The role of CK-MB in chest pain decision-making

J.R. HEDGES

Department of Emergency Medicine, Portland, OR, USA

INTRODUCTION

The diagnosis of myocardial infarction (MI) in patients presenting to the emergency department (ED) represents a clinical challenge. The multitude of potential chest discomfort diagnoses and the lack of unique clinical features for MI make treatment and disposition of chest discomfort patients without classic electrocardiographic (ECG) changes problematic.^{1,2} The fact that cardiac serum markers such as creatine kinase-MB-isoenzyme (CK-MB) can be used to diagnose MI in the hospital setting has led investigators to reconsider the application of cardiac enzymes to ED decision-making. The present paper addresses the arguments for and against use of CK-MB in the ED in the light of new technology and recent clinical data.

Key words: cardiac enzyme, chest pain, CK-MB, legal risk, myocardial infarction

THEORETICAL CONCERNS AND DISCUSSION

Cardiac serum marker tests take too long to obtain

The early cardiac isoenzyme serum marker assays were developed to confirm the diagnosis of MI.³ At the time when these markers were first introduced, MI was considered to be an irreversible phenomenon, and hence diagnosis was mainly used for prognostic purposes; rapidity of test performance did not become a clinical concern until within the last ten years. Interventional treatment for MI 'in evolution' and efforts to minimize in-patient resource use have changed laboratory testing priorities.

With the introduction of interventional therapy for MI and the desire to minimize resource use by non-MI patients, the rapid availability of cardiac serum markers has become a reality in many clinical chemistry laboratories. While some

laboratories still batch enzyme specimens for 'laboratory efficiency', many laboratories have adopted techniques for rapid automated or semi-automated analysis of single and serial specimens for in-patient chest pain decision-making.⁴⁻⁶ Studies in which new immunochemical CK-MB assays were subjected to field tests demonstrated turnaround intervals suitable for real-time ED use of CK-MB results.⁷⁻⁹ Subsequent prospective clinical trials have confirmed that serial CK-MB results can be provided during ED chest pain patient evaluation.^{10,11}

CK-MB levels are insensitive to early MI

The release of cellular markers from ischaemic tissue is time dependent. Enzymes and other markers must diffuse from infarcted tissue into cardiac veins or lymphatics and then return to the general circulation. Generally, the higher the concentration of the enzyme in the tissue and the more tissue that is infarcted, the higher the peak serum level. However, the interval between infarction and the onset of a measurable rise in CK-MB levels may also be related to adequate perfusion of the surrounding non-infarcted tissue, which enhances the return of marker-enriched blood and lymphatic fluid. This view is supported by observations that coronary reperfusion increases the rate of enzyme release from perfused tissue.¹²

More recent CK-MB immunochemical technologies using antibodies to both the 'B' and the 'M' subunits measure the *mass* of CK-MB, rather than the CK-MB *activity* measured by older immuno-inhibition assays. This laboratory advance permits the detection of minute increases in CK-MB, while retaining a high specificity for MI. Both techniques demonstrate greater sensitivity than the old electrophoretic technique of CK-MB measurement.

Historically, CK and CK-MB assays for

Correspondence:
J.R. Hedges
Professor & Vice
Chair, Oregon Health
Sciences University,
Department of
Emergency
Medicine, 3181 S.W.
Sam Jackson, Park
Road, Portland, OR,
97201-3098,
USA

confirmation of MI required high threshold values in order to achieve maximum test specificity. Furthermore, many laboratories did not perform CK-MB determinations unless the total CK level exceeded the population-based threshold value. However, increases in total CK levels lag behind rises in CK-MB.^{13,14} Furthermore, throughout the course of an MI, CK-MB levels can be elevated in the absence of total CK elevations.^{15,17} Another analytical concern with the older electrophoretic technique of CK-MB determination is the potential for interference caused by high concentrations of the CK BB-isoenzyme.¹⁸ Therefore, newer immunochemical tests which focus upon changes in the mass of circulating CK-MB have obtained high specificity by dual immunological techniques that permit lower thresholds for CK-MB, with resultant higher test sensitivity.

These new technologies have led to interest in earlier studies which related CK-MB levels to MI. For example, Hong *et al.* found that their patients with abnormal CK-MB levels but normal total CK levels were generally individuals with pre-existing cardiac disease; these patients had more ischaemic complications than the other MI patients.¹⁶ Similarly, the data of Ingwall *et al.* raise questions about the traditional use of a 5% serum ratio of CK-MB/total-CK as the MI threshold for all patients.¹⁹ Their data show that the CK-MB concentration of myocardial tissue is proportional to exposure to ischaemic conditions; healthy myocardium has a CK-MB/total-CK ratio of less than 2%.¹⁹ Sharkey *et al.* confirmed the dynamic nature of myocardial CK-MB content in a canine model.²⁰ Hence, while patients with pre-existing disease may have high tissue concentrations of CK-MB and demonstrate elevated serum ratios with small infarcts, patients with relatively healthy myocardium who suddenly thrombose a major coronary vessel may have elevated CK-MB levels associated with relatively normal serum ratios.

Several investigators have analysed the relationship between CK-MB mass assay sensitivity for MI and time from ED presentation (or from onset of symptoms). Collinson *et al.* demonstrated that the test was only c. 42% sensitive at the time of patient presentation, but its sensitivity improved to c. 95% within 2 h of presentation and 100% by 8 h following presentation.¹⁴ Gibler *et al.* noted that the CK-MB mass assay was c. 80% sensitive within 3 h of presentation and 100% sensitive within 12 h of symptom onset.⁸ Marin and Teichman noted that

two ED CK-MB mass measurements taken 2 h apart were 94% sensitive for MI.⁹ Hence the sensitivity of the test for MI can be satisfactorily estimated on the basis of the time interval between presentation (or symptom onset) and phlebotomy. Any application of CK-MB levels to clinical decision-making must take into consideration both the type of assay used (preferably a CK-MB mass assay rather than a CK-MB activity assay, and definitely not an electrophoretic assay) and the interval between symptom onset and specimen collection.

CK-MB levels are redundant with regard to ED ECGs

The presence of ST-segment elevation on the ECG is the most significant marker of ischaemia. Unless the ST-segment elevation is known to be old,²¹ it should be used to guide attempts at revascularization or intense supportive cardiac care. Although Brush *et al.*²² and others^{23,24} have reported that patients with ST-segment elevation and other ECG abnormalities are at increased risk of in-hospital complications, the contribution of the other ECG abnormalities to such a risk appears to be low.^{25,26} Among those patients who are haemodynamically stable and without ST-segment elevation, these other ECG abnormalities are non-specific markers for ischaemic complications. Since an elevated CK-MB appears to be a more specific marker than the ECG in these patients, it may be valuable for in-hospital disposition of otherwise stable patients without ST-segment elevation.^{26,27} Serial ischaemic changes in ECGs also appear to lag behind increases in CK-MB in patients without presenting ST-segment elevation.²⁸

CK-MB levels are non-specific markers for MI

The CK-MB level may be falsely elevated in several clinical situations.²⁹ The more common settings include certain neuromuscular disorders (e.g. muscular dystrophy),³⁰ myocarditis, cardiomyopathy, rhabdomyolysis, prolonged ischaemic skeletal muscle exertion (e.g. in marathon runners or military recruits),³¹ and unstable angina. Some clinicians consider that the latter (unstable angina) cases potentially represent otherwise unrecognized small MIs. Without myocardial tissue analysis, this difference cannot be detected. With regard to the other false-positive scenarios, patients with

muscular dystrophy and cardiomyopathy should be recognizable clinically. Such patients will have persistently elevated levels even without chest discomfort. Patients with rhabdomyolysis are easily detected by a concurrent extremely high total CK level. Patients with myocarditis or excessive muscular exertion and chest discomfort remain problematic and will probably be managed mainly on the basis of their clinical presentation rather than their initial CK-MB levels.

In the National Cooperative CK-MB project, which examined admitted chest discomfort patients, 5.4% of 4751 non-MI patients without ST-segment elevation had a positive CK-MB *mass* assay.²⁷ This figure is consistent with the false-positive rate observed in the Emergency Medicine Cardiac Research Group II (EMCREG-II) study of CK-MB *mass* assay use for ED decision-making.¹¹ In the EMCREG-II trial, there were also 5% false-positive cases among chest pain patients subsequently found to have unstable angina (*n* =146) or 'other diagnoses' (*n* =829). By contrast, 39% of the patients with 'other diagnoses' had abnormal ECGs (without ST-segment elevation) that fulfilled the criteria of Brush *et al.*²² in the EMCREG-II trial (unpublished data).

CK-MB levels adversely affect ED decision-making

Many have feared that the imperfect test sensitivity of the CK-MB assay would lead to inappropriate release of patients with MI or unstable angina from the ED.^{29,32-34} However, such warnings were published before CK-MB immuno-inhibition and CK-MB *mass* assays had become widely available. These authors also made the unwarranted assumption that emergency physicians would base patient disposition solely upon the result of a single serum marker test.

Interestingly, clinicians use the ECG, a test with considerably less sensitivity and specificity, in their daily chest pain decision-making. Rouan *et al.* noted retrospectively that in the Multicenter Chest Pain Study, 10% of MI patients presented with completely normal or non-specific ECGs, and only 79% presented with new ischaemic findings.³⁵ Similarly, Young and Green reported in a prospective study that only 56% of adult MI patients presented with new ST-segment, T-wave, or Q-wave ECG findings.³⁶ Furthermore, physicians may misinterpret ECGs in the ED.³⁷

In the EMCREG-I study, clinicians having *mass*

assay CK-MB data available for decision-making in the ED demonstrated an increased strength of conviction regarding MI and non-MI in patients who were subsequently confirmed (using an independent serum assay) to have these diagnoses, respectively.¹⁰ While stronger convictions may make the clinician feel better about decision-making, the impact of CK-MB data on actual decisions is a better measure of test value in the ED. The recent EMCREG-II study demonstrated that the availability of CK-MB *mass* measurements in the ED correctly increased the physicians' diagnosis of MI and planned admission to the critical care unit.¹¹ During both EMCREG studies in which CK-MB values were available during ED decision-making, no patient with unstable angina or MI was released from the ED.^{10,11} These studies suggest that physicians recognize the limitations of a CK-MB assay, and correctly use the assay when making real-time decisions in the ED.

Use of CK-MB levels represents a medico-legal risk

It has been argued that if an ED CK-MB value was obtained, then this implies that MI was considered likely by the physician, and that the patient should have been admitted to the hospital. This postulate could similarly be applied to any case in which the physician obtained an ECG and subsequently released the patient from the ED. The ordering of a CK-MB test is not a substitute for a final decision that the patient has an MI, any more than ordering of the ECG indicates a final decision. Rather, the CK-MB level is a supplementary tool that may be used during patient assessment. The results obtained using such a tool must be assessed together with the results of other components of the evaluation.^{10,11}

However, the role of the CK-MB level in decision-making should be documented in the patient's ED record. For example, in a patient with atypical chest discomfort who presents 12 h after the onset of the discomfort, a negative test is a strong indicator that the patient does not have an MI. The physician must then use other tools to decide whether the presentation warrants in-patient or out-patient treatment and further evaluation. The role of these other tools or findings in the decision-making process should also be documented in order to minimize retrospective assumptions by plaintiffs' attorneys.

Use of CK-MBs is not cost-effective

A formal cost-effectiveness analysis of ED CK-MB use has yet to be performed. Early retrospective studies suggested that the observed 4–5% inadvertent MI patient release rate could be reduced with ED availability of CK-MB levels.^{38,39} The EMCREG studies demonstrated CK-MB use without inadvertent release of MI or unstable angina patients.^{10,11} The financial saving achieved by averting a malpractice case is variable, but is probably in the range £33 000–330 000 in the U.S.A. Perhaps of more importance financially to health-care planners, the EMCREG-II study demonstrated a reduction in intended hospital admission for patients without MI or unstable angina. The financial benefits of these changes in decision-making must be weighed against the cost of administering the test and the cost of false-positive tests.

A rough estimate of the supplementary laboratory cost of performing two CK-MB analyses (one upon presentation and the other 3–4 h later in order to maximize test sensitivity) is c. £100. In the EMCREG-II study, the increased admission of MI patients to the critical-care unit was balanced by a corresponding decrease in admission of unstable angina patients to the critical-care unit.¹¹ This 'balance' may represent a cost saving if the life-threatening complications seen more commonly with CK-MB positive patients can be prevented by admission to the critical-care unit.^{26,27} Excluding any potential savings from reduced litigation by minimizing release of otherwise unrecognized MI patients, the largest potential cost-saving with CK-MB use is a reduced hospital admission rate for those patients without MI or unstable angina.¹¹ Using assumptions based upon U.S.A. ED costs, the maximum admission cost saving based upon the EMCREG-II study data would be £27 000 for a patient population of 1042 ED patients (i.e. c. £1000 per admission $\times$ 27 saved admissions). While the cost of performing the enzyme tests for the 1042 patients would be c. £104 200 (£100 per set of serial ED CK-MB levels $\times$ 1042 patients). However, these same enzyme tests would probably be performed for the admitted patients in any case. The more rapid availability of the test results for admitted patients could lead to further cost-savings by earlier discharge from the critical-care unit or other monitored bed setting.^{4–6} Hence, if the analysis is restricted to the marginal cost of ED CK-MB levels for the 265 patients released from the ED, the

additional cost would be c. £26 500. Thus, on the basis of these crude assumptions, the additional expense of ED CK-MB levels appears to be more than balanced by savings made elsewhere.

CLINICAL APPLICATION OF CK-MB ORDERING

In clinical practice at my institution, ED CK-MB ordering is more selective than in the crude financial analysis outlined above. For those patients whose symptoms are not compatible with cardiac ischaemia (e.g. a young patient with sore chest wall associated with coughing and respiratory illness), ordering of CK-MB levels is discouraged. For individuals with discomfort that began more than 9–12 h before presentation, a single CK-MB level determination is generally sufficient. For the patient who presents within several hours of the onset of discomfort and clinically warrants admission, measurement of CK-MB levels is generally deferred until at least 6 h following symptom onset. Finally, patients with significant ST-segment or T-wave changes generally do not require ED CK-MB levels, although these data may be ordered for in-patient prognostic use rather than ED decision-making.

CONCLUSIONS

While an imperfect tool, CK-MB *mass* measurement in the ED may aid clinical decision-making. It must be looked upon as a *supplement* to clinical decision-making and not be used to *supplant* clinical thinking. Formal cost-effectiveness analyses will require additional data on the impact of the test upon clinical decision-making and better estimates of the preventability of adverse outcomes by earlier MI recognition. However, given the preliminary data, the marginal expense of the CK-MB *mass* assay does not appear to prohibit its selective application in the ED.

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