Estimation of Infarct Size in Man and its Relation to Prognosis

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SUMMARY
Infarct size was assessed quantitatively in 33 patients with acute myocardial infarction with a new technic based on analysis of serial serum creatine phosphokinase (CPK) changes to determine its relationship to prognosis. We have recently measured infarct size in the conscious dog with this method which takes into account CPK distribution space, fractional disappearance rate, proportion degraded in myocardium, and proportion released into the circulation, and we have validated the method by measurement of myocardial CPK depletion in the same animals. In the present study, CPK activity (determined spectrophotometrically) and isoenzyme profiles (assayed electrophoretically) were measured in patient serum samples obtained every 2 hours. Infarct size was estimated by mathematical analysis of serial CPK changes utilizing the method previously developed in the conscious dog model. CPK isoenzyme profiles demonstrated prominent anodal bands, absent from normal serum, indicating that enzyme elevations reflected CPK released from heart rather than skeletal muscle. In 19 class I-II survivors (New York Heart Association) estimated infarct size was 31 ± 4 CPK-gram-equivalents (CPK-g-Eq). It was significantly larger (P < 0.01), 103 ± 14, in nine patients who died and in four class III or IV survivors (91 ± 8). Estimation of cumulative infarct size differentiated patients with electrocardiographic changes and clinical sequelae from complications such as pericarditis from those patients with extension of infarction. Thus, infarct size can be assessed quantitatively in patients with acute myocardial infarction and provide a useful diagnostic and prognostic index based on the extent of myocardial damage.

Additional Indexing Words:
Ischemic injury Myocardial necrosis Cell death Serum enzymes
Myocardial CPK CPK isoenzymes Serum CPK Power failure

Effective coronary care units have diminished mortality resulting from arrhythmia in patients with myocardial infarction. Accordingly, power failure has become the major cause of death in this setting. This syndrome is associated with necrosis of substantial portions of myocardium1,2 and it may reflect destruction of a critical mass of functional heart muscle. Infarct size can be modified in the experimental animal with technics potentially applicable to man,3 and the advent of saphenous vein coronary revascularization procedures makes reperfusion possible in patients with myocardial infarction at virtually all stages of evolution of this process. However, quantification of infarct

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INFARCT SIZE IN MAN

size and elucidation of the relationship between infarct size and prognosis in individual patients are necessary for assessment of efficacy of metabolic, pharmacologic, and surgical interventions in reducing infarct size and for appropriate selection of patients suitable for therapy associated with significant risk.

We have recently developed a method to measure infarct size noninvasively in the conscious dog on the basis of analysis of serial changes in serum creatine phosphokinase (CPK) activity.\(^4\) Infarct size was directly related to myocardial CPK depletion.\(^5\)\(^,\)\(^6\) Furthermore, CPK released into serum was a constant fraction of myocardial CPK depletion.\(^4\) CPK released could be calculated directly from serial serum enzyme values because the instantaneous disappearance rate of serum CPK was monoexponential with a constant fractional disappearance rate. In 22 conscious dogs, infarct size measured by this approach correlated closely with infarct size measured directly by analysis of myocardium in the same animals \(r = 0.96, N = 22\).\(^4\) Furthermore, alteration of infarct size produced by pharmacologic and physiologic interventions was reflected by corresponding changes in infarct size calculated indirectly from serum CPK changes and infarct size measured directly by analysis of myocardium.

In the present study estimation of infarct size by analysis of serial serum CPK changes was performed in patients with coronary artery disease. Infarct size was assessed by this technic in 33 patients admitted to the Myocardial Infarction Research Unit and related to clinical course and prognosis. Constants necessary for application of the mathematical analysis required to assess infarct size from serum CPK changes in man were obtained by determinations of CPK activity in human myocardium removed out of necessity during cardiac surgical procedures. A new method of analysis of CPK isoenzyme profiles in serum and tissue extracts was utilized to ascertain the myocardial origin of CPK contributing to total serum CPK values employed in the mathematical analyses of infarct size.

Methods

Patients Studied

Consecutive patients with acute myocardial infarction studied in the Myocardial Infarction Research Unit within 24 hours after the onset of symptoms were included in this investigation, except for those with marked hypotension (systolic pressure less than 85 or diastolic pressure less than 60 mm Hg) at the onset of the CPK sampling period, or those whose serum CPK was already maximum at the time of admission. The diagnosis of myocardial infarction was based on the presence of at least two of the following three criteria: (1) characteristic chest pain of greater than 1-hour duration; (2) transmural electrocardiographic changes including evolution of q waves; and (3) serial elevations of serum glutamic oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH), and CPK conforming to the pattern typically seen in patients with myocardial infarction. The diagnosis was corroborated by the presence of an abnormal LDH\(_1\)/LDH\(_2\) ratio. Thus, in all patients this ratio exceeded 1.1, in comparison to the mean \(\pm SE\) for a control population of 0.70 \(\pm\) 0.18.\(^7\) Surviving patients have been reevaluated every 2 months.

CPK Determinations

Myocardial CPK. CPK content and protein were determined in myocardial samples obtained at autopsy or from tissue which was removed of necessity at the time of valve replacement or during other cardiac surgical procedures as previously described.\(^8\)

Serum CPK Determinations

Samples were obtained every 2 hours from the time of admission until CPK activity returned to normal. Because of the nature of the cumulated CPK curve (see below), infarct size calculation generally required only data from the first 10–15 samples. The sampling procedure was simplified by the use of a heparin lock which was flushed prior to sampling. Blood was allowed to clot, centrifuged for 10 min at 7500 \(\times\) g at 4°C, and serum removed and quick frozen at \(-70^\circ\)C prior to storage for a maximum of 48 hours in a \(-20^\circ\)C freezer. Prior to assay, serum samples were thawed rapidly under tap water. CPK was assayed by the back reaction with cysteine activation according to the Rosalki method as previously described,\(^9\) in a final volume of 1.05 ml. When necessary, serum was diluted with 0.01 M TRIS (trihydroxymethylaminomethane hydrochloride), pH 7.4, containing 0.2% bovine serum albumin.

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CPK Isoenzyme Determinations

CPK isoenzymes were determined with a new procedure employing electrophoresis on cellulose acetate membranes and detection of isoenzyme bands by fluorescence scanning. In control experiments, activity of each isoenzyme was readily detectable when it was equal to or exceeded 10 mIU/ml. Isoenzyme determinations were performed with tissue extracts diluted to provide total CPK activity equal to 500 mIU/ml and with serum samples diluted to provide less than 500 mIU/ml. Electrophoresis was performed with 30 μl samples in TRIS-barbital, pH 8.8, 1 mM ethyleneglycoltetraacetic acid (EGTA), at 4°C for 65 min at 250 V constant voltage. Visualized was achieved by applying another strip, incubated in staining mix, to the sample, and incubating the two-strip sandwich for 25 min at 37°C. The staining mix contained 150 mM glycylglycine pH 7.2, 10 mM MgCl₂, 7.3 mM glucose, 1 mM sodium adenosine diphosphate (ADP), 1 mM sodium adenosine monophosphate (AMP), 0.3 mM nicotinamide dinucleotide phosphate (NADP), 1 mM dithiothreitol (DTT), 0.3 IU/ml hexokinase, 0.15 IU/ml glucose-6-phosphate dehydrogenase (G6PDH) ± 2 mM creatine phosphate (CP). The sample strip was then placed between two glass slides and scanned by fluorescence densitometry performed with a Turner model 111 Fluorometer equipped with a 7–37 primary and a 2A secondary filter. Peak areas were recorded with a Perkin-Elmer Potentiometric Recorder (5 mV full scale). The quantitative characteristics of the assay procedure used, its reproducibility, and its accuracy have recently been characterized.

Analysis of Data

Infarct size was calculated according to the formulae recently derived and described in detail in an animal study. The principle underlying the calculation is that the instantaneous rate of change of serum enzyme activity (dE/dt) is due to two competing phenomena: (1) release of myocardial CPK into the circulation as a function of time [f(t)] and (2) disappearance of CPK conforming to first-order kinetics with a constant fractional disappearance rate, kₐ. Thus:

\[ \frac{dE}{dt} = f(t) + k_a E \]  \hspace{1cm} (1)

where E = serum enzyme concentration. With knowledge of the distribution space into which CPK released from the heart is diluted, the instantaneous fractional disappearance rate of CPK (kₐ), the CPK concentration in normal myocardium ([CPKₙ]), the concentration of CPK in infarcted myocardium ([CPKᵢ]), and the total amount of myocardial CPK depleted (CPKᵢ), one can calculate infarct size (I) in CPK-g-Eq from the relationship:

\[ I = \frac{CPK_0}{[CPKₙ] - [CPKᵢ]} \]

One CPK-g-Eq is that quantity of tissue from which CPK depletion has occurred equal in magnitude to CPK depletion in 1 g of myocardium exhibiting homogeneous necrosis. CPKᵢ can be determined from total CPK released (CPKᵢ) when the fraction of CPKᵢ released into the circulation is known. CPKᵢ can be calculated by rearrangement of terms in equation 1 and integration providing the following:

\[ \int_0^t f(t) dt = \int_0^t \left( \frac{dE}{dt} - k_a E \right) dt = E_t - k_a \int_0^t Edt \]

in which the last term may be approximated by \( k_a \Delta t \). The value of the expression

\[ \int_0^t f(t) dt \]

represents the concentration of CPK (IU/ml of serum) released from the heart that would have been observed had there been no removal of CPK from serum. Accordingly, the amount of CPK released (CPKᵢ) = \( \int_0^t f(t) dt \) multiplied by the CPK distribution space.

In the dog, only 30% of the enzyme activity lost from myocardium is released into the circulation; the remainder undergoes local degradation. In order to obtain the corresponding value for this fraction in man, analysis of myocardium obtained within minutes after death would be required in a patient who died at a specified interval after the onset of his first episode of myocardial necrosis. Since such conditions are difficult to meet we have used the same fraction as that obtained in the dog (30%) in the present analysis. The fractional disappearance rate, kₐ, for CPK in man was estimated from the means of the terminal fractional disappearance rates observed in 24 patients with a single, discrete peak of CPK elevation, and was found to be 0.001 ± 0.0001 (mean ± SE). The terminal portions of these curves were used on the assumption that additional myocardial CPK release into the circulation had ceased when CPK disappearance became monoeponential. The value used for

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distribution volume of CPK was 11.4% of body weight.\textsuperscript{4, 9}

The value of \( \int_{0}^{t} f(t) \, dt \) was obtained in all patients by use of a Fortran program on a Sigma 3 computer. The computer program was utilized to plot serial serum CPK changes, calculated \( f(t) \), and \( \sum_{0}^{t} f(t) \Delta t \) as a function of time. Forty mIU/ml, the upper limit of normal CPK activity, was subtracted from all enzyme values prior to mathematical analysis.

**Results**

**Myocardial CPK Content**

Myocardial CPK activity was determined in three samples of left ventricular muscle and two left ventricular papillary muscles obtained at operation, and six autopsy specimens obtained 4-27 hours after death. CPK activity in fresh human ventricle was 540 ± 38 IU/g (mean ± se, \( N = 5 \)). Values in specimens obtained at autopsy ranged from 70 to 410 IU/g, with lowest values in samples obtained relatively long after death. However, values extrapolated to the time of death were comparable to those obtained in fresh tissues. Accordingly, in mathematical analyses, 540 IU/g was used as the value for normal myocardial CPK content.

**Myocardial CPK Isoenzymes**

Representative isoenzyme profiles of CPK in heart muscle extracts, skeletal muscle extracts and serum from a patient with myocardial infarction are shown in figure 1. An average of 46% of myocardial CPK appeared as an anodal band (MB)\textsuperscript{*} (range 39-51, \( N = 6 \)). In serum from patients with myocardial infarction a band with the same electrophoretic mobility appeared. On the other hand, eight samples of fresh human skeletal muscle (pectoral muscle and abdominal wall muscle) did not exhibit an MB band even though total tissue extract

\*MB = the isoenzyme of CPK composed of one subunit of the skeletal muscle type (M) and one of the brain type (B).

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**Figure 1**

CPK isoenzyme profiles from serum and tissue extracts. (A) Tracings of observed fluorescence associated with CPK isoenzyme distribution following electrophoresis on cellulose acetate. The dashed line indicates the serum or tissue extract front. (B) Fluorescence densitometry scans of the strips shown in A. As can be seen, heart, skeletal muscle, and serum all contain a band of the origin (MM). However, heart extracts and serum in patients with myocardial infarction contain a more anodal band (MB). No bands are visualized when creatine phosphate (CP) is omitted from the visualization mixture. This indicates that the visualized bands represent CPK isoenzymes. The small anodal peak in B is clearly associated with serum or tissue extract fronts and is not related to an isoenzyme of CPK.

CPK activity was adjusted to correspond to that in heart extracts. Apparent CPK activity was entirely dependent on the presence of substrate, and the isoenzyme detection method used was sensitive enough to visualize CPK activity readily in normal serum.

**Serial Serum CPK Changes following Myocardial Infarction**

In patients with uncomplicated myocardial infarction serum CPK activity began to rise 6-8 hours after the onset of chest pain, peaked within 16-30 hours, and fell to normal within 3-4 days. The typical shape of the serum CPK curve was similar to that seen in the conscious dog subjected to coronary artery occlusion.

Cumulated CPK release calculated according to the model described is illustrated in a representative case in figure 2. Again, in
general the shape of the cumulated CPK release curve in the conscious dog is similar to that in man. The terminal portion of the cumulated CPK curve becomes flat at a time when total serum CPK activity is still elevated. This occurs when serum CPK activity is decaying monoexponentially indicative of the absence of additional release of myocardial CPK into the circulation.

Infarct Size in Patients Studied

Mean patient age was 60 years, and overall mortality was 27%. The average interval of observation after infarction was 5.3 months. In general, patients with larger infarcts died or exhibited severe residual, functional cardiovascular impairment.*

Calculations of infarct size depend on the premise that CPK released into the circulation is derived from myocardium rather than other tissues such as skeletal muscle. Isoenzyme profiles of heart and skeletal muscle are shown in figure 1. As can be seen, heart muscle exhibits a prominent anodal band (MB) averaging 46% of total myocardial CPK (N = 6 fresh samples from different hearts). On the other hand, skeletal muscle samples studied failed consistently to exhibit MB (N = 8 muscles). Furthermore, in six patients with shock not associated with myocardial infarction MB in serum averaged only 1% of total CPK activity (range 0–3) even when total activity was elevated 10- to 30-fold. However, in patients with myocardial infarction MB represented at least 10% of total serum CPK and at least 16 mIU/ml when samples were obtained 24 hours after the onset of chest pain (range 10–34%, mean 21%, N = 13). In samples obtained earlier, the percent MB and absolute MB activity were frequently even higher. The fractional disappearance rate of MB was 0.2 ± 0.01%/min (mean ± se, N = 5). A representative example of the disappearance of MB CPK compared with total CPK in the same patient is shown in table I. MB consistently disappeared much more promptly from serum than total CPK after myocardial infarction. In all patients studied markedly elevated total serum CPK activity was associated with the maximum percent MB seen in the same patient, and late elevations of total CPK were associated with late elevations of MB CPK. Accordingly, it is unlikely that spurious

*Tabulated results of CPK data, clinical characteristics, and course of all patients are available upon request and have been omitted because of space limitations.
calculation of infarct size resulted from significant contributions of skeletal muscle CPK to total serum CPK activity. Thus, it appears that even in patients with severe hypotension, the method described is useful in determining infarct size when CPK isoenzyme determinations are performed on the same samples to exclude from the calculations total CPK elevations reflecting primarily contributions from skeletal muscle.

Infarct Size and Prognosis

Infarct size in CPK-g-Eq is closely related to mortality and to residual functional impairment in survivors. In the 33 patients studied there were nine deaths, eight of which resulted from power failure. The relationship between infarct size and mortality is illustrated in figure 3. Eight of 12 patients with infarct size exceeding 65 CPK-g-Eq died. On the other hand, only one of 21 patients with infarct size less than 65 CPK-g-Eq died \((P<0.001)\), and that death was sudden and unrelated to power failure. Infarct size in patients who died averaged 103 ± 14 CPK-g-Eq (mean ± se) compared to 41 ± 6 CPK-g-Eq in survivors \((P<0.001)\).

In addition to mortality, infarct size was closely related to clinical class of survivors, as shown in figure 4. In patients who died with power failure, infarct size averaged 109 ± 10 CPK-g-Eq. In patients who survived but manifested marked functional impairment (class III or IV) infarct size averaged 91 ± 8 CPK-g-Eq. In the one patient who died without power failure, infarct size was only 50 CPK-g-Eq. In patients who survived without marked functional impairment (clinical class I or II) infarct size was 31 ± 4 CPK-g-Eq. Infarct size in class III or IV survivors was significantly greater \((91 ± 8)\) than in class I and II survivors \((31 ± 4)\) \((P<0.001)\). All patients with >65 CPK-g-Eq infarcts were initially class I or II.

Infarct Size and Electrocardiographic Localization of Infarction

As shown in table 2, anterior transmural infarctions were considerably larger than inferior transmural infarctions in patients studied. Furthermore, subendocardial infarctions were consistently smaller than transmural infarctions. The average infarct size in 14 patients with anterior infarction was 82 CPK-g-Eq compared to 50 CPK-g-Eq in 14 patients with interior infarction and 14 CPK-g-Eq in five patients with subendocardial infarction. These findings are compatible with the prevailing view that subendocardial infarction generally involves a relatively small mass of myocardium.

![Graph](http://circ.ahajournals.org/)

**Figure 3**

Infarct size and mortality. When patients are divided according to infarct size in CPK-g-Eq, striking differences in mortality and clinical class of survivors are apparent as shown in the bar graphs.

**Figure 4**

Infarct size and clinical outcome. Bars and vertical slashes represent mean values ± SE for infarct size in CPK-g-Eq in the number of patients (n) indicated in each group categorized according to clinical outcome.
Table 2

Infarct Size and Location*

<table>
<thead>
<tr>
<th>Location</th>
<th>N</th>
<th>Infarct size (CPK-g-Eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>14</td>
<td>82 ± 10</td>
</tr>
<tr>
<td>Inferior</td>
<td>14</td>
<td>50 ± 8</td>
</tr>
<tr>
<td>Subendocardial</td>
<td>5</td>
<td>14 ± 7</td>
</tr>
</tbody>
</table>

*Results are expressed as means ± se. Significance was determined with Student's t test.

Detection of Extension of Myocardial Necrosis

In experiments in conscious dogs we have previously demonstrated that extension of infarction produced by isoproterenol administration is followed by a second peak of elevated serum CPK activity and a corresponding increase in the cumulated CPK released into the circulation. In the animal experiments, confirmation of the extension of myocardial necrosis was obtained at autopsy when infarct size determined directly corresponded closely to infarct size calculated from total cumulated CPK released. In the current patients, several instances of extension of infarction were observed manifested by changes in serum CPK activity and cumulated CPK released (fig. 5) similar to those seen in the dog. These episodes occurred in association with clinical evidence of extension of infarction such as chest pain, S-T-segment deviations in electrocardiograms, and subsequent rises in other serum enzymes. However, not all episodes of chest pain or electrocardiographic abnormalities were followed by enzymatic evidence of extension. As can be seen in figure 5, cumulated CPK released from myocardium calculated from serial changes in serum CPK activity facilitates interpretation of clinical manifestations of ischemia.

Discussion

Results obtained indicate that infarct size is a major determinant of prognosis after acute myocardial infarction. The method utilized permits estimation of infarct size itself rather than related phenomena such as impaired ventricular performance or diminished myocardial perfusion. Previous attempts to correlate peak levels of serum enzymes such as SGOT, LDH, and CPK with infarct size and prognosis have revealed a general parallel. In man SGOT peak values exceeding 250 Karmen units are associated with 50% mortality. However, peak values between 100 and 500 do not correspond closely to infarct size.

Mortality of patients with peak CPK values exceeding 600 mIU/ml was found to be 50% compared to 6% in patients with peak CPK values less than 600. However, because of unavoidable scatter in the data, the relationship could not be utilized to determine prognosis of the individual patient.

Estimation of infarct size by the analysis of serial CPK changes employed in the present study offers several advantages compared to determination of peak values alone. Peak serum enzyme activity is influenced by several factors in addition to infarct size including rate of enzyme release and contribution of enzyme from cells in the heart other than myocardium. Thus, patients with large infarcts who release large amounts of enzyme from the heart slowly will exhibit peak serum enzyme values considerably lower than those seen in patients with the same extent of myocardial damage who release enzyme into the circulation more rapidly. Furthermore, peak enzyme values may be the same in patients with and without multiple small extensions of infarction which in turn affect prognosis. The method described in this study permits estimation of infarct size and quantification of extension of infarction taking into account the rate of myocardial enzyme release as well as the magnitude of serum enzyme elevations.

Peak serum LDH and SGOT appear to
be influenced by enzyme contributions from inflammatory infiltrates in the heart associated with acute infarction. Thus, they do not necessarily bear a direct relationship to the mass of myocardium undergoing ischemic necrosis. On the other hand, we have previously shown that myocardial CPK depletion and total CPK released into serum are directly related to the extent of experimental myocardial infarction. In conscious and open-chest animals subjected to coronary artery occlusion myocardial CPK depletion is proportional to infarct size measured grossly by weight. It is directly related as well to the magnitude of reduction of regional myocardial blood flow 24 hours after occlusion and to the severity of derangement of mitochondrial function in local regions. Furthermore, the proportion of CPK depleted from myocardium released into serum in the conscious experimental animal is virtually constant even in the face of markedly altered hemodynamics fol-
lowing isoproterenol administration, inferior vena caval constriction, or ventricular pacing. In contrast, peak serum CPK activity is markedly influenced by the rate of release of enzyme from the heart.

Large contributions to elevated serum CPK from other tissues, especially skeletal muscle, could spuriously influence calculations of infarct size based on the method employed in this study. To avoid erroneous interpretations, we have analyzed serum CPK isoenzyme profiles in tissue extracts and in serum with a new method possessing the required sensitivity. Human skeletal muscle extracts exhibited almost entirely MM*CPK in marked contrast to myocardial extracts which contained an average of 46% MB. Patients with shock without myocardial infarction exhibited no appreciable elevation in serum of the MB isoenzyme of CPK. The fact that total serum CPK elevations were consistently associated with prominent MB bands in serum samples from patients with myocardial infarction suggests that the main source of serum CPK elevations used in calculations of infarct size was myocardium.

Results indicate that analysis of serial serum CPK changes can be used to assess infarct size in man and that prognosis is closely related to estimated infarct size. The technic should provide an improved basis for selection of patients for therapeutic procedures with significant risk and for evaluating the effects of therapeutic interventions on infarct size and prognosis.

References


*Isoenzyme of CPK composed of two subunits of the skeletal muscle type (M).


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