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Creatine Kinase MB in Cases of Skeletal Muscle Trauma

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Fifty-eight patients admitted through our emergency room with severe skeletal muscle injury but no obvious cardiac contusions were evaluated for creatine kinase isoenzyme MB (CK-MB). When such patients show an above-normal value for total CK, it is a question of whether or not myocardial injury has been sustained along with skeletal muscle injury when (*a*) there are no obvious chest contusions or (*b*) the patient is unconscious and unable to complain of chest pain. Whenever there is doubt concerning the cardiac status of a patient, lactate dehydrogenase (LD) isoenzymes, serial electrocardiograms, and CK isoenzymes are ordered. Our study revealed that serum of 8.6% of the trauma victims had CK-MB values exceeding 5.0 EU/L (reflecting abnormal CK-MB concentrations) as part of their increased total CK. All patients had normal electrocardiographic patterns along with negative results for LD isoenzymes; none had sustained any demonstrable myocardial injury. The CK-MB value must be interpreted together with the total CK value for appropriate diagnosis in patients with skeletal muscle trauma.

Additional Keyphrases: *heart disease* · *isoenzymes*

Measurement of the MB isoenzyme of creatine kinase (CK) in serum is highly effective in assessing the possibility and extent of acute myocardial infarction (AMI) or, more broadly, in differentiating myocardial injury from skeletal muscle damage (*1*).[3] The ratio of CK-MB to CK-MM isoenzymes is markedly higher in myocardium than in skeletal muscles, and the presence of CK-MB activity in serum is generally considered indicative of AMI whenever it exceeds 5 EU/L of total CK activity (*2, 3*) per liter. The ad hoc expression "EU/L" is one way of expressing the immunological activity and is related to enzymatic activity. The CK-MB results from the calibration curve in the EMBRIA-CK assay (International Immunoassay Labs, Inc., Santa Clara, CA 95054-1529) are expressed in terms of EU/L (equivalent units per liter). The calibrator values are based on the enzymatic activity of a CK-MB human tissue extract used in preparing calibrators. However, the EMBRIA-CK measures immunological activity of the CK-MB isoenzymes rather than their enzymatic activity (*4*). Not infrequently, patients with skeletal muscle trauma have CK-MB values exceeding 5 EU/L, but no apparent myocardial injury. These unexpectedly high CK-MB fractions pose a dilemma for the physician. Our study investigated different severities and etiologies of skeletal muscle trauma as we attempted to determine which types of trauma were more likely to reveal an increased CK-MB fraction, and whether or not the increased CK-MB fraction indicated true myocardial damage.

Earlier, assays of the three CK isoenzymes—CK-BB, CK-MM, and CK-MB—relied primarily on electrophoresis and ion-exchange chromatography. With recent advances in immunochemistry, it is now possible to determine CK isoenzyme concentrations by means of immunoprecipitation or immunoinhibition with a specific antibody, followed by identification of functional enzymatic activity. However, measurement of enzymatic activity often leads to an underestimation of CK concentrations because of nonspecific interference. Most recently, radioimmunoassays have been introduced for more precise quantification of CK isoenzymes by use of specific antibodies (*4, 5*).

It is difficult to measure accurately the amount of skeletal muscle damage in a trauma patient. Total CK was used in our study as a quantitative measurement of skeletal muscle trauma. We also used new radioimmunoassay kits from International Immunoassay Laboratories (for research only, not yet commercially available) for detecting CK-MM and CK-BB in trauma patients.

Materials and Methods

Patients and Samples

We studied 58 consecutive patients admitted through the emergency room after sustaining skeletal muscle trauma without apparent cardiac contusion. Blood was sampled from these patients at the time they were admitted to the emergency room.

Each trauma patient with a CK-MB value exceeding 5.0 EU/L was thoroughly evaluated for any possibility of myocardial damage. This evaluation included serial electrocardiograms, serial LD isoenzyme assays, serial cardiac examinations, and any history of cardiac disease or cardiac chest pain. All results were negative.

Patient demographics. The average age of our 58 trauma victims was 24 years, with a male:female ratio of 6:1. Forty-six percent of the injuries were stab wounds; automobile and motorcycle accidents accounted for 29%; and gunshot wounds accounted for 13% (Figure 1).

Degree of injuries. The extent of injury of the 58 trauma victims varied considerably. The most severe injuries involved victims of motorcycle accidents, who had multiple fractures, abrasions, and perforated viscera. The milder injuries included minor lacerations. Emergency-room assessment of blunt and penetrating trauma can be fraught with errors; reproducible noninvasive clinical criteria for

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[3] Nonstandard abbreviations: AMI, acute myocardial infarction; CK, creatine kinase (EC 2.7.3.2); EU, equivalent units, an ad hoc abbreviation for expressing immunological/enzymatic activity, peculiar to the assay used here.

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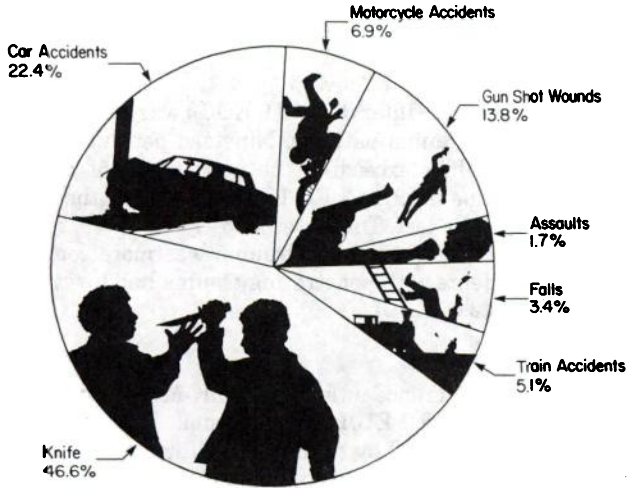

Fig. 1. Proportions of various types of skeletal muscle trauma presenting to our emergency room

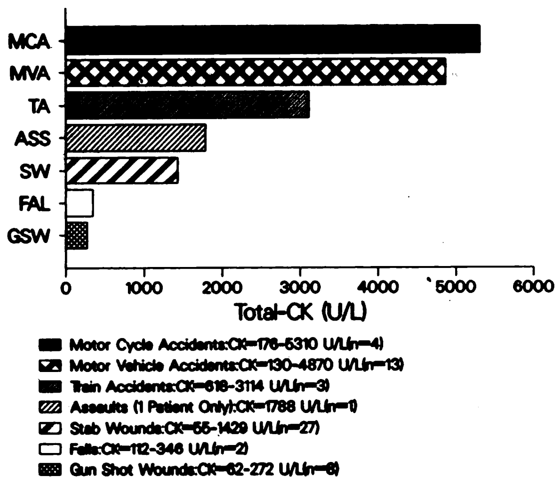

Fig. 2. Range of total creatine kinase among various types of skeletal muscle trauma

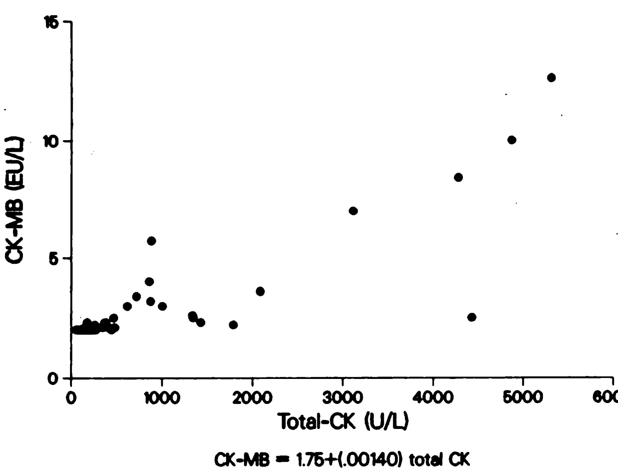

Fig. 3. CK-MB (EU/L) vs total CK (U/L)

As the total CK increases, so does the CK-MB fraction in patients with skeletal muscle trauma

judging extent of injury often prove inadequate. We have chosen CK-MM and total CK as our objective indices of skeletal muscle trauma (*6*).

Blunt vs penetrating trauma. A portion of our study consisted of subdividing all trauma patients (except six) into two groups, for comparison. Group 1 consisted of 17 subjects who had either an automobile or a motorcycle accident; Group 2 consisted of 35 subjects who had either a stab or a gunshot wound. The remaining six patients (who had suffered assaults, train accidents, or falls) were too diverse and small a group for comparison purposes.

Materials

Equipment. Total CK was measured with the "Paramax" (Baxter Healthcare Corp., Irvine, CA 92718-2017), in which the Oliver–Rosalki method is used (*7, 8*). The $NADP^+$ concentration was monitored bichromatically at 340/405 nm. CK-MB, CK-MM, and CK-BB isoenzymes were all measured by radioimmunoassay (RIA) with kits from International Immunoassay Labs, Inc. A Model 2020 gamma counter was used (IsoData, Rolling Meadows, IL 60008-1233).

RIA kits. The CK-MM and CK-BB RIA kits are not available commercially and were given to us by International Immunoassay Labs for research purposes only. Because no other company produces commercially available kits for CK-MM or CK-BB RIA, we evaluated CK-MM and compared it with our total CK measurement (both measure skeletal muscle damage). Values for CK-BB were compared with clinical evidence or history of head injury sustained during the traumatic event.

Statistics

Pearson's correlation coefficient and ordinary least-squares regression analysis were used to do two-tail t-tests. Ninety-five percent confidence intervals were evaluated on individual predictions given in the *Results* section (*9*).

We used two sample t-tests, with Satterthwaite's approximate t-test when variances were unequal by an F-test ($P \leq 0.01$), to compare means for the two groups (penetrating vs blunt trauma). Also, we used analysis of covariance to compare regression estimates for these two groups (*9*).

Results

CK-MM vs Total CK

There was an excellent linear correlation ($r \geq 0.93$) between CK-MM and total CK. Average CK-MM (no reference interval available) and total CK (reference interval 22–269 U/L) values for all 58 trauma victims were 236 EU/L and 755 U/L, respectively. CK-MM values ranged from 25 to 2035 EU/L; those for total CK, from 55 to 5310 U/L (Figure 2). With both CK-MM and total CK, lowest values were found in stab-wound victims and highest values in those involved in motor-vehicle and motorcycle accidents.

CK-MB vs Total CK

The CK-MB fraction (reference interval 0–4.9 EU/L) was highest in victims of motorcycle accidents, reaching a maximum of 12 EU/L; values for cases of automobile accidents (maximum of 10 EU/L) and train accidents (maximum of 7 EU/L) followed close behind. In all, 8.6% of our trauma victims had a CK-MB of >5.0 EU/L, and their mean total CK was 3287 U/L. The correlation (Figure 3) between total CK and CK-MB was highly significant at 0.85 ($P < 0.0001$).

Formulas Linking Total CK with CK-MB

Fitting the ordinary least-squares regression line to the relationship between total CK (x-axis) and CK-MB (y-axis) displayed in Figure 3, we derived the following formula:

$$\text{CK-MB} = 1.75 + 0.00140 \text{ (total CK)}$$

In developing this formula, we used data from all 58 trauma victims. With this formula one can estimate a mean CK-MB value that is attributable to the skeletal muscle trauma alone, by using the patient's total CK value.

Example: If a patient with skeletal muscle trauma is admitted to the hospital with a total CK of 3000 U/L:

$$\text{CK-MB} = 1.75 + 0.00140 \text{ (3000)} = 5.95$$

Another way to use our formula is: for every 500-U/L increment in total CK, the CK-MB value should increase by 0.70 EU/L from an initial CK-MB value of 1.75, i.e.:

$$[(\text{CK}/500) \times 0.70] + 1.75 = \text{CK-MB}$$

With either calculation, if the patient's CK-MB value is equal to or less than the calculated CK-MB value, then the patient's CK-MB result should not be considered to be increased for that amount of skeletal muscle damage. Interpretation of measured CK-MB values exceeding this calculated mean remains problematic.

The predicted value (95% confidence level) of the reference range of the CK-MB in a patient with a total CK of 3000 U/L is 3.7 to 8.2 EU/L. Unfortunately, the computations necessary to determine such a predicted reference interval are too intricate for rapid, routine clinical application (*9*).

Blunt vs Penetrating Trauma

We subdivided 52 of the trauma patients (excluding the six patients with train injuries, falls, and assaults) into two groups. Figure 4 shows the differences between the above-described two groups of patients used for comparisons.

The patients in Group 2 never attained a CK-MB value >3 EU/L, whereas the patients in Group 1 had CK-MB values ranging from 2 to 12.6 EU/L (Figure 4). The wide range of CK-MB values obtained for the two groups is not surprising in view of the individual differences in the amount of skeletal muscle trauma. Evidently, patients involved in motor-vehicle accidents can generally be expected to have both a higher total CK as well as a higher CK-MB than patients with penetrating wounds.

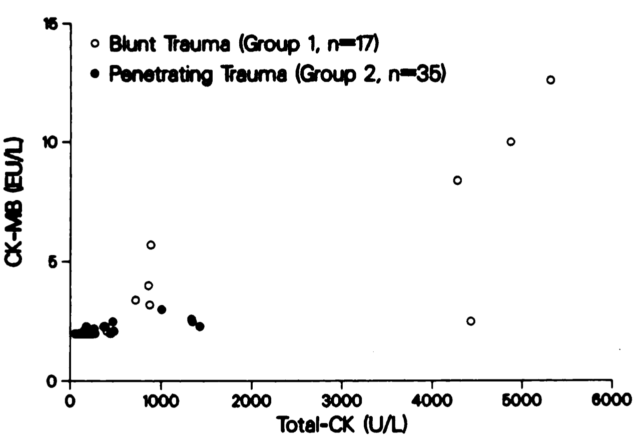

Fig. 4. CK-MB (EU/L) vs total CK (U/L) compared in two groups
Group 1, automobile and motorcycle accidents (n = 17), and Group 2, stab wounds and gunshot wounds (n = 35). Symbols for patients 9 and 20 are superimposed

Results for CK-BB

CK-BB (reference interval <13.9 EU/L) was measured for each of the 58 trauma patients. Nineteen percent of them had CK-BB values exceeding the upper limit of normal, ranging in value from 14.3 EU/L to >160 EU/L, the upper linear limit of the test. These were mostly victims of motor-vehicle accidents, where head trauma was more common. All of the patients with penetrating trauma had low values for CK-BB (<2.0 EU/L).

Discussion

Established reference intervals for CK-MB are such that results exceeding 5.0 EU/L are abnormal. We established this reference interval by examining values obtained for a wide variety of hospitalized individuals free of any significant myocardial injury (*4*). Increased CK-MB values commonly are presumed to be specific evidence of acute myocardial damage, to the exclusion of other possibilities. While it does contain CK-MB in high concentrations, myocardium is not the *sole* source of CK-MB. Skeletal muscle, although predominantly characterized by CK-MM, does contain a small proportion of CK-MB (*6*). Because this portion is ordinarily too small to alter results of CK-MB assays, skeletal muscle has been overlooked as a (potentially) significant source of CK-MB. However, should the absolute amount of total CK arising from skeletal muscle damage be large enough—i.e., severe skeletal muscle trauma—then the proportion of CK-MB in the circulation that has originated from skeletal muscle alone can become substantial.

Because we had observed patients with massive skeletal muscle trauma and increased CK-MB, we investigated the possibility of skeletal muscle as a source of the increased CK-MB, finding increased CK-MB values in 8.6% of 58 consecutive trauma patients, each occurring in the absence of any independent evidence of myocardial damage.

In our study, when the total CK exceeded 884 U/L, a CK-MB value exceeding 5.0 EU/L was found in 38% of the patients (Figure 3). In addition, CK-MB increased above 5 EU/L in direct proportion to the increase in total CK, at a relative rate that implied that the CK-MB increase was originating from that small proportion of CK-MB present in (the relatively large amount of) skeletal muscle. Total CK must be taken into account when a trauma patient's CK-MB is evaluated.

The excellent correlation between CK-MM and total CK was to be expected, because both variables reflect skeletal muscle damage. The ultimate advantage of measuring CK-MM rather than total CK is that in both CK-MM and CK-MB the same assay units (EU/L) are used for measurement, while total CK is expressed as U/L. Thus CK-MM and CK-MB values are directly comparable, albeit through a ratio.

Not surprisingly, the great majority of patients with increased CK-BB were those involved in motor-vehicle (particularly motorcycle) accidents, where head injuries are common.

We observed that certain types of trauma (mainly motor-vehicle accidents) are associated with increased CK-MB isoenzymes without true myocardial damage, and that the total CK value must be considered together with the CK-MB isoenzyme value.

Physicians faced with ambiguous or unexpected (unexplained) test-result abnormalities face a dilemma, and often feel compelled to order subsequent tests when they would not do so otherwise. With the aid of the formula [CK-MB = 1.75 + 0.00140 (total CK)] we hope to alleviate physicians' concern in assessing the myocardial status of the trauma victims they see.

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