ORIGINAL ARTICLES

Evaluation of a paired creatine kinase test for the diagnosis of acute myocardial infarction in patients with a non-diagnostic electrocardiogram

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Abstract

Objective—The rate of rise of total plasma creatine kinase (CK) activity in the first 12 hours from presentation can be used to diagnose acute myocardial infarction. The aim of this study was to evaluate the performance of an abbreviated form of this test in the diagnosis of acute myocardial infarction in patients in whom the initial electrocardiogram was inconclusive.

Methods—Using a protocol that requires only two CK measurements (separated by four hours) to estimate the rate of rise, the performance of the test was investigated using data accrued from 345 consecutive admissions with suspected acute myocardial infarction.

Results—A CK increment (Δ CK) of $> 20\%$ in the first four hours from presentation had a diagnostic sensitivity of 84.4% (95% confidence interval 75.5 to 93.3), specificity of 85.8% (80.1 to 91.5), positive predictive accuracy of 73.0% (62.9 to 83.1), and negative predictive accuracy of 92.4% (87.9 to 96.9). Using more stringent diagnostic criteria (Δ CK $> 20\%$ and 4 h CK value > 160 U/litre) resulted in an increase in specificity and positive predictive accuracy to 96.5% and 91.1% respectively, and a small reduction in sensitivity and negative predictive accuracy to 79.7% and 91.3%, respectively. 94% of all infarcts were correctly identified using the ECG as the initial investigation and paired CK measurement as an additional test when this was inconclusive. In the 44 patients who received thrombolysis on the basis of an early biochemical diagnosis of acute myocardial infarction, the median time delay (75th centile) to thrombolysis was 10.75 (SD 15.0) hours.

Conclusions—When the presenting ECG is non-diagnostic, sequential sampling of cardiac enzymes is a feasible alternative in the early diagnosis of patients with suspected myocardial infarction, even in the emergency setting. Further studies are required to define the optimal biochemi-

cal assay and timed sampling protocol.

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The presenting electrocardiogram (ECG) is a specific but relatively insensitive method for diagnosing acute myocardial infarction.¹⁻³ In the presence of regional ST segment elevation, acute myocardial infarction can be diagnosed with a high degree of certainty. However, the presenting ECG is normal or inconclusive in a significant proportion of individuals with acute myocardial infarction, and additional tests—such as serial electrocardiography and biochemical assays which measure plasma markers of myocardial necrosis—are required to confirm or exclude the diagnosis. Typically, these investigations provide retrospective information up to 72 hours after the onset of symptoms. A simple accurate test, which is diagnostic soon after coronary occlusion and readily available around the clock, might guide the early management of patients with chest pain and allow clinical trials to be undertaken in which early therapeutic interventions in patients with biochemical evidence of acute myocardial infarction (but non-diagnostic ECGs) can be evaluated.

Previous validation studies have shown that the rate of rise of total plasma creatine kinase (CK) activity in the first 12 hours after admission can be used to diagnose acute myocardial infarction.⁴⁻⁶ If serial CK values are plotted as a log CK activity/time graph, a gradient (or log slope) of > 0.015 can be taken as diagnostic.⁵ The percentage increase in CK activity in two samples separated by four hours (the first taken at admission) gives an estimate of the log slope, a 20% increment in CK activity at four hours corresponding to a log slope value of 0.02. Using this simplified protocol, which incorporates an assay available in most hospitals, a prompt biochemical diagnosis of acute myocardial infarction is now possible. We report on the implementation of this test in patients with suspected acute myocardial infarction and inconclusive ECGs.

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Methods

PATIENTS

The study population comprised 345 patients seen consecutively in the emergency department with suspected acute myocardial infarction in the nine months following the provision of an emergency CK service. Cases (identified retrospectively from a database of cardiac enzyme requests held in the biochemistry department) included patients with diagnostic ECGs at presentation (see below) in whom aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) were used to confirm acute myocardial infarction, as well as those patients with normal or inconclusive ECGs in whom AST and LDH values were the primary means of diagnosing or excluding infarction. Patients with diagnostic ECGs at presentation were managed conventionally with intravenous analgesia, aspirin, and thrombolysis (unless contraindicated). For those patients without diagnostic ECG changes admitted during the study period, a paired plasma CK measurement was also offered: total CK activity was measured at presentation (0h) and after four hours (4h) to determine the percentage CK change ($CK_{4h} - CK_{0h} / CK_{0h} \times 100\%$). A percentage CK increment (ΔCK) of $> 20\%$ was taken to be diagnostic and, although this result was available immediately, the final decision to administer or withhold thrombolysis was left to individual clinicians.

Clinical details were obtained by review of the case notes. For patients with multiple admission episodes during the study period, details of the index presentation alone were recorded. The admission ECG was categorised as "diagnostic" of acute myocardial infarction if it showed regional ST elevation of ≥ 1 mm in two limb leads or ≥ 2 mm in two precordial leads. "Non-diagnostic" ECGs (the remainder) were categorised as "normal", "left bundle branch block", "ST depression", "T wave changes" (in the absence of other abnormalities), or "rhythm disturbances". The activities of total CK (at 0 and 4 hours), AST (at 24, 48, and 72 hours) and LDH1 and LDH2 (at 72 hours), together with details of the ECGs from the second and third days of admission, were documented. A final diagnosis of acute myocardial infarction was made if one or more of the following were present in association with a history of prolonged chest pain: the development of new pathological Q waves on serial ECGs, an increase in plasma AST to more than twice the upper limit of normal (with a rise and fall), a rise in plasma LDH at 72 hours (with a characteristic isoenzyme profile), or necropsy evidence of acute myocardial infarction.

ANALYSES

Blood samples for total plasma CK activity were drawn into lithium-heparin tubes. Paired samples were analysed together immediately on receipt of the second sample to optimise quality control. All measurements were performed by a medical laboratory scientific officer (MLSO). CK and AST were both measured at 37°C on an Olympus AU510

Table 1 Presenting ECGs in 342 consecutive cases of suspected myocardial infarction

Diagnostic	116
Non-diagnostic	226
T wave inversion	71
Q waves	44
Normal	41
ST depression	32
Left bundle branch block	17
* Rhythm disturbance	19
† Other	2
Total	342

* Atrial fibrillation 8; right bundle branch block 4; supraventricular tachycardia 3; sinus bradycardia 1; 2:1 atrio-ventricular block 1; ventricular tachycardia 1; paced rhythm 1.

† Left ventricular hypertrophy 1; poor R wave progression 1.

automated analyser (Olympus, Eastleigh, United Kingdom). Total CK measurement used a hexokinase/glucose-6-phosphate dehydrogenase linked N-acetylcysteine activated method and AST measurement used Scandinavian recommended conditions. Total CK activity (normal < 160 U/litre) and ΔCK were reported to the requesting clinician by telephone as soon as they were available. Plasma AST and LDH were measured as part of the routine laboratory service.

STATISTICS

Sensitivity and specificity, together with 95% confidence intervals (CI), and predictive values for positive and negative results, were used to assess the performance of the presenting ECG and the paired CK test.⁷⁻⁹ In patients without a final diagnosis of acute myocardial infarction, values for ΔCK of $< 20\%$ were classified as true negative (TN) and values $> 20\%$ as false positive (FP). In patients with a final diagnosis of acute myocardial infarction, values for $\Delta CK < 20\%$ were classified as false negative (FN) and $> 20\%$ as true positive (TP). Sensitivity was defined as $TP / (TP + FN)$ and specificity as $TN / (TN + FP)$. The predictive accuracy of a positive result was defined as $TP / (TP + FP)$ and that of a negative result as $TN / (TN + FN)$. Exact confidence intervals for a binomial distribution were calculated. The significance of the difference in mean ΔCK between groups was evaluated using the Mann-Whitney U test.

Results

There were 382 admission episodes among 345 patients during the study period. Admission ECGs were available in 342 subjects (259 males, 83 females), mean age 65.7 (SD 12.8) years. Acute myocardial infarction was eventually confirmed in 197 and excluded in 145. Three hundred and seven subjects presented with chest pain, 14 with pulmonary oedema, 13 with syncope, four with palpitations, two with epigastric pain, one was referred by his general practitioner for evaluation of an abnormal ECG, and one presented with a cardiac arrest.

The presenting ECG was diagnostic in 116/342 patients (34%) and inconclusive in 226/342 (66%) (table 1). Acute myocardial infarction was confirmed in all 116 patients with a diagnostic presenting ECG and in a further 81 out of 226 subjects with non-diagnostic ECGs, giving a sensitivity of 58.9% and a specificity of

Table 2 Performance of the paired CK test in 205 patients with suspected acute myocardial infarction (MI) and non-diagnostic ECGs (criterion for a positive test, $\Delta CK > 20\%$)

	MI	No MI	Total
Test positive	54	20	74
Test negative	10	121	131
Total	64	141	205

100% for the presenting ECG. The predictive accuracy of a negative ECG was 64.2% and that of a positive ECG, 100%.

Of 226 patients with inconclusive ECGs, a paired CK test was requested in 205. acute myocardial infarction was eventually confirmed in 64/205 patients and excluded in 141/205 (table 2). Of the remaining 21 patients, 17 were subsequently shown to have suffered acute myocardial infarction. ΔCK was $> 20\%$ in 74/205 (54 TP, 20 FP) and $< 20\%$ in 131/205 (121 TN, 10 FN). The paired CK test using these criteria had a diagnostic sensitivity of 84.4% (95% CI 75.5 to 93.3) and specificity of 85.8% (80.1 to 91.5). The predictive accuracy of a positive test was 73.0% (62.9 to 83.1) and that of a negative test 92.4% (87.9 to 96.9). The median (interquartile range) ΔCK was 203.0% (62.4 to 368.1) in the 64 patients with a final diagnosis of acute myocardial infarction and -7.5% (-15.6 to 4.3) in the 141 subjects in whom infarction was excluded ($P < 0.0001$).

The data were re analysed using a CK_{4h} value > 160 U/litre as an additional criterion for a positive test result. This produced 51 TP, 5 FP, 136 TN, and 13 FN test results among the 205 paired CK requests (table 3). Sensitivity, specificity, and positive and negative predictive accuracy were 79.7% (69.8 to 89.6), 96.5% (93.5 to 99.5), 91.1% (83.6 to 98.5), and 91.3% (86.8 to 95.8), respectively.

Using the initial diagnostic criteria ($\Delta CK > 20\%$) the test was falsely positive in 20 patients. Only one of these patients ($\Delta CK = 66.5\%$) was given thrombolytic treatment. This patient had received an intramuscular injection before admission. In 15 of the remaining 19 subjects, absolute CK values failed to exceed the reference range for the laboratory (160 U/litre) and clinicians elected to overrule a CK increment of $> 20\%$ under

Table 3 Performance of the paired CK test in 205 patients with suspected acute myocardial infarction (MI) and non-diagnostic ECGs (criteria for a positive test, $\Delta CK > 20\%$ and $CK_{4h} > 160$ U/litre)

	MI	No MI	Total
Test positive	51	5	56
Test negative	13	136	149
Total	64	141	205

these circumstances. The CK increment was falsely negative in 10/205 measurements. In 7/10 cases, both CK values were substantially greater than 160 U/litre but there was little change in absolute values over four hours.

Of the 116 patients with a diagnostic presenting ECG, 103 received thrombolysis. Conventional contraindications excluded the remainder. The median time delay (75th centile) from symptom onset to treatment in this group was 4.0 (SD 6.75) hours; 44/205 patients with a non-diagnostic ECG received thrombolysis on the basis of $\Delta CK > 20\%$ with median time delay 10.75 (SD 15.0) hours (figure 1).

Discussion

In this study more than half (66%) of all admissions with chest pain and suspected acute myocardial infarction had inconclusive ECGs at presentation, which exceeds some previously published estimates.^{1-3,10} The reason for this difference is not clear, but a lowering of the threshold for hospital referral following the advent of thrombolytic treatment is one possible explanation. These individuals represent a large subset of admissions with chest pain and many (36% in our study) will eventually be shown to have suffered an acute infarct, emphasising the relatively low sensitivity of the ECG as a single diagnostic test. Using the paired CK test as an adjunct to the presenting ECG, 170/180 (94.4%) of acute infarcts were accurately identified in this population early after the onset of symptoms—64.4% on the basis of the presenting ECG and an additional 30% by the biochemical test.

Out of a possible 226 patients with inconclusive ECGs, the paired CK test was requested in 205, an uptake rate of 91%. Although the sensitivity, specificity, and predictive values for the CK protocol measured here compare favourably with those found for other biochemical markers,¹¹ we were unable to match the high sensitivity reported in the early evaluations of this test.^{4,5} In contrast to those studies, where timed plasma samples were stored frozen for subsequent analysis during office hours, our samples were all analysed as urgent specimens in order to provide immediate diagnostic information. It is possible that values calculated here more accurately reflect the performance of this test in an emergency. Furthermore, we studied all presentations with suspected acute myocardial infarction and non-diagnostic ECGs and not just a pre-selected group admitted to a coronary care unit in whom the prevalence of infarction may be higher. The sensitivity obtained in our study population may serve

Figure 1 Cumulative frequency plot of pain to thrombolysis times for patients diagnosed by presenting ECG ($n=103$) and by the paired CK test ($n=44$).

as a more reliable guide to the performance of the test in the routine clinical setting.

The CK increment was falsely positive in 20 subjects, of whom only one received thrombolysis. In 15 of the remaining 19 cases, absolute CK values were all < 160 U/litre (the upper limit of the normal range) and clinicians elected to disregard an increment > 20% unless one or both CK values were in excess of 160 U/litre. Previous studies have suggested that the specificity of the paired CK test can be increased by defining a positive test result as a CK increment of > 20% together with a four hour CK value in excess of the laboratory reference range.¹² When we reanalysed the data using this definition, specificity and positive predictive values increased at the expense of a small reduction in sensitivity. There were 10 false negative paired CK tests; in seven of these both 0h and 4h CK values exceeded 160 U/litre, but Δ CK was < 20%. Five of these seven subjects presented more than 10 hours after the onset of pain and it is possible that in these individuals blood samples spanned the peak of the CK rise. The value of this protocol may thus be limited in subjects presenting many hours after the onset of chest pain.

While several major mortality trials have clearly shown the benefits of thrombolysis in patients presenting with ST elevation,¹³⁻¹⁵ it is uncertain whether the benefits of treatment outweigh the risks in patients with other ECG abnormalities (with the exception of left bundle branch block). The apparent failure of thrombolysis to influence the high mortality of subjects with ST depression¹⁶ is surprising, but might be the result of a distinct pathological process operating in such patients, for example ongoing endogenous fibrinolysis and coronary recanalisation. However, since such patients have been relatively poorly represented in the major outcome studies, the failure to detect an influence of treatment may reflect diminished statistical power in the analysis of subgroups. A recent meta-analysis, which included five trials where the eligibility for thrombolysis was not dependent upon ECG changes, was unable to resolve this issue.¹⁷ Although the TIMI-IIIb trial failed to show any benefit for thrombolysis (in the form of alteplase) over and above standard anti-ischaemic and anticoagulant treatment in patients with unstable angina or non-Q wave myocardial infarction, the mortality in the placebo group in this study was low (2-3%) and the dose of alteplase used may have been suboptimal.¹⁸ In accordance with these findings, however, present guidelines suggest that thrombolytic treatment should be reserved for patients presenting with chest pain and ST segment elevation or left bundle branch block.¹⁹ To date, many of the major trials have excluded subjects without diagnostic ECG changes of infarction. Those trials with less stringent entry criteria have still not used biochemical markers to confirm acute myocardial infarction before intervention in patients in whom the ECG is non-diagnostic. Further studies are thus required to determine whether outcome can be modified by targeted revascularisation (using thrombolytics or other agents)

in those patients with very early biochemical evidence of infarction.

In our study, the decision to use thrombolysis was left to individual clinicians. As a result, 44 patients were given thrombolysis on the basis of a CK increment and these subjects provide useful data on the diagnostic delay introduced by a protocol requiring serial blood sampling. The median (75th centile) delay from symptom onset to thrombolysis in this group was 10.75 (SD 15.0) hours compared to 4.0 (6.75) hours in the 103 patients who received thrombolysis on the basis of the admission ECG. However, only two CK measurements are required with the strategy described and, with the appropriately equipped service, it should be possible to reduce the in-hospital diagnostic delay to approximately 4.5 hours. Provided that emergency call to arrival times can be reduced (in accordance with recent guidelines),¹⁹ the delay from symptom onset to biochemical diagnosis in subjects with inconclusive ECGs might be of the order of six hours, allowing early management decisions based upon the result.

Other early biochemical markers of myocardial necrosis exist (including CK mass, CK-MB isoenzyme, troponin C, troponin T, and myoglobin), but few of the newer markers have been evaluated in the context of serial measurements.^{11 20-23} The performance of single measurements is markedly dependent on time after the onset of symptoms, and receiver-operator characteristics dictate that the diagnostic blood sample for these assays be obtained some time (up to six hours or more) after the onset of symptoms. The delay associated with serial CK measurements thus compares favourably with the existing alternatives. Further studies are required to determine whether the delays introduced by serial measurements can be reduced by the use of chemical reagent strips,²⁴ or by the use of a shorter sampling interval facilitated by the use of a log CK activity/time nomogram.⁶

The ECG remains the most rapid, convenient, and specific test for acute myocardial infarction.²⁵ Biochemical tests should be viewed as an adjunct to—rather than a replacement for—the ECG, and the performance of biochemical assays is most appropriately assessed in those patients in whom the ECG is inconclusive. We have shown that paired, sequential creatine kinase measurement can be implemented round the clock in the acute clinical setting and that the analysis (even by wet chemistry methods) can be rapid enough to allow treatments based upon the result to be given within 12 hours of the onset of symptoms in most cases. A large number of additional infarcts can be identified early after the onset of chest pain using this strategy. Furthermore, in the presence of both a negative ECG and a negative CK test, acute myocardial infarction can be excluded with a high degree of certainty. The best use for such information in the clinical situation has yet to be defined. It may help in the allocation of resources such as coronary care beds and assist in prediction of future risk.^{26 27} The use of protocols of this type

in controlled clinical trials might allow the role of therapeutic interventions in patients with early biochemical evidence of acute myocardial infarction but non-diagnostic ECGs to be more rigorously assessed.

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