

# Biochemical markers in the management of suspected acute myocardial infarction in the emergency department

A M Huggon, J Chambers, N Nayeem, P Tutt, M Crook, S Swaminathan

## Abstract

**Objectives**—To compare cardiac troponin T, myoglobin, CK, CKMB activity, CKMB mass and the initial electrocardiogram in the early diagnosis of myocardial infarction in the emergency department.

**Methods**—Biochemical markers were measured at presentation in patients with a possible diagnosis of acute myocardial infarction. Based on the clinical notes, patients were grouped as “definite myocardial infarction” (n = 50), “definite no myocardial infarction” (n = 81) and “uncertain” (n = 96). Sensitivity and specificity and positive and negative predictive values were calculated using the 131 patients with definitely present or absent myocardial infarction.

**Results**—The initial electrocardiogram was more sensitive than any of the markers in the first six hours from symptom onset—sensitivity 74% (95%CI 61% to 88%). The positive predictive value of the initial electrocardiogram was 97% in the first six hours; the markers ranged from 47% to 67%. The negative predictive value of the initial electrocardiogram was 85% in the first six hours; the markers ranged from 61% to 70%. Four patients with non-diagnostic electrocardiograms presenting beyond six hours after pain onset had a myocardial infarct detected by at least three of the biochemical markers in each case.

**Conclusions**—The electrocardiogram is of more diagnostic use than biochemical markers in the first six hours after the onset of pain, but biochemical markers give additional positive diagnostic information in patients presenting later than this. The negative predictive accuracy of biochemical markers is too low for a single sample to be useful for excluding myocardial infarction in the first six hours after onset of symptoms.

(*Emerg Med J* 2001;18:15-19)

Keywords: acute myocardial infarction; cardiac enzyme; troponin T; myoglobin; CKMB mass

The final diagnosis of myocardial infarction is made from a combination of chest pain characteristics, evolutionary changes on the electrocardiogram and serial analysis of cardiac enzyme levels.<sup>1</sup> However, if possible, an early diagnosis should be made in the emergency department in order to guide decisions about admission and thrombolysis. Levels of the

enzyme creatine phosphokinase (CK) are widely available, but are of limited use in the emergency setting as they only begin to rise four hours after the onset of myocardial infarction. Levels of myoglobin, troponin T and CKMB may be useful early after infarction<sup>2-5</sup> and can be measured at the bedside<sup>6-9</sup> making testing in the emergency department possible.

Cardiac troponin T is a structurally bound protein unique to the heart, which is a sensitive indicator of myocardial necrosis. Patients with acute myocardial ischaemia in whom levels of troponin T are raised have an increased risk of myocardial infarction and death.<sup>9-14</sup> The maximal level in the first 24 hours after the onset of pain gives prognostic information in unstable angina and non-Q wave infarction, but a level below the reference range does not exclude myocardial ischaemia.<sup>13</sup> Myoglobin is an intracellular protein, which facilitates oxygen transport in muscle. After myocardial infarction, levels reach a peak early,<sup>5, 15</sup> but then fall rapidly resulting in a shorter diagnostic period than troponin T. CKMB is an isoenzyme of CK, which is relatively specific for myocardium. CKMB activity is usually measured but CKMB mass may be useful in excluding myocardial infarction.<sup>16</sup>

The reported sensitivities and specificities of these biochemical markers vary between studies partly because the study populations differ in size and clinical characteristics and partly because of differences in cut off values. Most studies have compared only two or three markers at the same time and have not compared them with the initial electrocardiogram. The aim of this study was therefore to compare the sensitivities of troponin T, myoglobin, total CK, CKMB activity and CKMB mass and the initial electrocardiogram against the final diagnosis for patients presenting to the emergency department.

## Methods

### PATIENTS

Between November 1991 and December 1993, doctors in the emergency department were asked to take extra blood in all patients with chest pain or a history suspicious of myocardial infarction, if they already intended to request cardiac enzyme analysis. No attempt was made to selectively enter patients with a clinically obvious myocardial infarction. Patients were entered into the study regardless of intention to admit and some were discharged home. Of 323 patients, there were 96 exclusions. In 17 patients, the time interval from onset of the pain was not noted, in 13 there was

Department of  
Accident and  
Emergency, Guy's and  
St Thomas' Hospitals,  
London  
A M Huggon  
N Nayeem

Department of  
Cardiology, Guy's and  
St Thomas' Hospitals  
J Chambers

Department of Clinical  
Biochemistry, Guy's  
and St Thomas'  
Hospitals  
P Tutt  
M Crook  
S Swaminathan

Correspondence to:  
Dr Huggon, Accident and  
Emergency Department,  
University Hospital  
Lewisham, Lewisham High  
Street, London SE13 6LH,  
UK  
(amhuggan@hotmail.com)

Accepted 27 April 2000

Table 1 Time from onset of symptoms to presentation

Diagnosis	≤6 h	>6≤24 h	>24 h	Total
Definite MI	39	7	4	50
No MI	56	11	14	81
Uncertain	69	21	6	96
Total	164	39	24	227

insufficient blood, in four there was no initial electrocardiogram in the hospital records, and in 62 the records could not be found.

#### RETROSPECTIVE DIAGNOSIS

The hospital notes were examined after the completion of investigations including coronary angiography where indicated and the patients were placed into three groups (table 1). A group (n = 50) with “definite acute myocardial infarction” was defined by the presence of two or more of the following<sup>1</sup>: (1) a history of typical chest pain; (2) serial electrocardiograms showing evolutionary changes; (3) serial CK values rising above twice the upper limit of normal. The evolutionary electrocardiographic changes were ST segment elevation, followed by new Q waves and T wave inversion, or stable T wave changes with or without prior ST segment elevation. These patients had a mean age 65 years, 22 of 50 (44%) were female and 39 of 50 (78%) presented before six hours after pain onset.

A group, (n = 81) with “no myocardial infarction” was defined by (1) insufficient criteria for the diagnosis of infarction and; (2) the presence of a probable alternative cause for pain, for example chest infection. These were mean age 61 years, 27 of 81 (33%) were female and 56 (69%) presented before six hours after pain onset.

The third “uncertain” group (n = 96) was defined by exclusion and was by its nature heterogeneous. Some patients had evidence of ischaemic heart disease, for example a past history of infarction, coronary angioplasty or bypass grafting and five had unstable angina on the basis of chest pain and ST depression on the electrocardiogram. Other patients in the “uncertain” group had no such evidence.

#### INITIAL ELECTROCARDIOGRAM

The initial electrocardiogram was considered diagnostic for myocardial infarction if there was ST segment elevation of 2 mm or more in two contiguous chest leads, or ST segment elevation of 1 mm or more in two contiguous limb leads. Left bundle branch block was not considered as diagnostic for myocardial infarction.

#### ANALYSIS OF SAMPLES

The doctor who saw the patient noted the time from onset of the symptoms to the time the blood sample was taken. Venous blood was taken for immediate total CK analysis and then frozen for later analysis of troponin T, myoglobin, CKMB activity and CKMB mass. These results were not available at the time the patient attended or when the retrospective diagnosis was made. An unspecified and unselected number did not have the required sam-

ple taken. The blood samples from 6 of the 50 patients with “definite myocardial infarction” and 5 of 81 with “no myocardial infarction” were sufficient for only four of five biochemical tests.

The troponin T was assayed on an ES 300 analyser (Boehringer Mannheim, Lewes, Sussex), and myoglobin on a Behring nephelometer. Creatine kinase total and CKMB activity were assayed on a Hitachi 911 (Boehringer Mannheim, Lewes, Sussex). The CKMB mass was assayed on a Behring Opus Immunoassay system initially (the first 184 samples analysed) and later in the study on a CIBA Corning ACS 180. The cut off values were those recommended by the manufacturers: troponin T 0.1 ng/ml; myoglobin 90 ng/ml; total CK 170 U/l women, 190 U/l men; CKMB activity 24 U/l; CKMB mass 5 ng/ml (Behring) then 7.5ng/ml (CIBA Corning).

#### STATISTICS

The sensitivity, specificity, positive and negative predictive values for the diagnosis of myocardial infarction, including 95% confidence intervals, were calculated for each biochemical marker, based only on the 131 patients with “definite myocardial infarction” and “no myocardial infarction”. Results were calculated separately for the 95 patients presenting before six hours. The 96 patients in the “uncertain” group were those in whom a diagnosis could not be made and these were analysed separately.

#### Results

##### SENSITIVITY, SPECIFICITY, POSITIVE AND NEGATIVE PREDICTIVE VALUES

The results in the whole patient population are given in table 2 and in the patients presenting before six hours in table 3. For the patients presenting within six hours of the onset of pain the sensitivity of the initial electrocardiogram was 74% while the biochemical markers ranged between only 23 and 44%. The specificities were 98% for the electrocardiogram and 82 to 91% for the biochemical markers.

A false positive electrocardiogram occurred in one patient with pericarditis who had ST elevation meeting the criteria for myocardial infarction. There were eight false positives for troponin T as follows: (1) status epilepticus, (2) collapse and atrial flutter, (3) ST depression, but serial CK normal, (4) dizzy after taking Ecstasy, (5) loss of consciousness, on floor? overdose, (6) viral illness, (7) chest pain for four days but no myocardial infarction, (8) vague pain three days previously, paced rhythm. Some of these could have had unstable angina or even atypical infarction. There were 11 false positives for myoglobin, three in common with troponin T: (1) supraventricular tachycardia, (2) chest trauma, (3) brain tumour, (4) chronic obstructive airways disease, old myocardial infarction, (5) left ventricular failure, (6) ST segment depression, but serial CK normal, (7) fall, (8) road traffic accident, (9) loss of consciousness? overdose, (10) chest infection, (11) vague pain three days previously, paced rhythm.

Table 2 Sensitivity, specificity, positive and negative predictive values for all patients (0–168 h) (95% confidence intervals given in parentheses)

Test	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
ECG	70 (57, 83)	99*	97*	84 (77, 92)
Troponin T	40 (26, 54)	90 (84, 97)	71 (55, 88)	71 (62, 80)
Myoglobin	44 (30, 58)	86 (79, 94)	67 (51, 83)	71 (62, 80)
Total CK	40 (26, 54)	86 (79, 94)	65 (48, 81)	70 (61, 79)
CKMB activity	33 (20, 47)	90 (84, 97)	67 (48, 86)	70 (61, 78)
CKMB mass	52 (38, 67)	88 (81, 95)	74 (59, 88)	76 (67, 85)

\*Using the standard formula for confidence interval analysis it was not possible to calculate the limits for such high percentages.

Table 3 Sensitivity, specificity, positive and negative predictive values at ≤ 6 hours from symptom onset (95% confidence intervals given in parentheses)

Test	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
ECG	74 (61, 88)	98*	97*	85 (76, 93)
Troponin T	26 (12, 39)	91 (84, 99)	67 (43, 91)	64 (53, 74)
Myoglobin	36 (21, 51)	84 (74, 94)	61 (41, 81)	65 (54, 76)
Total CK	23 (10, 36)	82 (72, 92)	47 (25, 70)	61 (50, 72)
CKMB activity	24 (10, 37)	86 (77, 95)	53 (29, 77)	62 (52, 73)
CKMB mass	44 (28, 61)	85 (76, 95)	67 (48, 86)	70 (59, 81)

\*Using the standard formula for confidence interval analysis it was not possible to calculate the limits for such high percentages.

Table 4 Patients with myocardial infarction and non-diagnostic ECGs at the time of presentation (0–24 h)

Time from pain onset	Number of patients	Initial ECG	Raised troponin T	Raised myoglobin	Raised total CK	CKMB activity	CKMB mass
≤2 h	4	4=C	1	0	0	1	0
>2≤4 h	4	4=C	1	3	0	0	2
>4≤6 h	2	1=N	0	0	0	0	1
		1=C	0	0	0	0	0
>6≤24 h	4	4=C	4	3	4	3	3 *n=3

\*n = indicates where the number of patients with a result available is fewer than the number of patients in that group. C = ST depression, T wave inversion or ST elevation insufficient to be diagnostic. N = normal.

PATIENTS WITH MYOCARDIAL INFARCTION AND NON-DIAGNOSTIC ELECTROCARDIOGRAMS AT THE TIME OF PRESENTATION (0–24 HOURS)

Ten of 39 (26%) patients presenting in the first six hours with “definite myocardial infarction” did not have a diagnostic electrocardiogram (table 4), but in only one was the electrocardiogram completely normal. In the other nine, there were minor ST segment or T wave changes. None of these had a raised total CK, but the other biochemical markers were raised in seven of the patients as follows: troponin T n=2, myoglobin n=3, CKMB activity n=1, CKMB mass n=3. Two patients had two raised markers and five patients had one raised marker.

PATIENTS CATEGORISED AS “UNCERTAIN”

A similar proportion of patients in the no myocardial infarction and uncertain groups had raised biochemical markers (table 5). Of the five patients with unstable angina, CKMB mass was raised in one patient; all of the other markers were within the normal range.

Table 5 The relative percentages of raised markers in the uncertain group compared with the no MI group (95% confidence intervals in parentheses)

	Troponin T (%)	Myoglobin (%)	Total CK (%)	CKMB activity (%)	CKMB mass (%)
No MI (n=81)	10 (3, 16)	14 (6, 21)	14 (6, 21)	10 (3, 16)	12 (5, 19) *n=76
Uncertain (n=91)	10 (4, 16)	8 (2, 13)	8 (2, 13) *n=90	11 (5, 17)	15 (8, 23) *n=84

\*n = indicates where the number of patients with a result available is fewer than the number of patients in that group.

Discussion

One of the main priorities after acute myocardial infarction is to decide on the need for thrombolysis. This study shows that the initial electrocardiogram was more sensitive than any of the markers for detecting myocardial infarction in the first six hours.

For those patients with myocardial infarction who did not have a diagnostic electrocardiogram, the biochemical markers performed well in the four patients who presented more than six hours from symptom onset. However, thrombolysis is less effective beyond six hours after the onset of pain and remains indicated solely on acute electrocardiographic changes, with no proven benefit based on biochemical markers alone.<sup>17</sup>

When the decision to discharge a patient depends on the exclusion of myocardial infarction, the negative predictive value of a test is also important. The negative predictive values of all of the markers in the first six hours were too low to be useful for exclusion of myocardial infarction. It is important to remember that if the level of the markers is below the reference range, this does not exclude myocardial ischaemia. The negative predictive value of the electrocardiogram in the first six hours was 85%. Ten patients with acute myocardial infarction presented in the first six hours without diagnostic changes on the initial electrocardiogram; 9 of 10 had ST segment changes. One had a completely normal electrocardiogram. However, even a normal initial electrocardiogram does not exclude myocardial ischaemia, for which exercise testing, myocardial perfusion or coronary angiography may be necessary. The decision to admit a patient with chest pain must ultimately be based on clinical factors including the evolution of pain and the presence of risk factors for coronary disease. Biochemical markers particularly troponin T can, however, help identify such patients at high risk of infarction and death for whom earlier and more invasive investigation is indicated.<sup>13</sup>

The biochemical markers should be measured during their “diagnostic window”. In this study, the mean time from symptom onset for patients with definite myocardial infarction who presented within the first six hours was only 1.95 hours. This is before the “diagnostic window” of most of the biochemical markers. However, our patient population reflected reality in any emergency department. One longitudinal study<sup>18</sup> found troponin T to have a sensitivity of 100% during a “diagnostic window” between 10.5 to 140 hours after the onset of symptoms. However, keeping patients until more than 10 hours from the onset of symptoms may not be practical in many

emergency departments. Some groups have proposed serial sampling.<sup>9 19-22</sup> For example, if the myoglobin level does not double within two hours from presentation and is normal at six hours, the negative predictive value is 97%.<sup>23</sup>

Although bedside testing kits or near patient testing offers the possibility of a result that is rapidly available, care has to be taken in sample handling, timing and interpretation of the troponin T rapid assay system outside the laboratory.<sup>24</sup> The choice of near patient testing or laboratory testing will be partly influenced by the volume of tests performed.<sup>25</sup> The cost/benefit ratio of using cardiac markers is very difficult to calculate. It depends on the clinical characteristics of patients it is used on in an individual department, and whether serial testing is used. Serial testing could be expensive particularly if it is used freely for patients where there is a low index of suspicion of myocardial infarction. Some patients with myocardial infarction and non-diagnostic electrocardiograms could be detected by applying these tests before the “diagnostic window”. However, any negative tests would need to be repeated, so immediately increasing the cost. The emergency department would be likely to bear the costs of serial testing in terms of assays, staff time and cubicle space but would be unlikely to benefit from the saving made in avoiding an admission to hospital.

#### LIMITATIONS OF THE STUDY

The setting of the study in the emergency department meant that in a large number of the patients the diagnosis of myocardial infarction could not be confidently confirmed or excluded. Of those patients who were discharged home, some were assigned to the “no myocardial infarction” group and some were “uncertain”. It was felt that the patients with “uncertain” diagnosis could not be assigned to a true or false positive or negative group and so were not included in the analysis; it is therefore difficult to know the “true” performance of the markers. Definitive diagnoses have been possible in studies set in coronary care where serial electrocardiograms and enzymes and other tests are available.

There were relatively few patients who presented greater than six hours from symptom onset, (see table 1) in a wide time interval. Calculation of test performance characteristics in this time interval resulted in wide confidence intervals and was thought not to be useful. However, they were included in an overall assessment of the tests in all patients (table 2). The patients in this time interval who had positive markers and non-diagnostic electrocardiograms are recorded in table 4.

The diagnosis of infarction on WHO criteria involves serial CK values and serial electrocardiogram changes, introducing potential bias of the results towards these measurements. However, we calculated sensitivity of CK and electrocardiogram at presentation, whereas the diagnosis depended on serial values. It is of note that the sensitivity for CK was no better than the other biochemical markers.

#### Conclusion

In the first six hours after symptom onset, the electrocardiogram was more sensitive than biochemical markers for the detection of acute myocardial infarction. Biochemical markers detected a small number of patients with myocardial infarction and non-diagnostic electrocardiograms presenting later than six hours after the onset of chest pain. The negative predictive value of the biochemical markers was too low for a single sample to be useful in excluding myocardial infarction in the first six hours from onset of symptoms.

We would like to thank Dr M Ooi for her help with the study and Nigel Smeeton of Department of Public Health Medicine Guy's Hospital for statistical advice. Thanks also to Sue Arnold and Tracey Dawes for their help in obtaining case notes.

#### Contributors

Anne-Marie Huggon participated in the design and the execution of the study, tabulated the data, performed the statistical analysis, and wrote the draft and final paper. John Chambers participated in the design of the study, made the retrospective diagnoses, supervised some retrospective diagnoses by Anne-Marie Huggon and May Ooi, and edited the draft and final paper. Nadeem Nayeem participated in the design and execution of the study, and advised on the draft paper. Peter Tutt participated in the design of the study, performed the sample analysis, tabulated the laboratory data and advised on the draft paper. Martin Crook participated in the design and execution of the study and advised on the draft paper. Professor Swaminathan initiated the study, participated in the design and execution of the study, and edited the draft paper.

- 1 World Health Organisation. *WHO criteria for the diagnosis of acute myocardial infarction. Proposal for the multinational monitoring of trends and determinants of cardiovascular disease.* Geneva: Cardiovascular diseases Unit, WHO, 1981
- 2 Bakker AJ, Koelmeij MJ, Gorgels JP, et al. Troponin T and myoglobin at admission: value of early diagnosis of acute myocardial infarction. *Eur Heart J* 1994;15:45-53.
- 3 Collinson PO, Moseley D, Stubbs PJ, et al. Troponin T for the differential diagnosis of ischaemic myocardial damage. *Ann Clin Biochem* 1993;30:11-16.
- 4 Brogan GX Jr, Friedman S, McCuskey C, et al. Evaluation of a new rapid quantitative immunoassay for serum myoglobin versus CK-MB for ruling out acute myocardial infarction in the emergency department. *Ann Emerg Med* 1994;24:665-71.
- 5 Mair J, Artner-Dworzak E, Lechleitner P, et al. Early diagnosis of acute myocardial infarction by a newly developed rapid immunoturbidimetric assay for myoglobin. *Br Heart J* 1992;68:462-8.
- 6 Antman EM, Grudzien C, Sacks DB. Evaluation of a rapid bedside assay for detection of serum cardiac troponin T. *JAMA* 1995;273:1279-82.
- 7 Mach F, Lovis C, Chevrolet JC, et al. Rapid bedside whole blood cardiospecific troponin T immunoassay for the diagnosis of acute myocardial infarction. *Am J Cardiol* 1995; 75:842-5.
- 8 Lee HS, Cross SJ, Garthwaite P, et al. Comparison of the value of novel rapid measurement of myoglobin, creatine kinase, and creatine kinase-MB with the electrocardiogram for the diagnosis of acute myocardial infarction. *Br Heart J* 1994;71:311-15.
- 9 Hamm CW, Goldmann BU, Heeschen C, et al. Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med* 1997;337:1648-53.
- 10 Hamm CW, Ravkilde J, Gerhardt W, et al. The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;327:146-50.
- 11 Christenson RH, Azzazy HM. Biochemical markers of the acute coronary syndromes. *Clin Chem* 1998;44B:1855-64.
- 12 Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischaemia. *N Engl J Med* 1996;335:1333-41.
- 13 Lindahl B, Venge P, Wallentin L. Relation between troponin T and the risk of subsequent cardiac events in unstable coronary artery disease. *Circulation* 1996;93:1651-7.
- 14 Stubbs P, Collinson P, Moseley D, et al. Prospective study of the role of cardiac troponin T in patients admitted with unstable angina. *BMJ* 1996;313:262-4.
- 15 de Winter RJ, Koster RW, Sturk A, et al. Value of myoglobin, troponin T, and CK-MB mass in ruling out an acute myocardial infarction in the emergency room. *Circulation* 1995; 92:3401-7.
- 16 Hedges JR. The role of CK-MB in chest pain decision-making. *J Acad Emerg Med* 1995;12:101-6.
- 17 Fibrinolytic Therapy Trialists' Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311-22.
- 18 Katus HA, Remppis A, Neumann FJ, et al. Diagnostic efficiency of troponin T measurements in acute myocardial infarction. *Circulation* 1991;83:902-12.

- 19 Gibler WB, Young GP, Hedges JR, *et al.* Acute myocardial infarction in chest pain patients with nondiagnostic ECGs: serial CK-MB sampling in the emergency department. *Ann Emerg Med* 1992;**21**:504–11.
- 20 Johnston JD, Collinson PO, Rosalki SB. MIDAS: Myocardial infarct diagnosis by assessment of slope. *Ann Clin Biochem* 1993;**30**:407–9.
- 21 Hingorani AD, O'Hanlon S, Halloran SP, *et al.* Evaluation of a paired creatine kinase test for the diagnosis of acute myocardial infarction in patients with a non-diagnostic electrocardiogram. *J Accid Emerg Med* 1997;**14**:134–8.
- 22 Collinson PO, Stubbs PJ. Early 'rule-in' diagnosis of acute myocardial infarction 4 h post admission for rapid risk stratification by creatine kinase increment (creatine kinase change). *Ann Clin Biochem* 1996;**33**:308–13.
- 23 Tucker JF, Collins RA, Anderson AJ, *et al.* Value of serial myoglobin levels in the early diagnosis of patients admitted for acute myocardial infarction. *Ann Emerg Med* 1994;**24**:704–8.
- 24 Tarpey A, Leonard M, Pennycook M. Troponin T in patients with cardiac chest pain. [Letter]. *J Accid Emerg Med* 1997;**14**:200–1.
- 25 Brogan GX Jr, Bock JL. Cardiac marker point-of-care testing in the emergency department and cardiac care unit. *Clin Chem* 1998;**44B**:1865–9.