Timed sequential analysis of creatine kinase in the diagnosis of myocardial infarction in patients over 65 years of age

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Abstract

Aim—To assess the value of timed sequential analysis of creatine kinase (CK) activity for the early diagnosis of acute myocardial infarction (AMI) in patients over 65 years of age.

Method—Samples were collected on admission and eight to 12 hours later from 156 patients over 65 years of age. Routine cardiac enzyme activities were determined and serial electrocardiograms (ECGs) recorded. The predictive value of timed samples for CK activity, standard cardiac enzyme activities, and ECGs was compared with the final diagnosis on discharge.

Results—Forty one patients had a discharge diagnosis of AMI, 83 of angina pectoris, and the remaining 32 patients had other diagnoses. Electrocardiograms had a sensitivity of 55% and a specificity of 96%, giving a predictive value of 86% for a negative and 84% for a positive ECG. Standard cardiac enzymes had a predictive value of 99% for a negative result but only 68% for a positive result. The logarithm of the rate of change of CK activity had a predictive value of 97% for a negative result and 95% for a positive result.

Conclusion—This study has shown that slope analysis of CK activity can be used for the early diagnosis of AMI in patients over 65 years of age, and that this was not affected by the presence of possible confounding diagnoses.

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The rapid confirmation of a diagnosis of acute myocardial infarction (AMI) is desirable for the efficient clinical management of patients and resources. Standard cardiac enzymes collected over three days after admission to hospital provide a retrospective diagnosis but do not influence immediate patient management.

Measurement of timed sequential creatine kinase (CK) activity in serum has been proposed as one method for early confirmation of a diagnosis of AMI.¹⁻⁶ Like other tests for the diagnosis of AMI, this test has been evaluated in patients admitted to a coronary care unit,^{1,2} however, only small numbers of patients were included in these early studies. Other investigators who studied slightly larger groups of patients found that the test gave false negative results and could not be used to exclude

reliably a diagnosis of AMI.^{7,8} Although a coronary care unit provides a well controlled environment in which to conduct the evaluation of a test requiring carefully timed samples, the populations studied so far have been preselected with a high incidence of AMI, up to 55%,⁹ and other possible confounding diagnoses may have been excluded. As a result, the test's performance may not be as accurate when evaluated in unselected elderly subjects presenting with acute chest pain. This group of subjects may also have other potential confounding diagnoses not found in younger age groups.

The predictive value of a test improves with selection of the population studied and collection of samples under well controlled conditions. We therefore investigated the value of this test in patients over 65 years of age admitted to a busy district general hospital with acute chest pain.

Over five months, 156 patients (88 women) presenting with acute chest pain were studied. All were over 65 years of age. The time of onset of chest pain in relation to the time of admission was recorded. Three serial electrocardiograms (ECGs) were collected, standard cardiac enzyme activities comprising total CK and lactate dehydrogenase (LDH) were determined on the three days following admission, and the results recorded. The final diagnosis at the time of discharge was also recorded.

The study was approved by the District Ethics Committee and all patients gave informed consent.

Methods

Blood samples for timed CK analysis were collected on admission and eight to 12 hours later. All blood samples for cardiac enzyme analysis were centrifuged, the serum separated and analysed at the time received to simulate the provision of a routine clinical service.

Creatine kinase activity was measured at 37°C with a Beckman CX7 analyser (Beckman Instruments, High Wycombe, UK) using commercially available reagents (Randox, Dublin, Republic of Ireland). The between batch imprecision of this method was 4.1% at 147 IU/l and 2.3% at 467 IU/l. The laboratory upper reference range for CK was 195 IU/l for men and 170 IU/l for women.

Lactate dehydrogenase activity was measured using the same instrument and reagents from the same supplier. The between batch imprecision of this method was 1.6% at 354

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Table 1 Time from onset of chest pain until admission to hospital*

Time from onset of chest pain	AMI	Other causes of chest pain
Less than six hours	27	44
Six to 12 hours	6	21
More than 12 hours	4	30

*Significantly less ($p < 0.001$) for patients with myocardial infarction compared with the other diagnostic groups.

Table 2 Discharge diagnosis of patients over 65 years of age following admission with acute chest pain

Diagnostic category	Number of patients
Angina pectoris	63
Myocardial infarction	41
Gastrointestinal disease	11
reflux oesophagitis	5
hiatus hernia	2
gastritis	1
dysphagia	1
oesophageal ulceration	1
gastrointestinal haemorrhage	1
Angina pectoris plus dysrhythmia	10
Angina pectoris plus cardiac failure	10
Musculoskeletal pain	5
Pneumonia	4
Non-specific chest pain	4
Pulmonary emboli	2
Hypotension	2
Hypertension	2
Cerebrovascular accident	1
Micturition syncope	1
Adenocarcinoma with metastases	1

IU/l and 1.0% at 923 IU/l. The laboratory reference range for LDH was 230–460 IU/l.

The logarithm of the rate of change in CK activity was calculated from the change in CK activity between the admission sample and the second sample collected eight to 12 hours later, as described by Collinson *et al.*¹ The logarithm of the change in CK activity was only calculated when one of the two CK values was greater than 170 IU/l. If neither of the CK values in the timed samples were greater

than 170 IU/l, the patient was classified as having a normal timed CK result. A logarithm of the rate of change of CK activity/hour over 0.015 was considered to be a positive result indicative of AMI.¹

The electrocardiographic criteria used for the diagnosis of AMI were ST elevation, T wave inversion, and the development of Q waves.

Distribution of results within patient groups was compared using the Wilcoxon sign rank test, means were compared using the Student's *t* test, and the distribution of results between groups compared using the χ^2 test.

Results

A final diagnosis of AMI was made in 41 (26%; 18 women) of the 156 patients studied. The mean (SEM) age of those who sustained an AMI was 76 (6.5) years compared with 75.5 (7.2) years ($p = 0.611$) for those who had not.

Patients had difficulty recalling the exact time of onset chest pain. Estimation of the duration of chest pain before admission was only possible for 132 patients. Most of the patients who had sustained an AMI presented less than six hours after the onset of chest pain compared with more than six hours for those who had not ($p < 0.001$) (table 1).

The final diagnosis recorded at discharge was made on the basis of clinical presentation, clinical course, CK and LDH values during the three days following admission, and serial ECGs. Myocardial infarction was the second most frequent diagnosis with angina pectoris the most common (table 2). Other diagnoses included pneumonia, musculoskeletal pain, and gastrointestinal causes of lower chest pain (table 2).

Peak CK activity in samples from patients who had sustained an infarction overlapped considerably with that in those who had another cause of chest pain (fig 1). The sensitivity of the peak CK value for the diagnosis of AMI was 97.5% and the specificity 83%, giving a predictive value of 99% for the exclusion but only 68% for a diagnosis of AMI.

Peak LDH activity contributed little to the diagnosis. The sensitivity of a peak LDH value greater than the reference range for AMI was 100%, but the specificity was only 47.8%. This gave a predictive value of 100% for a normal result but of only 40% for a raised LDH result.

When the admission ECGs were examined, there were no signs of AMI in 17 of the 41 patients later diagnosed as having sustained an AMI (fig 2). The sensitivity of the admission ECG, therefore, was only 55%, although the specificity was 96%. The predictive value of a normal admission ECG for the exclusion of AMI was 86% and was 84% for an ECG with changes consistent with AMI.

Calculation of the logarithm of the rate of change of serum CK activity between the samples collected on admission and eight to 12 hours later clearly separated the patients whose discharge diagnosis was AMI from

Figure 1 Peak serum CK activity in samples collected during hospital stay.

Figure 2 Number of patients with changes on admission ECG diagnosed as having an AMI compared with those with other causes of chest pain.

those whose chest pain resulted from other causes. There were three apparently false negative results. One because the patient had infarcted following admission to hospital; this occurred after both timed CK samples had been collected.

There were two false positive results. On examination of the case notes, these patients probably sustained an AMI, a diagnosis based on standard ECG and cardiac enzyme results, and clinical history. If the false positive and negative results were included then the timed samples for CK analysis had a sensitivity of 93% and a specificity of 98% for the detection

of AMI. This resulted in a predictive value of 97% for excluding and 95% for confirming a diagnosis of AMI, with the misclassification of only five (3%) patients within 12 hours of admission. If the three misclassified patients were excluded, the predictive value of a negative timed CK result was 99% and that of a positive result was 100%.

Discussion

This study has shown that the collection of two timed samples for CK analysis and the calculation of the rate of change of CK activity/hour can be used to confirm a diagnosis of AMI within 12 hours of admission.

The differences in the predictive value of the timed CK analysis between this study and the others may be explained by differences in the illnesses present in the population studied. The small number of coronary care unit patients ($n = 30$) originally studied by Collinson *et al*¹ may explain why they achieved better predictive values. The larger number of coronary care unit patients ($n = 101$) studied by Vijan *et al*⁷ may explain the lower predictive value of a negative result.

All patients over 65 years of age presenting with acute chest pain were eligible for inclusion in this study. Therefore, more patients were studied ($n = 156$) and a smaller proportion sustained an AMI (26% compared with 53% in the study by Collinson *et al*¹ and 43% in that of Vijan *et al*⁷). A larger number of patients had confounding diagnoses ($n = 115$) and, therefore, the results of this study may represent the performance of timed CK analysis in routine clinical practice more accurately.

Timed CK samples do not confirm the diagnosis of AMI sufficiently rapidly to influence treatment with thrombolytic agents. Confirmation of the diagnosis within 12 hours of admission, however, will influence subsequent patient management and could lead to more efficient use of beds in coronary care units.⁵

Determination of the concentrations of Troponin t, myoglobin, and the MM and MB isoenzymes of CK (CK-MM and CK-MB, respectively) has been proposed as a method of confirming a diagnosis of AMI.⁹⁻¹³ None of the above tests are suitable for the early diagnosis of AMI and, therefore, do not influence the decision to administer thrombolytic treatment. Difficulties with these tests include non-specificity and the need for dedicated equipment. Accurate timing of the collection of single samples in relation to the onset of chest pain for the measurement of the CK-MB concentration, and CK-MM and CK-MB isoforms may be difficult. In this study patients found it difficult to recall exactly the onset of their chest pain.

Current evidence suggests that thrombolytic treatment is most effective when administered as soon as possible after the onset of chest pain, therefore, any delay could impair patient outcome. Laboratory tests for AMI will probably continue to be used to confirm diagnosis and for subsequent patient

Figure 3 Slope change in CK activity/hour in patients with AMI compared with those with other causes of chest pain. The black bar represents patients whose CK activity did not rise above 170 IU/l between the first two samples and whose CK slope activity was not analysed.

management, but will not influence the decision to administer thrombolytic treatment. Timed sequential analysis of CK activity has one disadvantage in that two samples are required; however, this test is more specific, does not need specialised equipment, and may be provided on a 24 hour basis. The false positive and false negative results produced by timed CK analysis support the recommendation of Collinson *et al*¹ that this test should be used in association with a confirmatory test, such as CK-MB analysis. Earlier confirmation can be achieved if slope analysis is used in association with one of the other sensitive early tests, such as determination of the myoglobin concentration or analysis of the CK-MM or CK-MB isoforms.

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