Clinical Utility of a Two-Site Immunoradiometric Assay for Creatine Kinase-MB in the Detection of Perioperative Myocardial Infarction

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In 144 patients, creatine kinase MB was measured serially at 0, 8, 16, 24, 48, and 72 hr using a two-site immunoradiometric assay (IRMA). Cardiac enzymes were also measured, including SGOT, LDH, total CPK, and CK-MB by electrophoresis. The presence of perioperative myocardial infarction (poMI) was established in 24 patients by the appearance of new electrocardiographic Q waves and/or new wall motion abnormalities detected by radionuclide ventriculography. In patients without poMI, CK-MB (IRMA) was elevated (6.4 ± 4.9 equivalent units per liter) at 0–8 hr but decreased to 3.4 ± 1.3 EU/l by 16 hr. In patients with poMI, peak values occurred at 16–24 hr (21.0 ± 19.8 EU/l). Using a threshold value of 8.5 EU/l, patients with poMI could be distinguished from those without with 97% accuracy (sensitivity = 88%, specificity = 99%). The CK-MB (IRMA) was more reliable than the other enzyme assays, for which we used both empirically elevated threshold values based upon previous experience, and also threshold values retrospectively optimized for the study population. We conclude that the CK-MB (IRMA) can serve as a valuable postoperative screening test for poMI.

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Measurement of the MB fraction of creatine kinase (CK-MB) has been shown to be a highly sensitive and specific marker of acute myocardial infarction in nonsurgical patients (*1*). Recently, immunoradiometric assays specific for the MB fraction of creatine kinase [CK-MB (IRMA)] have been introduced and shown to be more sensitive and specific markers of myocardial necrosis than column chromatographic, electrophoretic, and conventional radioassay methods (*2–6*). The purpose of the present prospective study was to use IRMA to characterize the pattern of CK-MB release in patients after aortocoronary bypass, and to correlate postoperative values with markers of poMI including the development of electrocardiographic Q waves and of new regional wall-motion abnormalities demonstrated by radionuclide ventriculography (RNV).

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METHODS

Patient population. One hundred forty-four patients undergoing aortocoronary bypass surgery were studied. Patients undergoing other concomitant cardiac surgery such as aneurysm resection or valve replacement were excluded. Several patients whose perioperative course was totally uneventful without any evidence of myocardial infarction were dropped from the study due to failure to obtain the complete postoperative cardiac enzyme battery or postoperative radionuclide ventriculography. The study population was therefore somewhat biased in favor of patients with postoperative complications, including poMI. The study protocol was approved by our institutional review boards, and all patients gave written informed consent.

Aortocoronary bypass surgery. Following midline sternotomy and cardiac arrest with cold cardioplegia solution, saphenous vein aortocoronary bypass grafts were placed. Venting was performed by a needle inserted into the ascending aorta after cross-clamping. In our institution the typical ischemic time (period of aortic cross-clamping) is 15 to 30 min, and the typical cardiopulmonary bypass pump time is 30 to 50 min. For patients in this study the average number of grafts was 3.2.

Blood sampling. Peripheral venous blood samples were obtained for total CK, CK-MB by electrophoresis [CK-MB (elect)], and CK-MB (IRMA) at 0, 8, and 16 hr after operation. Subsequent samples were obtained on the first three postoperative mornings at 6 a.m. If the timing of the 16-hr specimen occurred within 4 hr of the day-1 postoperative specimen, the former was omitted. Serum glutamic oxalacetic transaminase (SGOT) and total lactic dehydrogenase (LDH) were measured on the first three postoperative mornings.

Electrophoresis of patient sera was performed using the agarose gel technique. CK isoenzymes were examined under ultraviolet light and verified densitometrically, and the results recorded as the percent of total CPK. Abbott reagents were used in the determination of total CPK activity, LDH, and SGOT.

The normal ranges for these tests in our institution are: CK-MB (elect) = 0 U/l; total CPK = 36-190 IU/l; SGOT = 7-40 U/l; LDH = 100-225 U/l. However, from our accumulated experience in the postoperative setting, we consider only the following values suspicious for the presence of poMI: CK-MB (elect) >50 IU/l; total CPK >1000 IU/l; SGOT >200 U/l; and total LDH >500 U/l.

CK-MB radioassay. CK-MB was measured by a two-site sandwich immunoradiometric assay* designed to quantitate this isoenzyme specifically. The first step of this system involves a solid-phase primary immunoadsorption of the patient's serum by anti-CK-B-subunit specific antibody to bind CK-MB, CK-BB, and macro-CK. After a 1-hr incubation and centrifugation, I-125-labeled anti-CK-M-subunit specific antibody is added to bind to the immobilized CK-MB. Following a second 1-hr incubation and centrifugation, the bound radioactivity is compared with that obtained using purified human CK-MB calibrators. Immunologically active CK-MB is measured, with the results arbitrarily expressed in equivalent units per liter (EU/l).†

Two serum controls provided by the manufacturer were used to establish between-assay precision, expressed as coefficients of variation, and two serum pools were used for within-assay precision. Serial dilutions of several patients' sera containing elevated levels of CK-MB were tested for parallelism with the standard curve. Specificity was evaluated by adding concentrations of greater than 6000 units per liter of purified human CK-MM, or 800 units per liter of CK-BB, to a normal serum pool. Recoveries of CK-MB were measured from dilutions of the 160 EU/l calibrator added to negative human serum.

Criteria of perioperative myocardial infarction. There is currently no "gold standard," either invasive or noninvasive, for the definitive diagnosis of poMI. Because of their recognized specificity, the appearance of new persistent electrocardiographic Q waves and/or the development of a new abnormality of regional wall motion were used as criteria of poMI in the present study. Due to their nonspecificity in the perioperative setting, standard cardiac enzymes, total CPK, SGOT, and LDH, were not used.

Electrocardiography. Twelve-lead electrocardiograms (ECG) were obtained on the first three postoperative mornings and before hospital discharge, and were compared with preoperative baseline tracings. All postoperative tracings were interpreted by experienced cardiologists without knowledge of the cardiac-enzyme or radionuclide findings. Only new persistent Q waves >40 msec in duration were considered diagnostic of poMI.

Radionuclide ventriculography. In all patients, gated radionuclide ventriculography (RNV) was performed seven to ten days after operation, using standard imaging and computer-processing methods. After in vivo labeling of red blood cells by injection of 3.5 mg of stannous pyrophosphate, followed in 20 min by 25-30 mCi of pertechnetate (Tc-99m), gated images were obtained in the 30° right anterior oblique and "best septal" (approximately 45°) left anterior oblique views. Images were viewed by three experienced observers, and wall motion was assessed semiquantitatively. The motion of each of five myocardial segments (anterolateral, apical, septal, inferior, and posterolateral) was graded on a scale of −1 to 2 (−1 = dyskinetic, 0 = akinetic, 1 = hypokinetic, 2 = normal). For all patients, postoperative studies were compared with preoperative gated studies (in 71 patients) or with contrast ventriculograms (in 73 patients) that had been graded in a similar fashion. In patients who had undergone only single-plane contrast ventriculography (in which the posterolateral segment is not visualized), this segment was excluded from the postoperative comparison. All postoperative studies were interpreted without knowledge of the cardiac-enzyme or ECG results. A worsening of the motion of any segment (with the exception of the septum) by one grade or more was considered diagnostic of poMI. Since exaggerated anterior translational motion of the heart due to pericardial effusion and/or pericardiotomy may occur postoperatively, resulting in decreased septal excursion, only worsening of septal motion by two or more grades was considered indicative of poMI (*7,8*).

Statistical analysis. Inter- and intragroup comparisons were analyzed using Student's t-test for unpaired data. Determinant analysis (SPSS) (*9*) was used to determine

TABLE 1. CK-MB RECOVERY IN HUMAN SERUM

CK-MB added (EU)	CK-MB measured (EU)	Percent recovery (%)
21.8	21.0	94
11.9	12.2	102.5
7.0	7.4	105

which test or combination of tests best predicted the presence of poMI. Between-test correlation (r) was determined by linear regression analysis.

RESULTS

In vitro assay performance. Precision between assays (n = 11), expressed as coefficients of variation, routinely averages 6.2% at 7.5 EU/l and 13.5% at 3.1 EU/l, while within-assay precision (n = 6) is 3.7% and 3.9% for serum pools at 2.7 and 11.4 EU/l, respectively. Recoveries of CK-MB added to a normal serum averaged 101.5% (Table 1). Dilutions of patient samples containing elevated levels of CK-MB demonstrated acceptable parallelism with the standard curve over a range from 40 to EU/l. Sensitivity (least detectable concentration), defined as the concentration corresponding to two standard deviations below the measured mean value for normal serum samples (n = 12), was 1.6 EU/l. Addition of more than 6000 U/l of CK-MM or 800 U/l of CK-BB resulted in no detectable displacement in the CK-MB assay system.

Diagnosis of perioperative infarction. Of the 144 patients undergoing aortocoronary bypass, poMI was diagnosed in 24 (17%). Nine patients met both ECG and RNV criteria of poMI, ten had ECG evidence only, and five had RNV evidence only. There were no postoperative deaths. Since the study population is somewhat biased in favor of patients with postoperative complications, the incidence of poMI in these patients is considerably higher than the 7% incidence generally recognized in our institution.

Pattern of postoperative CK-MB release. In patients without ECG or RNV evidence of poMI there was an initial elevation of CK-MB (IRMA) to 6.4 ± 4.9 EU/l (range 2.4–17.8) at 0–8 hr after operation which subsequently decreased to 3.4 ± 1.3 EU/l (range 2.4–8.6) by 16 hr (Fig. 1). In the patients with infarction, peak values occurred at 16 hr (21.0 ± 19.8 EU/l, range 6.3–73.0), thereby permitting optimal recognition of these patients at this time. No significant correlation could be demonstrated between the occurrence of poMI or peak CK-MB (IRMA) levels and the number of bypass grafts. Of the 24 patients with poMI, only eight had persistently elevated CK-MB (IRMA) values on the second postoperative morning. Each of these patients had had markedly elevated values (>10 EU/l) at 16 hr.

Correlation of CK-MB (IRMA) and ECG and RNV criteria of poMI. For the CK-MB (IRMA) assay, no patients with 16–24 hr values ≤5.0 EU/l had poMI, and all patients with values >10.0 EU/l had poMI. The greatest accuracy in discriminating patients with poMI was achieved using a threshold value of 8.5 EU/l. This is higher than the threshold value of 5.0 EU/l established previously in nonsurgical patients with acute myocardial infarction.[‡]

With the 8.5 EU/l threshold there was one "false-positive" and 3 "false-negative" diagnoses. In the one false-positive case (a patient who received two saphenous vein grafts), a peak CK-MB (IRMA) of 8.6 EU/l was recorded at 16 hr. Other cardiac enzymes were also elevated, including SGOT = 207 U/l, CPK = 1780 IU/l, and CK-MB (elect) = 146 IU/l. It is therefore likely that this patient sustained subendocardial myocardial necrosis not detected by ECG or RNV. In one of the three false negatives, with CK-MB (IRMA) = 7.8 EU/l at 16 hr, new postoperative inferior Q waves developed without new wall-motion abnormalities by RNV. Other peak values for cardiac enzymes were SGOT = 118 U/l, total CPK = 483 IU/l, and CK-MB (elect) = 30 IU/l. Although a new inferobasal wall-motion abnormality might not have been detected by RNV, it is most likely that the patient's new Q waves were related to postoperative changes in orientation of the heart within the thorax rather than to poMI. In the other two false-negative cases [CK-MB (IRMA) = 6.3 and 5.8 EU/l] both the ECG and RNV studies demonstrated new postoperative abnormalities and the total CPKs were elevated (1935 and 1096 IU/l), although the other enzymes, including CK-MB (elect), were not abnormal.

Peak CK-MB (IRMA), CK-MB (elect), and total CPK measured at 16–24 hr after operation, and peak SGOT and LDH, each detected patients with poMI, with p values <0.00001 (Table 2, Fig. 2). However, CK-MB (IRMA) demonstrated the highest specificity,

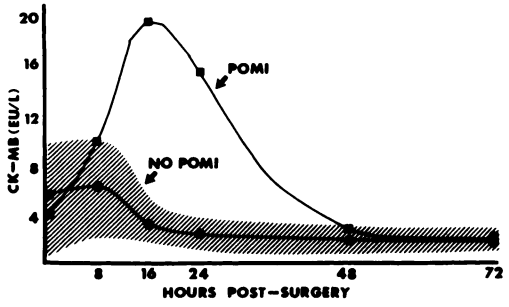

FIG. 1. Time course of CK-MB release as determined by immunoradiometric assay in patients with (squares) and without (circles) perioperative myocardial infarction. One standard deviation from the mean is indicated by cross-hatching for patients without poMI. Patients with poMI could be differentiated at 8 hr ($p < 0.001$), 16 hr ($p < 0.0001$), and 24 hr ($p < 0.0001$).

TABLE 2. CK-MB (IRMA) AND OTHER CARDIAC ENZYME ASSAY RESULTS FOR PATIENTS WITH AND WITHOUT poMI*

	CK-MB(IRMA) (EU/l)	CK-MB (elect) (IU/l)	Total CPK (IU/l)	SGOT (U/l)	LDH (U/l)
−poMI (mean ± 1 s.d.)	3.4 ± 1.3	15.5 ± 22.2	667.6 ± 410.6	55.4 ± 31.6	328.1 ± 125.9
+poMI (mean ± 1 s.d.)	21.0 ± 19.8	161.4 ± 119.0	2031.2 ± 977.8	240.1 ± 142.2	591.6 ± 209.6
p (+ vs − poMI)	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001

* The CK-MB (IRMA), CK-MB (elect), and total CPK values are for 16–24 hr postoperative specimens, whereas for the other tests peak values occurring within the first three postoperative days are expressed.

positive predictive value, and accuracy (Table 3). In patients with poMI there was a fair correlation (r = 0.83) between the CK-MB (IRMA) and CK-MB (elect) results.

The ability of each test to identify patients with poMI was also evaluated using discriminant analysis. For the analysis of tests other than CK-MB (IRMA) we used both the threshold values based upon previous experience in our institutions as well as those retrospectively optimized for this particular study population (values which most accurately differentiated patients with poMI as compared with the ECG and RNV criteria). CK-MB (IRMA) was superior to each of the tests, or to combinations of them, if previously determined threshold values were used (Table 4). With the retrospectively optimized thresholds, CK-MB (IRMA) still seemed the best discriminator of poMI, although its superiority over CK-MB (elect), or over combinations of tests including CK-MB (elect), did not reach statistical significance.

DISCUSSION

The reliable diagnosis of poMI is clinically important in the early and late postoperative management of patients with aortocoronary bypass. Those with poMI have a higher incidence of perioperative mortality and postoperative severe congestive heart failure (*10,11*). Furthermore, those with poMI have a significantly lower five-year survival (*12*).

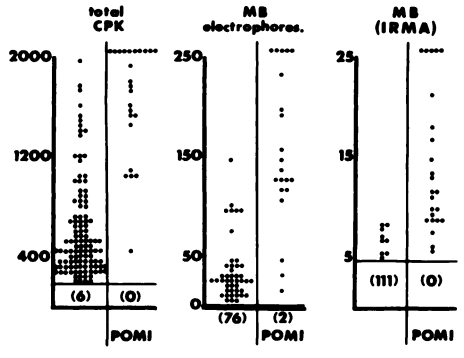

FIG. 2. Distribution of peak values for total CKP (IU/l), CK-MB (elect) (IU/l), and CK-MB (IRMA) (EU/l) at 16 to 24 hr postoperatively in patients with and without poMI. Threshold values of abnormality for nonsurgical patients are indicated by horizontal lines. Numbers below in parentheses indicate number of patients in each category with normal values. Values greater than upper limit of ordinate are grouped just above this upper limit. poMI = perioperative myocardial infarction.

Using standard ECG and enzymatic criteria, the diagnosis of poMI in patients undergoing aortocoronary bypass surgery is particularly difficult. Since electrocardiographic ST-T wave abnormalities frequently occur due to pericarditis, ischemia, and conduction disturbances, only the appearance of new persistent Q waves is generally regarded as a specific criterion of perioperative transmural infarction (*13–15*). However, subendocardial necrosis cannot be detected, and several investigators have demonstrated that this ECG criterion is insensitive, estimated to diagnose only approximately 50% of perioperative infarcts (*16,17*). Furthermore, even the appearance of new Q waves has been associated with conditions other than poMI such as hypothermia, hyperkalemia, and unmasking of old infarcts by revascularization of the contralateral ventricular myocardium (*18,19*).

The sensitivity of diagnosis of poMI can be improved by using additional criteria of infarction including Tc-99m pyrophosphate imaging and/or RNV (*20,21*). However, even using these methods in conjunction with serial ECGs, small transmural infarctions or subendocardial necrosis may escape detection. Furthermore, probably neither is justified as a screening test for poMI from a cost-effectiveness standpoint.

The standard "cardiac" enzymes, CPK, SGOT, and LDH, are released from noncardiac tissue during open-heart surgery. In many institutions in which aortocoronary bypass surgery is routinely performed, elevated threshold values are used in the postoperative setting. Although these special postoperative criteria have proved useful in uncomplicated cases, patients with hepatic, renal, or hemapoietic disorders may show marked elevations not specific for myocardial damage (*22*). An assay specific for the myocardial fraction of creatine kinase should therefore be a more specific marker for poMI, and could serve as a cost-effective postoperative screening test (*23*).

TABLE 3. DIAGNOSTIC PARAMETERS OF PERIOPERATIVE MYOCARDIAL INFARCTION FOR CK-MB (IRMA) AND OTHER CARDIAC ENZYMES

	Sensitivity (%)	Specificity (%)	+Predictive value (%)	Accuracy (%)
CK-MB (IRMA)	88	99	95	97
Total CPK	96	86	59	88
CK-MB (elect)	83	93	71	91
SGOT	58	98	88	91
LDH	71	90	63	86

The sensitivity of qualitative electrophoretic techniques for the detection of CK-MB is approximately 5-10 IU/l (*24-26*). Therefore, modest elevations of CK-MB may not be easily recognized by this technique. Accuracy may also be decreased due to nonspecific fluorescence (*27,28*). Although column chromatographic techniques are more sensitive than electrophoresis in detecting CK-MB, sensitivity may be limited due to dilution, incomplete separation, and protein denaturation on chromatographic medium, and specificity may be decreased due to nonspecific binding (*29-32*). The first radioimmunoassay methods introduced to measure CK-MB actually measured the B subunit (*33-37*). CK-BB released from other tissues such as the brain, GI tract, adrenal, and lung, and also IgG-bound CK-BB, are potential sources of nonspecificity (*38-41*). Consequently the CK-B assay has been shown to be no better than serum electrophoresis in detecting transmural myocardial infarction (*42*).

Previous investigators have estimated total CK-MB release postoperatively by calculating the concentration time-integral for the 36 hr after operation using the electrophoretic method (*43,44*). Although this method of sampling serially every 6 or 12 hr has been shown to diagnose poMI accurately, such frequent sampling in a routine clinical setting is both tedious and expensive.

In the present study using ECG and RNV criteria of infarction, a diagnosis of poMI was possible with 97% accuracy using a single serum CK-MB (IRMA) obtained at 16-24 hr after operation. Elevation of CK-MB at this time is most likely due to reperfusion of the infarcted zone, resulting in delayed release of the isoenzyme into the serum.

CK-MB elevation was present at 0-8 hr postoperatively in patients both with and without poMI. Early CK-MB release in patients without poMI may be due to surgical manipulation of the heart and/or mild subendocardial necrosis due to hypothermia or intraoperative ischemia. These factors are obviously variable, depending on the individual patient and the surgical technique. For instance, in a study reported by Baur et al., CK-MB remained significantly elevated at 24 hr postsurgery in patients without poMI (*45*). In their series, surgical venting was performed via the left atrium in some patients, and the average pump time was 127 min (range 49-264), which is considerably longer than for the patients in our series. In a study by Pyle et al., elevated CK-MB values at 6-12 hr were associated with pump times of greater than 90 min (*44*). Thirteen percent of our patients, including 41.7% of those with poMI and 7.5% of those without, had CK-MB (IRMA) levels between 5 and 10 EU/l at 16-24 hr. We therefore rec-

TABLE 4. RESULTS OF DISCRIMINANT ANALYSIS OF CK-MB (IRMA) AND OTHER CARDIAC ENZYME ASSAYS IN THE DIAGNOSIS OF poMI

	CK-MB (IRMA)	CK-MB (elect)	total CPK	SGOT	LDH
Optimized threshold	8.5 EU/l	85 IU/l	1328 IU/l	154 U/l	456 U/l
accuracy (%)	97.2	95.7	90.0	90.5	83.3
Wilk's lambda*	0.172	0.470	0.511	0.454	0.651
p [vs. CK-MB (IRMA)]		NS	<0.025	<0.05	<0.001
Predetermined threshold		50 IU/l	1000 IU/l	200 U/l	500 U/l
accuracy (%)		91.4	87.9	90.5	86.1
Wilk's lambda		0.558	0.590	0.483	0.663
p [vs. CK-MB (IRMA)]		0.06	<0.025	<0.05	<0.005

* In discriminant analysis the Wilk's lambda is an inverse measure of the discriminating power of a variable. Thus the smaller the lambda the better the discriminating power.

ommend cautious interpretation of peak values within this range, and threshold values for poMI within this "gray zone" may need to be established for each institution. Furthermore, due to variability in the time and degree of infarct reperfusion, there may be interpatient differences in the actual time of peak CK-MB levels. Therefore, blood sampling at several times in and around the 16- 24-hr postoperative interval may improve sensitivity in a routine clinical setting.

An alternative explanation of mild CK-MB (IRMA) elevation at 16–24 hr in patients without ECG or RNV evidence of poMI is one based on the greater sensitivity of the serum assay. It is possible, and perhaps likely, that these patients did indeed sustain mild perioperative myocardial necrosis not recognized by other tests. However, in the present study without a "gold standard" for poMI short of autopsy, this is only speculative.

We conclude that CK-MB (IRMA) is a useful test to identify patients with poMI. Using an elevated threshold value for the test and samples obtained at 16–24 hr postoperatively, assay results correlate well with ECG and RNV criteria of poMI and appear to be more reliable than previously available methods.

FOOTNOTES

* EMBRIA-CK, International Immunoassay Laboratories, Inc., Santa Clara, CA.

† EU/l (equivalent units per liter) = immunological activity of CK-MB isoenzyme equivalent to enzymatic activity (IU/l) of freshly prepared calibrators as measured by Calbiochem-Behring "STAT Pack" at 30°C.

‡ According to the manufacturer's package insert, the normal range for hospitalized patients is 3.3 ± 0.9 EU/l. This value was derived from clinical samples from approximately 200 patients from various hospitals analyzed by a large commercial laboratory. Thus a threshold of 5.0 EU/l represents a value approximately two standard deviations above this mean.

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