Serum CPK isoenzymes after cardiac catheterization

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Exclusion of acute myocardial infarction preoperatively, particularly in patients undergoing cardiac catheterization, is an important requirement for optimal results following coronary revascularization. Unfortunately, activity of conventionally measured serum enzymes (AST, LDH, total CPK) is frequently raised because of enzyme released from non-cardiac sources during the catheterization procedure.

However, serum activity of the MB-CPK isoenzyme, an isoenzyme found primarily in heart muscle, appears to be more specific. Accordingly, the present study, total CPK and MB CPK activities were determined in serum samples from 53 patients undergoing diagnostic catheterization, immediately before study and serially for 24 hours afterwards. A comprehensive range of catheterization procedures included selective coronary arteriography in 39 patients by brachial (17) or femoral (22) artery approaches. Myocardial infarction was excluded by clinical and electrocardiographic criteria in all patients before and after the procedure. MB CPK isoenzyme activity was also measured in serum samples from 50 patients with acute myocardial infarction documented electrocardiographically, and in 20 controls admitted to hospital but without cardiovascular disease.

In patients with acute myocardial infarction, both total CPK and MB CPK isoenzyme levels were significantly raised (0.78 ± 0.087 and 0.086 ± 0.037 IU/ml, respectively), exceeding the upper limit of normal in all cases. MB CPK activity remained within normal limits (< 0.004 IU/ml) in all 20 subjects without cardiovascular disease. Peak total serum CPK activity exceeded control levels in all patients undergoing catheterization (0.260 ± 0.023). However, in each case, MB CPK isoenzyme activity remained within normal limits (< .004). Thus, in contrast to an increase of activity of conventionally used serum enzymes, increased MB CPK isoenzyme activity is a reliable indicator of myocardial infarction, even in patients undergoing cardiac catheterization.

The use of coronary arterial by-pass grafting for patients with angina pectoris has increased the importance of cardiac catheterization and coronary arteriography in patients with coronary artery disease. Sometimes surgery is contemplated on an urgent basis, particularly in patients with 'preinfarction' coronary insufficiency (Favaloro et al., 1971). It appears likely that correct selection of patients for coronary bypass surgery requires identification and perhaps exclusion of evolving infarction, since operation may lead to extension of the infarct, or the result of the operation may be unsatisfactory (Roberts and Sobel, 1974; Dawson et al., 1974). During catheterization, patients with severe coronary insufficiency sometimes develop chest pain or electrocardiographic abnormalities compatible with myocardial damage (Ross and Gorlin, 1968).

Furthermore, despite improved techniques of cardiac catheterization, myocardial infarction, albeit infrequent, remains a possible complication, particularly in patients with severe proximal coronary obstruction (Lavine et al., 1972) or advanced left ventricular dysfunction (Takaro et al., 1973). There is therefore a need for a means for the objective detection of myocardial injury in relation to these investigations.

Conventional criteria of myocardial injury may be unreliable in patients undergoing cardiac catheterization. Often, electrocardiographic abnormalities related to previous myocardial infarction or conduction abnormalities are present and may cloud the issue. Conventionally measured serum enzymes, including serum aspartate transference, lactic acid dehydrogenase (LDH), LDH iso-enzyme, and total serum creatine phosphokinase (CPK), may be raised after catheterization (Adrouny et al., 1963; Burckhardt et al., 1968), in part because of non-
cardiac soft tissue injury (Wolfe, Ruttenberg, and Moss, 1970), and thus cannot be used as reliable indices of myocardial infarction (Marpole et al., 1968; Michie et al., 1970). Recently, we and others have shown that raised serum MB CPK activity, an isoenzyme found primarily in myocardium, is not only a sensitive (Roe et al., 1972; Konttinen and Somer, 1972) but also a remarkably specific index of myocardial injury (Roberts et al., 1975). Three serum CPK isoenzymes have been recognized and referred to as MM, BB, and MB on the basis of subunit composition. Only four human tissues are rich in CPK activity: skeletal muscle, myocardium, brain, and the gastrointestinal tract (Roberts et al., 1975). We have recently surveyed surgically obtained human tissues and found that myocardium is the only one containing more than trace amounts of MB isoenzyme under standardized assay conditions. We previously demonstrated that raised serum CPK activity after intramuscular injections is not associated with increased MB CPK activity (Klein, Shell, and Sobel, 1973), nor is non-cardio-thoracic, abdominal, genitourinary, or orthopaedic surgery (Gowda, Roberts, and Sobel, 1974). Accordingly, the present study was designed to determine whether raised serum CPK activity after cardiac catheterization is caused by release of enzyme from the heart, and whether increased MB CPK remains a reliable index of myocardial ischaemic injury in this setting.

Until recently, it has not been possible to measure serum CPK isoenzyme activity accurately because of insensitivity or imprecision in assay procedures (Roberts and Sobel, 1973). The recent availability of a fluorometric kinetic assay system permits precise quantification of individual serum CPK isoenzyme activity even in samples from normal subjects with low activity (Roberts et al., 1974). In the present study, this technique was used; total CPK and CPK isoenzyme activity was determined in serial samples from 53 patients after cardiac catheterization. Results were compared with those obtained in 50 patients with documented myocardial infarction and in 20 patients in hospital without cardiovascular disease.

### TABLE 2 Electrocardiographic findings before catheterization

<table>
<thead>
<tr>
<th>Abnormalities</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transmural infarction</td>
<td>5</td>
</tr>
<tr>
<td>Nonspecific ST-T changes</td>
<td>16</td>
</tr>
<tr>
<td>Ventricular hypertrophy</td>
<td></td>
</tr>
<tr>
<td>LVH</td>
<td>8</td>
</tr>
<tr>
<td>RVH</td>
<td>3</td>
</tr>
<tr>
<td>Conduction disturbances</td>
<td>5</td>
</tr>
<tr>
<td>None</td>
<td>16</td>
</tr>
</tbody>
</table>

**Subjects and methods**

The patients undergoing cardiac catheterization comprised 33 men and 20 women, age range 17 to 67 (mean 44.3 years). Clinical assessments (Table 1) included suspected coronary insufficiency and chest pain (31 patients), valvular heart disease (15), and congenital cardiac defects (7). Two patients were investigated for prosthetic valve dysfunction and 2 were studied to determine graft patency 3 months after coronary arterial bypass grafting. Catheterization was performed on an emergency basis in 5 patients in whom recent exacerbation of angina pectoris was considered to represent 'pre-infarction'. Remote previous infarction was demonstrated by the electrocardiograms in 5 (Table 2). Clinical evidence of congestive heart failure was present in 3 patients, 1 with tricuspid atresia and 2 with mixed aortic and mitral valve disease. Neither prolonged chest pain nor major arrhythmia requiring electrical cardioversion occurred during catheterization. Frequent ventricular premature contractions were observed in 4 patients with coronary artery disease, but were readily controlled by intravenous lignocaine ("xylocaine"). No patient sustained a major complication (Braunwald and Swan, 1968). Specifically, no clinical or electrocardiographic signs of myocardial infarction were observed. Minor complications were limited to superficial groin haematoma in 4 patients undergoing percutaneous femoral artery procedures. All patients were premedicated 30 minutes before the procedure with 5 to 10 mg of diazepam ("valium") and 100 mg pentobarbitone ("nembutal") intramuscularly. Sites for percutaneous puncture and brachial cutdown were anaesthetized by infiltration of 20 ml of 2 per cent lignocaine. Systemic anticoagulation with heparin, 100 units per kilogram body weight, was employed in all cases. Right and left heart catheterization with angiography was performed in 36 patients, and left heart catheterization alone with angiography in 17. Selective coronary angiography was performed in 39 patients, using the brachial artery approach (Sones and Shirey, 1962) in 17, and the per-
cutaneous femoral artery technique (Judkins, 1967) in 22.
Adequate non-selective coronary opacification was obtained in the remaining 14 cases during root cineangio-
graphy. Cardiac output was determined in all cases, by
use of the Fick principle, indocyanine green dilution,
or thermodilution techniques. Hydrogen studies were
performed for the detection of intracardiac shunts in all
7 patients with suspected congenital heart disease. The
haemodynamic response to exercise performed on a
bicycle ergometer was evaluated in 4 patients with mitral
disease. His bundle electrography with atrial pacing was performed as part of the investigation in 3
cases. In 9 patients, temporary right ventricular endo-
cardial pacing was performed during selective coronary
arteriography. Angiocardiography was performed with
pressure injection of 35–50 ml of 75 per cent Hypaque M
(sodium diatrizoate). Manual injections of 6 to 12 ml
Renografin 76 (meglumine diatrizoate and sodium
diatrizoate) were employed for selective coronary
arteriography.

The criterion for the diagnosis of significant coronary
artery disease was 70 per cent or greater obstruction
visualized by multiple projection arteriography. Left
ventricular function was assessed by visual inspection of
left ventriculograms filmed in one or two planes, vent-
tricular haemodynamics, and ejection phase indices of
performance, including ejection fraction, mean circum-
ferential fibre shortening rate (Karliner et al., 1971), and
normalized mean systolic ejection rate (Peterson et al.,
1974).

Blood samples for total CPK and CPK isoenzyme
activity determinations were obtained immediately
before catheterization and every 2 hours thereafter for a
total of 24 hours. Blood samples were collected in 0.005
mole neutralized EGTA, centrifuged at 2000 g for 10
minutes, decanted, and protected with 0.010 moles
mercaptoethanol (final concentration). Samples were
assayed immediately for CPK isoenzyme activity or fast
frozen, stored at –20°C, and assayed within 4 weeks.
Samples stored under these conditions do not show loss
of activity for at least 6 weeks (Roberts et al., 1974).

The results of the CPK isoenzyme determinations in
patients undergoing catheterization were compared to
those obtained from 50 patients admitted to the cardiac
care unit who sustained electrocardiographically docu-
mented transmural myocardial infarction, and from 20
controls in hospital but without significant cardiovas-
cular disease. In patients in the cardiac care unit, blood
samples were collected every 2 hours through a periph-
eral venous heparin lock for a total of 48 hours and
assayed for total CPK and CPK isoenzyme activity
exactly as in patients who were catheterized.

Total CPK and CPK isoenzyme
determinations
Total CPK activity was determined spectrophotometri-
cally (Rosalki, 1967) in serum samples diluted with Tris,
0.01 moles, pH 7.4 containing 0.2 per cent bovine serum
albumin such that CPK activity was within the range of
linearity of the assay (Bresnahan et al., 1974). CPK
activity was assayed in 50 µl aliquots in a final volume of
1.050 ml at 30°C. Results were expressed in international
units/ml (IU/ml). The upper limits of normal in our
laboratory are 0.040 IU/ml and 0.050 IU/ml for women
and men, respectively. Assays were performed with
and without creatine phosphate as substrate to exclude
spurious contributions to apparent CPK activity from
myokinase and other isoenzymes.

Activity of CPK isoenzymes was determined quali-
tatively by cellulose acetate electrophoresis as previously
described (Klein et al., 1973) and quanti-
tatively with a fluorometric, kinetic assay recently de-
veloped in our laboratory (Roberts et al., 1974). For
qualitative analysis of serum CPK isoenzymes, 10 µl
aliquots of samples diluted to contain 0.1 IU/ml were
separated by cellulose acetate electrophoresis at a con-
vantage of 250 volts for 60 minutes at 4°C in 0.05 moles Tris barbioné, pH 8.8 containing 0.001
EGTA. Isoenzyme bands were visualized by applying
cellulose acetate strips previously soaked in
NADPH generating medium. This technique permits
detection of isoenzyme activity exceeding 0.010 IU/ml
(Kontinen and Somer, 1972). Quantitative deter-
minations of activity of individual CPK isoenzymes
were performed with a kinetic fluorometric procedure as
recently described (Roberts et al., 1974). Results with
this method are linear with respect to time and enzyme
activity and reproducible within 3 per cent. Its sensi-
tivity is less than 0.002 IU/ml and it avoids several
difficulties associated with quantification of isoenzyme
activity by fluorescence scanning of electrophoretic
media. Serum from normal subjects assayed under these
conditions contains less than 0.005 IU/ml of MB CPK
(Roberts et al., 1974).

Results
Peak total serum CPK activity was raised above
control levels in all patients undergoing catheteriza-
tion (mean peak 0.260 ± 0.063 IU/ml) (range 0.036–
0.570) (Fig. 1). In 41 patients, peak levels exceeded
the upper limits of normal for this laboratory; in the

![FIG. 1 Mean peak serum total CPK activity after
myocardial infarction (left bar graph) and after cata-
therization (right bar graph). Although the bars begin at
the abscissa, the range of patient values was 180–1360
(left bar) and 36–570 (right bar). The vertical line
represents ± 1 SD.](http://heart.bmj.com/BrHeartJ: first published as 10.1136/hrt.37.11.1144 on 1 November 1975. Downloaded from http://heart.bmj.com/ on October 23, 2023 by guest. Protected by copyright.)
In spite of the obvious increase in total serum CPK activity generally observed in these patients, MB CPK isoenzyme activity determined quantitatively remained within the normal range in all cases after catheterization, with no value exceeding 0.004 IU/ml (Fig. 3). Results of the qualitative assay showed no MB CPK in any of the cases, with MM CPK as the only isoenzyme visualized. As we have previously shown, the quantitative procedure used detects some MB CPK in serum from normal subjects though qualitative assay of the same sample fails to do so. No patient undergoing catheterization developed clinical or electrocardiographic evidence of myocardial infarction, arrhythmia, or haemodynamic decompensation. Thus, cardiac catheterization was not associated with increased MB CPK despite substantial rise in total serum CPK activity.

In 50 patients with documented acute myocardial infarction, total peak CPK averaged 0.780 ± 0.087 (SD), (range 180–1360) (Fig. 1), exceeding the upper limit of normal in all cases. Furthermore, in contrast to patients undergoing catheterization, MB CPK isoenzyme activity was significantly raised in all cases after infarction with peak MB CPK averaging 0.086 ± 0.037 (SD) (range 23–96) (Fig. 3).

As can be seen in Fig. 3, MB CPK activity in samples from normal subjects was indistinguishable from activity in samples from patients undergoing catheterization. However, tenfold increases in MB CPK were evident in patients with infarction.

**Discussion**

The interpretation of serum enzyme increases after cardiac catheterization and coronary arteriography has been difficult. Significant rise in serum aspartate transferase (AST) has been reported in up to 55 per cent of cases (Adrouny et al., 1963), while other investigators have observed only trivial changes (Harrison, Matloff, and Wexler, 1972). Raised lactic dehydrogenase has been observed (Burckhardt et al., 1968) but not consistently (Chahine, Eber, and Kattus, 1974; Michie et al., 1970). Significant rises in total serum CPK activity after cardiac catheterization have been reported frequently (Chahine et al., 1974; Harrison et al., 1972) and it is, therefore, apparent that detection of myocardial infarction after cardiac catheterization cannot be based on total serum CPK rises (Marpole et al., 1968). Some imply that raised serum CPK activity after coronary arteriography reflects release of enzyme from the heart (Sitzman and Gutheil, 1966), though contributions from intramuscular injections (Harrison et al., 1972; Meltzer, Mrozak, and Boyer, 1970) or
other soft tissue trauma have been recognized (Wolfe et al., 1970). Since patients with 'pre-infarction angina' commonly receive parenteral medications before being admitted to hospital, enzyme increases may be particularly difficult to interpret in this group. Accurate detection of myocardial infarction in the immediate post-catheterization period in these patients is of paramount importance, since the success of coronary revascularization may be compromised in the presence of evolving or established infarction (Roberts and Sobel, 1974).

In the present study, serum CPK isoenzyme activity was determined in serial samples from 53 patients after cardiac catheterization. All patients received intramuscular premedication. In keeping with results of other studies (Marpole et al., 1968; Michie et al., 1970), total serum CPK activity was significantly raised in 41 patients and minimally increased in the remainder. However, MB CPK activity remained within the normal range in all cases, indicating that myocardial damage did not occur and that increased serum CPK activity did not reflect release of enzyme from the heart. This interpretation was supported by the lack of clinical and electrocardiographic evidence of myocardial injury.

Results were quite different in 50 patients with proven myocardial infarction. All patients with confirmed myocardial infarction had a significant increase in serum MB CPK within 6 to 8 hours of the onset of chest pain. Thus, it appears likely that a rise in MB CPK within 6 to 8 hours after cardiac catheterization would occur in patients with coronary artery disease who have sustained myocardial infarction before, or even precipitated by, the procedure. Detection of infarction on the basis of CPK isoenzymes in this context may be particularly critical since the electrocardiogram may be misleading or difficult to interpret because of previous infarction, conduction defect, ventricular hypertrophy, arrhythmia, tachycardia, or non-specific changes. Thus, determination of MB CPK activity is particularly useful in the selection of patients for coronary revascularization, particularly those with 'pre-infarction angina' and those at high risk with left main coronary disease or conditions such as calcific aortic stenosis for whom prompt surgery is frequently contemplated.

Our results indicate that in contrast to an increase in activity of conventionally measured serum enzymes, increased MB CPK isoenzyme activity is a sensitive and useful criterion of myocardial infarction in patients undergoing cardiac catheterization.

References


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