)	60 (42)
Smoking	63 (41)	53 (37)

*Significant difference between patients with and without myocardial infarction group (P=0.023).

infarction was excluded: 70 patients were classed as having unstable angina pectoris (three patients received thrombolysis) and 58 as having no acute ischaemic heart disease (one patient received thrombolysis). Other cardiac diseases were diagnosed in 11 patients (one patient received thrombolysis), four patients had no definitive diagnosis. No significant differences in baseline characteristics

Frequency of biochemical markers at admission above normalised concentrations in patients with no acute ischaemic heart disease and in those with unstable angina pectoris. Values in parentheses after biochemical markers are upper limit of normal values.

(age, sex, clinical history, and risk factors) with the exception of a history of angina were found between patients with and without myocardial infarction (table 1).

VERIFICATION OF NORMAL RANGES IN PATIENTS WITHOUT ACUTE ISCHAEMIC HEART DISEASE

The upper limit of normal values for the three markers was verified using the results obtained at admission for the patients (n = 58) classed as having no acute ischaemic heart disease. For creatine kinase MB mass concentration 95% (in estimating the normal range usually the 95% range is calculated) of the results obtained in the admission samples were less than or equal to the upper limit of normal values, while only 79% and 84% of the results for creatine kinase and creatine kinase MB activity were within the normal range (figure). The 5% limit for creatine kinase MB mass concentration was 4.0 µg/l, for creatine kinase MB activity 41 U/l, and for creatine kinase 1.56 times the upper limit of normal values.

Further analysis of the data showed that most of the raised creatine kinase and creatine kinase MB activities were false positive results with respect to the diagnosis of myocardial infarction. These activities were raised in six patients because of muscle injury as the ratio of creatine kinase MB to total creatine kinase activity was normal (a ratio <6% excludes myocardial infarction), in three patients because of the presence of a macromolecular creatine kinase (creatine kinase in two of them and creatine kinase MB in all three), and in seven patients because haemolysis freed adenylate kinase from erythrocytes (creatine kinase in four patients, and creatine kinase MB in all seven). Two patients had a raised creatine kinase MB concentration. One had non-specific thoracic pain and a macromolecular creatine kinase with a creatine kinase MB mass concentration of 7.5 µg/l; the other had rheumatoid arthritis and hypertension and a creatine kinase MB mass concentration of 6.0 µg/l, but total creatine kinase and creatine kinase MB activities were low (creatine kinase 20 U/l; creatine kinase MB 3 U/l). The raised creatine kinase MB mass concentration could not be explained in either patient. Electrocardiographic findings on admission were rated ischaemic in six (10%) patients, non-conclusive in seven (12%), and normal in 45 (78%) patients with no acute ischaemic heart disease.

FREQUENCY OF RAISED RESULTS IN PATIENTS WITH UNSTABLE ANGINA PECTORIS

The results at admission for patients with unstable angina pectoris (n = 70) were also compared with the upper limit of normal values (figure). In this group 95% of the results for the activities of creatine kinase and creatine kinase MB was within the normal range. For creatine kinase MB mass concentration, however, 17% (12/70) of the results were above the upper limit of normal values, and 5% of the results were > 12 µg/l.

Table 2 Diagnostic sensitivity, specificity, and positive and negative predictive values (%) at admission for biochemical markers of myocardial damage

Marker	Time between onset of pain and admission (h)							
	<4				4-12			
	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Creatine kinase activity	20	89	66	51	59	83	79	65
Creatine kinase MB activity	16	87	57	50	53	87	82	63
Creatine kinase MB mass concentration	45	94	89	62	76	79	80	75

Electrocardiographic findings on admission were rated ischaemic in 15 (21%) of the patients, non-conclusive in 20 (29%), and normal in 35 (50%).

FREQUENCY OF RAISED RESULTS IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

In patients with acute myocardial infarction raised results at admission were encountered more frequently for creatine kinase MB mass concentration (60%) than for creatine kinase and creatine kinase MB activities (40% and 34%). Electrocardiographic findings on admission were rated ischaemic in 66 (43%) patients, non-conclusive in 60 (39%) patients, and normal in 28 (18%) patients. On admission 13 patients with acute myocardial infarction (8%) had normal electrocardiographic findings combined with a diagnostic creatine kinase MB activity. One patient received thrombolysis because of electrocardiographic changes, but subsequent rises in creatine kinase and creatine kinase MB activities were not observed. In this patient creatine kinase

MB mass concentration was slightly raised in the sample at admission (7.3 µg/l) but not thereafter.

PATIENTS WITH OTHER, NON ISCHAEMIC, CARDIAC DISEASE

Five patients had pericarditis, four arrhythmias, and two congestive heart failure. One patient with pericarditis had raised results for the three markers (creatinine kinase activity 419 U/l; creatine kinase MB activity 37 U/l; creatine kinase MB mass concentration 42.1 µg/l), while the other four patients had all three markers within the normal range. Only one patient with arrhythmia had a raised creatine kinase MB mass concentration (5.3 µg/l); one patient with congestive heart failure had a raised creatine kinase MB activity (21 U/l) and creatine kinase MB mass concentration (8.5 µg/l), while the other had all results within the normal range. Electrocardiographic findings on admission were ischaemic in one patient with pericarditis (the patient with raised values for the three markers), in one patient with arrhythmia, and in one patient with congestive heart failure. Electrocardiographic findings were non-conclusive in one patient with pericarditis and in three patients with arrhythmia.

Table 3 Distribution of results and statistical characteristics of diagnostic tests for myocardial infarction

	Patients with acute myocardial infarction	Patients without acute myocardial infarction	Relative risk (95% confidence interval)	Likelihood ratio
<i>Admission within 4 h after onset of chest pain</i>				
Electrocardiographic findings:				
Ischaemic (n = 47)	35	12	3.41 (2.22 to 5.22)	2.76
Non-conclusive (n = 46)	29	17	2.89 (2.00 to 4.18)	1.62
Normal (n = 55)	12	43		0.26
Creatine kinase*:				
Normal (n = 125)	61	64		0.90
Raised (n = 23)	15	8	1.34 (0.90 to 1.99)	1.78
Creatine kinase MB:				
Activity:				
Normal (≤15 U/l) (n = 127)	64	63		0.96
Raised (>15 U/l) (n = 21)	12	9	1.13 (0.75 to 1.71)	1.26
Mass concentration:				
Normal (≤5 µg/l) (n = 110)	42	68		0.59
Raised (>5 µg/l) (n = 38)	34	4	2.34 (1.72 to 3.16)	8.00
<i>Admission 4-12 h after onset of chest pain</i>				
Electrocardiographic findings:				
Ischaemic (n = 45)	31	14	2.54 (1.76 to 3.66)	2.02
Non-conclusive (n = 45)	31	14	2.54 (1.76 to 3.66)	2.02
Normal (n = 59)	16	43		0.34
Creatine kinase*:				
Normal (n = 91)	32	59		0.49
Raised (n = 58)	46	12	2.26 (1.67 to 3.06)	3.48
Creatine kinase MB:				
Activity:				
Normal (≤15 U/l) (n = 99)	37	67		0.54
Raised (>15 U/l) (n = 50)	41	9	2.19 (1.63 to 2.95)	4.15
Mass concentration:				
Normal (≤5 µg/l) (n = 75)	19	56		0.31
Raised (>5 µg/l) (n = 74)	59	15	3.15 (2.24 to 4.41)	3.58

*Upper limit of normal values 130 U/l for men and 90 U/l for women.

DIAGNOSTIC PROPERTIES OF MARKERS FOR MYOCARDIAL DAMAGE

Because the release of markers after myocardial infarction depends on the time elapsed since the onset of necrosis and because thrombolysis is most effective when started within four hours after the onset of chest pain, we related the diagnostic properties of the markers to the time between the onset of chest pain and admission (table 2). Table 3 shows the frequency of normal and abnormal results at admission on electrocardiography and for the biochemical markers, together with the relative risk and likelihood ratios.

COMBINATION OF ELECTROCARDIOGRAPHIC FINDINGS WITH ONE BIOCHEMICAL MARKER IN IDENTIFYING MYOCARDIAL INFARCTION

To determine the effect of combining the diagnostic tests, the electrocardiographic results, activities of creatine kinase and creatine kinase MB activities, and creatine kinase MB mass concentration were entered into a model for stepwise logistic regression analysis. In the group admitted within 4 hours after onset of chest pain the independent predictors

Table 4 Independent predictors of myocardial infarction at admission indentified by stepwise logistic regression analysis

Variable	Coefficient	SE	Odds ratio*	95% confidence interval
Admission within 4 h after onset of chest pain				
Creatine kinase MB mass concentration	2.60	0.61	13.4	4.0 to 44.4
Electrocardiographic findings:				
Ischaemic	2.38	0.51	10.8	3.9 to 29.9
Non-conclusive	1.59	0.50	4.9	1.8 to 13.3
Constant	-1.75	0.38		
Admission 4–12 h after onset of chest pain				
Creatine kinase:				
Activity	1.66	0.57	5.2	1.7 to 16.2
Mass concentration	1.55	0.46	4.7	1.9 to 11.8
Electrocardiographic findings:				
Ischaemic	1.78	0.55	5.9	2.0 to 17.5
Non-conclusive	1.95	0.55	7.1	2.4 to 21.1
Constant	-2.28	0.45		

*Odds of disease given a positive test divided by the odds of disease given a negative test. This means, for example, that odds for myocardial infarction in patients with raised creatine kinase MB mass concentration is 13.4 times higher than that in patients with normal creatine kinase MB mass concentration.

of myocardial infarction were electrocardiographic findings on admission and creatine kinase MB mass concentration (table 4). Creatine kinase MB mass concentration strongly enhanced discrimination between patients with and without myocardial infarction when electrocardiographic findings were normal or non-conclusive. Table 5 shows the probabilities of myocardial infarction given admission electrocardiographic findings alone and in combination with one of the biochemical markers (the respective probabilities were calculated in a logistic regression model considering the combination of electrocardiographic findings and each marker separately). In the patients admitted between four and 12 hours after onset of chest pain the activity of creatine kinase MB was an independent predictor of myocardial infarction in addition to

the electrocardiographic findings and creatine kinase MB mass concentration.

Discussion

Establishing the diagnostic value of tests requires proper validation of normal ranges, which are usually estimated in serum samples from healthy blood donors or laboratory staff; these subjects are young and healthy compared with the patients the test is meant for. We therefore verified the upper limit of normal values for the cardiac markers in patients who were admitted for evaluation of possible myocardial infarction, and classed as having no acute ischaemic heart disease at discharge from hospital. Falsely raised results for creatine kinase and creatine kinase MB activities were found as a result of known causes such as muscle injury,⁵ the occurrence of macromolecular creatine kinase,⁷⁻⁹ and the release of adenylate kinase from haemolysed erythrocytes.^{5,6} Raised results in patients with no evidence of acute ischaemic heart disease were encountered to a far lesser extent for creatine kinase MB mass concentration. Although creatine kinase MB mass concentration may rise above the upper limit of normal values after heavy physical exercise,²³ no evidence of muscular damage was found in the first patient with a raised creatine kinase MB mass concentration. In the other patient with a raised creatine kinase MB mass concentration, creatine kinase and creatine kinase MB activities were raised as a result of the presence of a macromolecular creatine kinase, so muscular damage could not be excluded with certainty. For creatine kinase MB mass concentration the upper limit of normal values found in our study was supported not only by the findings in the patients with no acute ischaemic heart disease but also by the

Table 5 Probabilities of myocardial infarction obtained by logistic regression analysis, given electrocardiographic results on admission alone and in combination with three biochemical markers

<i>Electrocardiographic results on admission</i>			<i>Electrocardiographic results combined with:</i>			
			<i>Test result</i>	<i>Creatine kinase MB mass concentration</i>	<i>Creatine kinase MB activity</i>	<i>Creatine kinase activity</i>
<i>Admission within 4 h after after onset on chest pain</i>						
0.51	Normal (n=55)	0.22	Raised	0.70	0.27	0.35
			Normal	0.15	0.21	0.20
	Non-conclusive (n=46)	0.63	Raised	0.92	0.70	0.77
			Normal	0.46	0.62	0.60
	Ischaemic (n=47)	0.74	Raised	0.96	0.79	0.85
			Normal	0.65	0.73	0.72
<i>Admission 4–12 h after onset of chest pain</i>						
0.52	Normal (n=59)	0.27	Raised	0.59	0.62	0.57
			Normal	0.13	0.12	0.14
	Non-conclusive (n=45)	0.69	Raised	0.87	0.94	0.90
			Normal	0.42	0.56	0.53
	Ischaemic (n=45)	0.69	Raised	0.86	0.93	0.89
			Normal	0.38	0.54	0.51

results reported in other studies.^{13 24 25} The accidents causing raised creatine kinase and creatine kinase MB activities therefore do not seem to have any effect on creatine kinase MB mass concentration.

Verifying the upper limit of normal values by results from patients with a final diagnosis of unstable angina pectoris does not seem valid. Whereas in the patients with unstable angina pectoris the 95% limits for creatine kinase and creatine kinase MB activity are not different from the upper limit of normal values, creatine kinase MB mass concentration is raised in a fair proportion of these patients (17%). No myocardial damage was established in these patients according to the World Health Organisation's criteria for diagnosing myocardial infarction (based on the insensitive methods for measuring enzyme activity), but this does not imply that minor myocardial damage was excluded. This supposition is supported by two recent studies, which show that patients with unstable angina pectoris and a raised creatine kinase MB mass concentration had a significantly higher risk of developing acute myocardial infarction or requiring revascularisation.^{26 27} As a consequence, minor myocardial damage, which remained undetectable with the less sensitive assays for creatine kinase and creatine kinase MB activities used so far, is probably present in patients with unstable angina pectoris and a raised creatine kinase MB concentration. To adapt the upper limit of normal values for creatine kinase MB mass concentration on the basis of the results in patients with unstable angina pectoris is not therefore justified.

In patients presenting with acute chest pain shortly (<4 hours) after onset accurate early diagnosis is an important requirement to assure proper allocation of expensive coronary care beds, to identify patients with acute myocardial infarction who may benefit from interventions aimed at limiting the size of the infarct,^{3 28-31} and to avoid premature discharge from hospital of patients with myocardial infarction. Selection of therapeutic measures is guided by clinical history, age of the patient, coagulation state, and the diagnostic facilities available to the physician. Objective biochemical data, although desirable, are not currently available for the decision making process because the currently used markers, creatine kinase and creatine kinase MB activities, have a low diagnostic sensitivity at admission (creatinine kinase 20%, creatine kinase MB 16%). Creatine kinase MB mass concentration seems to have a significantly better diagnostic sensitivity (45%) shortly after onset of chest pain.^{12 13 16} Moreover, this biochemical assay can be performed rapidly.¹⁷ The electrocardiogram on admission is another objective measure for early detection of myocardial infarction. ST segment changes were found to be the most sensitive criterion.^{2 32-34} Specific ST changes may, however, be absent in the early phase of acute myocardial infarction in 40-60% of patients (in our study, 57%). Although electrocardiographic recordings can be performed easily and rapidly, the diagnostic

accuracy shortly after onset of chest pain is limited.

To improve the diagnostic possibilities at admission shortly after onset of chest pain, we investigated the diagnostic power of combining the electrocardiographic findings on admission with creatine kinase MB mass concentration on admission. With this combination of tests, which both can be performed rapidly, the diagnostic accuracy increases considerably in comparison with electrocardiographic findings, alone or in combination with creatine kinase or creatine kinase MB activity. In patients admitted between four and 12 hours after the onset of chest pain the results are less convincing for creatine kinase MB mass concentration as a consequence of the high false positive rate in patients with unstable angina pectoris. The higher sensitivity of creatine kinase MB mass concentration for myocardial cell necrosis is accompanied by a lower specificity because patients with minor myocardial damage and a raised creatine kinase MB mass concentration will be called false positive according to the WHO criteria. Such a classification, however, does not account for the significance of detecting minor myocardial cell damage in patients not yet fulfilling the WHO criteria for diagnosis of myocardial infarction. These patients carry an increased risk of dying or having a major myocardial infarction,^{26 27} and they may be detected by measuring creatine kinase MB mass concentration. Thereby these patients constitute a subgroup, which might benefit from a more aggressive treatment—that is, coronary angiography followed by subsequent revascularisation.

Usually, the presence of specific ST changes has such a high positive predictive value for the diagnosis of myocardial infarction^{2 34} that little further information is needed when this electrocardiographic finding is present, especially in conjunction with appropriate symptoms. Unfortunately, many patients with myocardial infarction will have other findings on an admission electrocardiogram. Many patients presenting with suggestive symptoms and without characteristic findings on an admission electrocardiogram will have unstable angina or non-cardiac diagnoses, while others will have myocardial infarction. Our results show that creatine kinase MB mass concentration constitutes a major improvement in the diagnostic process. Further improvement probably can be obtained by using creatine kinase MB subforms,³⁵ but such measurements are not yet practicable because labour and time consuming electrophoretic methods are needed. In patients with non-conclusive electrocardiographic findings—that is, patients with a left bundle branch block—and clinical suspicion of myocardial infarction creatine kinase MB mass concentration might be helpful in deciding whether thrombolysis is needed.

In conclusion, we have four main findings.

(1) Creatine kinase MB mass concentration is more sensitive in detecting patients with acute myocardial infarction than creatine

kinase and creatine kinase MB activities.

(2) Creatine kinase MB mass concentration in combination with electrocardiographic findings on admission best distinguishes patients with myocardial infarction from those without when admission is within 4 hours after the onset of chest pain.

(3) In patients with a final diagnosis of no acute ischaemic heart disease considerably less false positive results were encountered using creatine kinase MB mass concentration instead of creatine kinase and creatine kinase MB activities.

(4) In patients with unstable angina pectoris creatine kinase MB mass concentration was raised in a considerable number of patients in contrast with creatine kinase and creatine kinase MB activities, thereby allowing detection of a subgroup of patients with possibly an increased risk for major cardiac events.

We conclude that for early diagnosis of myocardial infarction rapid assays for the determination of creatine kinase MB mass concentration should replace the measurements of creatine kinase and creatine kinase MB activities.

The reagents for the immunological determination of creatine kinase MB mass concentration were given by Abbott.

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