Estimation of Acute Myocardial Infarct Size in Man by Serum CK-MB Measurements

PEER GRANDE, M.D., BIRGIT FISCHER HANSEN, M.D., CLAUS CHRISTIANSEN, M.D.,
and JØRGEN NÆSTOFT, M.Sc.

SUMMARY This study was performed to determine the relationship between myocardial infarct size estimated by serum CK-MB methods and the extent of irreversible injury in acute myocardial infarction. In 321 consecutive patients, infarct size was estimated by different mathematical models, and in 22 patients who died in hospital, the extent of myocardial necrosis was determined by autopsy. We also investigated the depletion of CK-MB in infarcted tissue, the recovery of CK-MB in the plasma volume, and the elimination of CK-MB from plasma.

Myocardial CK-MB depletion was relatively greater in the larger infarcts, whereas the recovery of enzyme in plasma was independent of the infarct size. Correction of serum CK-MB for changes in plasma volume improved the estimate significantly (p < 0.05). The correlation between the measured infarct size (g) and the estimated infarct size (units per liter and gram-equivalents) was highly significant (r = 0.85–0.89, see = 23–27%, p < 0.001). Thus, a semiquantitative expression of the extent of myocardial necrosis can be determined in vivo.

THE REASON for developing methods to assess the extent of acute myocardial infarction (AMI) arises from the hypothesis that infarct size (IS) is a major determinant of prognosis and that treatment of the ischemic injury can influence the prognosis favorably.

One of the most promising techniques used to estimate infarct size is quantification of the release of creatine kinase (CK) by frequent serum samples. In experimental studies in healthy dogs, this serum determination correlates almost perfectly with the depletion of CK in the infarcted myocardium. Studies of AMI in man have demonstrated reasonable agreement between infarct size estimated by serum CK models and left ventricular hemodynamics, prognosis, and postmortem macroscopic infarct size measurements. However, some investigators have criticized the enzymatic models and could not reproduce some of the results from experimental dog studies. Theoretically, an estimation of IS by measuring CK-MB should improve the reliability of the quantification. Recent studies comparing IS estimated from serum CK-MB with indirect indicators indicate that this is the case.

We demonstrated that the IS can be calculated just as well with few blood samples as with serial samples, allowing us to examine the reliability of enzymatically estimated IS in a large group of patients with AMI.

Patients and Methods

From June 1, 1978, to May 31, 1979, 846 patients were admitted to the coronary care unit at Glostrup Hospital with suspected AMI. According to the World Health Organization criteria, 20, 21, 393 had AMI. Of these, 72 were excluded: 48 because the symptoms of AMI had lasted more than 15 hours before admission or because the second blood sample did not show higher CK-MB activity than the first and 24 because not enough blood samples had been obtained because patients died or were transferred to another department. The remaining 321 patients form the study group. Forty-three of these patients died within 18 days and were divided into group A, which included 22 patients in whom a detailed heart autopsy was performed, and group B, which included 21 patients in whom no detailed heart autopsy was performed. All patients autopsied had survived for at least 48 hours from the appearance of CK-MB activity in serum and there were no signs of reinfarction before death. Furthermore, all plasma curves showed a pure elimination phase (first-order kinetics).

The 22 patients in group A included 12 women and 10 men who died at a mean age of 69.7 years (range 49–88 years). The median time from onset of symptoms until death was 6.4 days (range 2–14 days). Cardiogenic shock was the main cause of death in 12 patients and recurrent ventricular fibrillation in six patients. Two died from asystole and two from non-cardiac causes.

Heart biopsies were taken postmortem every 6 hours for 30 hours in eight patients from group B. The total enzyme depletion in whole heart homogenates was measured in 10 other patients.

In 10 patients who died without signs of heart disease, myocardial biopsies were made to estimate CK and CK-MB activity. In 13 patients, consecutively admitted to the coronary care unit within less than 5
hours from onset of symptoms, blood samples for CK-MB determination were taken every 2 hours until CK-MB had returned to base level.

**Blood Sampling Procedure**

Blood samples were taken from all 321 patients immediately after admission, at 8 a.m., 2 p.m. and 9 p.m. on the next three days, and thereafter at 8 a.m. daily. If pronounced pain recurred, the frequent blood sampling procedure was repeated.

**Biochemical Measurements**

CK was measured according to the Scandinavian recommended methods and CK-MB determination was performed by electrophoresis on agarose gel followed by fluorescence scanning. The interassay variations are below 10%. Serum α₂-macroglobulin concentration was determined by electroimmunoassay and serum protein concentration by the Biuret method.

**Tissue Extract Measurements**

Tissue extracts were made from about 0.3 g tissue (wet weight) in a mixture of 10 ml 0.25 mol/l sucrose, 3 ml 0.01 mol/l TRIS buffer (pH 7.4), 3 ml 1 mmol/l EGTA (pH 7.4) and 3 ml 1 mmol/l mercaptoethanol, and homogenized on ice in an Ultra Turax blender for 1 minute. The homogenate was centrifuged (3500 g) and the supernatant was used to determine isoenzyme activity. The samples were diluted with heat-inactivated serum or TRIS buffer to the linear part of the standard curve.

**Postmortem Examination of the Heart (Group A)**

Autopsy was performed within 24 hours of death. The heart was removed and studied immediately without knowledge of the results of serum enzyme measurements. The ventricular myocardium was sliced transversely at intervals of about 1 cm from the apex of the heart to the apex of the papillary muscles.

The nitroblue tetrazolium (NBT) test was performed on all the myocardial slices. Quantification of AMI is performed by the point-counting technique within 2 days of fixation in formalin to avoid shrinkage. Each of the NBT-tested myocardial slices is covered by a transparent celluloid film on which is drawn a regular net of quadrants 2 x 2 mm. The total area of ventricular myocardial mass, including the interventricular septum, is counted first, then the area of AMI. The extent of the infarct was expressed as a percentage of each slice. The amount (g) of infarct was calculated from the weight of the slice. To control the validity of the NBT test, transmural samples of the ventricular myocardium were fixed in formalin and histologically examined.

The central slice of the infarct was weighed and divided horizontally into two thin sections. One was used for the NBT test and the other was examined for enzyme content (fig. 1). Each slice was divided from epicardium to endocardium in continuous longitudinal biopsies. These were subdivided into three or four smaller pieces before the enzyme activities in the tissue extracts were determined. In the transmural infarctions, CK-MB activity decreases toward the center of the infarct (see Results section). Therefore, corrections were made as illustrated in figure 2.

**Calculations for Estimating IS by Serum CK-MB Activity**

IS can be estimated as

\[
\text{Cumulated concentration of enzyme} \times \frac{\text{Size of distribution appearing in distribution space (U/l)}}{\text{Fraction of depleted enzyme distribution space (l)}} \times \frac{\text{Size of distribution appearing in distribution space (U/l)}}{\text{Fraction of depleted enzyme}}
\]

The amount of enzyme in the distribution space has been studied by three models based on:

\[
IS = \int_0^T f(t) dt = k_e \int_0^T E(t) dt + E(T) \approx k_d \int_0^T E(t) dt
\]

where E(t) is the specific CK-MB activity (U/l) in serum at time t (hours). The function f(t) is the appearance function, i.e., the hypothetical value of dE/dt without any elimination. The factor kₐ is the elimination constant (assuming first-order kinetics). T is the time until the CK-MB level can no longer be detected.

The first, accumulation, model is:

\[
\int_0^T E(t) dt = \sum_{i=1} E(t_i) \Delta t_i,
\]

where \(\Delta t_i \approx 8\) h \[\Delta t_i = \frac{(t_{i+1} - t_{i-1})}{2}\].

This is a simple summation of the serum enzyme levels, taking the time into account.
FIGURE 2. The CK-MB and CK contents in the entire infarct were estimated from one slice. A transmural myocardial infarct viewed from the epicardium could be described approximately as a circle. After measuring the enzyme content in biopsies derived from one slice of the infarct, the mean activity was calculated from the biopsies corresponding to the three areas shown. The activity in the entire infarct was calculated as: (CK-MB₁ × 1/9 of IS) + (CK-MB₂ × 3/9 of IS) + (CK-MB₃ × 5/9 of IS). IS is the total amount of myocardial necrosis determined by histochemical and histologic techniques.

The second, log normal, model, is:

\[ E(t) = \frac{C₀ \times k₁^2}{k_d - k₁} \left( t \cdot e^{-k₁t} + \frac{1}{k_d - k₁} (e^{-k₂t} - e^{-k₁t}) \right) \]  

where \( C₀ \) expressed the IS in U/l; \( k₁ \) and \( k₂ \) are set equal for the sake of simplicity. By the compartment model, the ascending and descending parts of the curve are determined separately, as opposed to the log normal model.

The distribution space for CK molecules equals the plasma volume (PV): 

\[ PV = (100 - \text{hematocrit}) \times \text{blood volume} \]

Blood volume was estimated according to Feldschuh and Enson. Serum activities of CK-MB were corrected to constant levels of either serum \( \alpha₂ \)-macroglobulin or serum protein to eliminate changes in plasma volume during the blood sampling period. The corrections for changes in plasma volume were done by multiplying the enzyme activities by the correction factor \( A₀/A₁ \). \( A₀ \) is the concentration of \( \alpha₂ \)-macroglobulin or protein, respectively, in the first blood sample drawn, and \( A₁ \) is the concentration of \( \alpha₂ \)-macroglobulin or protein determined in the subsequent samples together with the enzyme activity.

**Statistical Methods**

Unless otherwise stated, the \( t \) test for unpaired data and linear and multiple regression analysis were used. The data are given with ± 1 coefficient of variation (CV%) or 1 SEM.
Results

Heart Autopsy

In the 14 patients with transmural infarcts, the median IS was 89 g (range 54–160 g), whereas the median of eight subendocardial infarcts was 61 g (range 4–78 g) (p < 0.01, two-sample Wilcoxon test). The coronary arteries were occluded by thrombosis in 10 of the 14 transmural infarcts, compared with one of the eight subendocardial infarcts (p < 0.05, Fisher’s test). There was, however, no correlation between the fraction of myocardial-depleted enzyme reaching the plasma volume (k_d) and the occlusion of the coronary arteries.

Determination of the Amount of CK-MB

Reaching the Plasma Volume

The amount of enzyme that appeared in plasma corresponds to the area below the plasma curve (AUC) multiplied by the elimination constant (k_d).

Table 1 shows that the “true” plasma curve and the area estimated from a few blood samples were highly correlated (r = 0.97–0.995) in the 13 patients who had blood samples drawn every 2 hours. Reproducibility was calculated from different estimates of IS obtained by using different sets of three daily samples of serum CK-MB. The log normal and compartment model had the best reproducibility. The IS in all 321 patients was calculated by all three models. In 12 cases, the IS calculated by the log normal model was wrong, evaluated from k_d estimation; the other two models did not show this type of error.

The monoexponential part of the plasma curve was used to estimate k_d. Table 2 shows the mean k_d of CK-MB and CK in patients with uncomplicated AMI and in those where AMI occurred with liver disease or cardiogenic shock. The mean values in the three patient categories were similar. The mean k_d for CK was half the mean k_d for CK-MB, corresponding to half-lives of 20 and 9 hours, respectively.

Table 3 demonstrates the relationship between k_d and infarct size in the 226 patients without previous infarct. The k_d was independent of the infarct size. Table 3 also shows that the biologic variation of k_d was of the same order in three infarct size groups (mean 0.021 hr⁻¹), whereas the methodologic variation changed considerably as a function of infarct size. All patients with large infarcts, 83% of the median size infarcts, and 20% of the small infarcts had curve-fit precision below 0.021 hr⁻¹.

Among the 226 patients, 21 had reinfarction during hospitalization. In this subgroup, the mean k_d was 0.071 ± 0.008 during the first infarction and 0.077 ± 0.007 during the reinfarction (mean ± SEM, NS).

Corrections for Changes in Plasma Volume During Infarction

The percentages of over- and underestimation of the IS in 13 patients without correction and after serum protein correction were compared with values after \( \alpha_2 \)-macroglobulin corrections. The assumption for the \( \alpha_2 \)-macroglobulin correction is: unchanged \( \alpha_2 \)-macroglobulin mass in the plasma when the plasma volume derangement accompanying AMI and treatment occurs. When no correction was used, the error in IS ranged from an overestimation of 18% to an underestimation of 12%. With protein correction, the corresponding values ranged from 7% overestimation to 6% underestimation. The median deviation of the absolute value before correction was 9.5%, compared with 4.7% after protein correction (p < 0.05, Wilcoxon test for paired differences).

Content of CK-MB in Normal Myocardium

The myocardial CK-MB activity in 10 tissue extracts from 10 human hearts (100 biopsies) obtained at autopsy was 268 U/g (± 17% CV) and 1338 U/l (± 16% CV) for CK. This is not significantly different from the activity in seven left ventricular myocardial tissue specimens removed during heart surgery: The CK activity was 1375 U/l (± 14% CV) and the CK-MB activity was 246 U/l (± 21% CV). All autopsy investigations were carried out within 24 hours of death. A slight fall in enzyme activity from epicardium to endocardium was observed. CK-MB constituted 20% of CK (range 17–22%). To determine how autolysis affected the tissue concentration of CK-MB, biopsies on eight patients were made at autopsy every 6 hours for 30 hours. Figure 4 demonstrates a significant fall of 24% in the CK-MB activity in tissue extract within 24 hours of death (p < 0.05). However, no significant differences in the decrease of CK-MB activity between normal and necrotic tissue were observed.

Depletion of CK-MB from the Infarcted Myocardium

Figure 5 shows CK-MB activity in the series of biopsies taken from healthy tissue and necrotic myocardium in the 14 patients with transmural infarction.

Table 1. Correlation Between Estimated and Measured Course of the Serum CK-MB Curves

<table>
<thead>
<tr>
<th>Estimation model</th>
<th>Frequent sampling model r</th>
<th>SEE%</th>
<th>Reproducibility</th>
<th>sd (U/l)</th>
<th>CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log normal</td>
<td>0.995</td>
<td>7</td>
<td>43</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Accumulation</td>
<td>0.99</td>
<td>10</td>
<td>92</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Compartment</td>
<td>0.97</td>
<td>17</td>
<td>57</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. The Mean Elimination Constants of CK-MB and CK in 99 Patients Suffering from Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Patient category</th>
<th>n</th>
<th>CK-MB Mean ± SEM (hours⁻¹)</th>
<th>CK Mean ± SEM (hours⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMI</td>
<td>50</td>
<td>0.076 ± 0.003</td>
<td>0.032 ± 0.002</td>
</tr>
<tr>
<td>uncomplicated</td>
<td>27</td>
<td>0.072 ± 0.005</td>
<td>0.035 ± 0.002</td>
</tr>
<tr>
<td>AMI and liver disease</td>
<td>22</td>
<td>0.073 ± 0.006</td>
<td>0.029 ± 0.002</td>
</tr>
<tr>
<td>AMI and cardiogenic shock</td>
<td>22</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: AMI = acute myocardial infarction.
Table 3. The Relationship Between Infarct Size and Elimination Constant of CK-MB in 226 Patients After Their First Acute Myocardial Infarction

<table>
<thead>
<tr>
<th>Infarct size</th>
<th>No. of pts</th>
<th>Mean $k_d$ (hours$^{-1}$)</th>
<th>Biologic variation* (hours$^{-1}$)</th>
<th>Mean methodologic variation† (hours$^{-1}$)</th>
<th>No. and range of CK-MB values used for $k_d$ mean (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small ($\leq 450$ U/l)</td>
<td>75</td>
<td>0.079</td>
<td>0.024</td>
<td>0.290</td>
<td>4.0 (3−6)</td>
</tr>
<tr>
<td>Medium (451−1075 U/l)</td>
<td>76</td>
<td>0.076</td>
<td>0.018</td>
<td>0.051</td>
<td>5.1 (3−9)</td>
</tr>
<tr>
<td>Large ((\geq 1076$ U/l)</td>
<td>75</td>
<td>0.074</td>
<td>0.021</td>
<td>0.008</td>
<td>6.3 (3−9)</td>
</tr>
<tr>
<td>All</td>
<td>226</td>
<td>0.076</td>
<td>0.021</td>
<td>0.117</td>
<td>5.1</td>
</tr>
</tbody>
</table>

*Standard deviation of $k_d$.
†Standard deviation of the curve fit for $k_d$ estimation.
Abbreviation: $k_d$ = elimination constant.

The fall in CK-MB activity from the periphery to the center of infarct was highly significant, with the largest infarctions having the lowest activity remaining in the center. In the eight patients with subendocardial infarction, the remaining CK-MB activity was independent of the distance from the lateral infarct border (mean CK-MB activity $41 \pm 2.8\%$). No correlation between time from onset of symptoms until death and CK-MB depletion was found.

Because the tissue content of CK-MB cannot be determined from myocardial slices used for the NBT test, the enzyme content in the whole infarct was calculated from one slice (fig. 2). This assumption was controlled by correlating the depletion calculated from one slice, and the depletion measured in the whole infarct was $r = 0.82$, $p < 0.01$, $n = 10$). Without the corrections described, the correlation was lower ($r = 0.71$).

A highly significant correlation between the amount of CK-MB depletion (calculated as the difference between necrotic and normal tissue enzyme activity) and the size of necrosis is demonstrated in figure 6 ($r = 0.87$). The correlation was not linear because of the greater depletion in the largest infarctions (fig. 5). The depletion of CK-MB as a function of the estimated IS is shown in figure 7. A significant correlation was observed ($r = 0.61$). To estimate the depletion of CK-MB (CK-MB$_d$) in survivors, this curve or the mean value (121 U/g) can be used.

Fraction of Depleted CK-MB Reaching the Plasma Volume

The recovery of CK-MB ($k_r$) was calculated as the fraction of depleted enzyme reaching the plasma volume, and is therefore based on the same assumption as stated above. No significant correlation between IS and $k_r$ could be demonstrated. The mean CK-MB$_d$ values for the 14 transmural infarctions and for the eight subendocardial infarctions were 0.25 and 0.35, respectively ($p < 0.05$). The overall mean value was 0.29 (48% CV).

Estimated Versus Measured Infarct Size

Figure 8 shows the association between the IS estimated by CK-MB or CK using the compartment model curve-fit technique and the amount of myocardial necrosis. The coefficients of correlations were 0.87 and 0.71, respectively, and the difference between these two values was significant ($p < 0.05$). The figure demonstrates that IS was overestimated for the largest infarcts with either enzyme.

Table 4 shows the coefficient of correlation between the different expressions of serum CK-MB-estimated IS and the measured myocardial necrosis. Although the SEE values were similar (23−27%), correlation coefficients tended to be slightly higher if more detailed equations were used ($r = 0.78−0.89$).

Discussion

Although the in-hospital mortality rate in AMI patients during recent years has almost halved, the prognosis in patients with cardiac failure and cardiogenic shock has not changed. This may be caused by the extent of myocardial damage during AMI. An IS estimation in vivo is therefore desirable. This estimate might indicate the prognosis of the individual AMI patient and be useful as a scale to determine whether therapeutic intervention could reduce the development of myocardial necrosis. The present
study was made to determine the relation between IS estimated by serum CK-MB methods and the extent of irreversible myocardial injury, and to determine the CK-MB depletion in the damaged myocardium.

The present study shows that the agreement between the IS estimated by CK-MB and the measured IS is surprisingly good, considering the coefficients of correlation. The correlation coefficient, however, is highly dependent on the range (4-160 g in the present study). The SEE is about 25%, which, on average, gives a 95% confidence limit of ± 50% for the individual IS. Studies in man concerning the accuracy of estimating IS by serum CK and CK-MB measurements have shown a good correlation between accumulated serum CK and CK-MB and different indirect expressions of IS. Whether the kinetics of CK-MB should be described as a one- or multicompartment model has been discussed. The one-compartment theory is supported by a monoexponential elimination of labeled CK in experimental dog studies, but this is probably a simplification of a complex biologic system. Frequent measurements of serum CK-MB are obviously the best way to determine AUC. Theoretically, a multicompartiment model should be used, but the work of Sobel et al. with a one- or two-compartment model demonstrated only minor differences.

In larger infarcts, the $k_d$ is easily determined from the monoexponential part of the plasma curve. In smaller infarcts, the imprecision of the individual $k_d$ often overrides the variation in the mean $k_d$ (table 3). In these cases, the use of a mean $k_d$ is preferable. The changes in plasma volume after AMI introduce an error in IS from 30% to -23% using

![Figure 5](image1.png)  
**Figure 5.** Mean CK-MB activity in tissue extracts from consecutive transmural biopsies through the infarct. The most peripheral biopsies (from normal tissue) were used as reference (100% on the ordinate). The number of biopsies on the abscissa are indicated from the lateral zones of the infarcts. Thus, eight biopsies were taken from the two smallest infarcts (nos. 1, 2, 3, 4, 4, 3, 2, 1) and 18 from the largest infarcts.

![Figure 6](image2.png)  
**Figure 6.** Correlation between the total CK-MB depletion (CK-MB$_d$) in myocardial infarcts and the amount of necrosis measured in 22 patients who died from acute myocardial infarction ($y = -1.14 \times 10^{-3}x^2 + 6.85 \times 10^{-5}x + 24.8$).

![Figure 7](image3.png)  
**Figure 7.** Correlation between the estimated myocardial infarct size and the amount of CK-MB depletion per gram (CK-MB$_d$) of infarcted tissue ($y = 0.0472x + 72$) ($p = 0.001$).
The present study demonstrated a close relation between the decrease in CK-MB activity and the distance from healthy tissue (fig. 5). This relationship can be explained either by a decreasing content of surviving myocardial cells centrally in the infarct, or by a difference in the degree of ischemic cellular injury and leakage of enzyme. The hypothesis that islands of surviving cells are most frequent near the border zone of infarction is supported by the experimental findings of Hirzel et al., who demonstrated small areas with intact blood flow scattered in the infarcted myocardium with the highest frequency of surviving cells in the periphery.

Enzyme release from infarcted myocardium has been studied in dogs. Determination on whole heart homogenates showed an almost constant enzyme depletion. In our study the enzyme depletion in the slice corresponding to the center of the transmural infarct was relatively higher in the largest infarcts, which supported a curvilinear relationship between the total appearance of enzyme in serum and the weight of necrotic tissue. To elucidate this unexpected finding, we calculated the total enzyme depletion in the infarcts from one slice (fig. 2).

*24, 27* The correlation between the CK-MB depletion and the IS estimated at autopsy was 0.87 (fig. 6). Although the total CK-MB depletion is calculated from the measured necrosis, the present human studies demonstrate a positive IS-dependent enzyme depletion (fig. 5). Theoretically, the validity of the combined histochromic estimate of IS is questionable because the histologic examination was performed to delineate the infarct and the histochromic methods do not detect microscopic unstained areas. This could lead to overestimation of IS at autopsy. Nevertheless, the net effect was a small enzymatic overestimation, which has also been demonstrated in an experimental dog study. Thus, the use of a constant CK-MB depletion probably results in an overestimation of larger infarcts.

![Figure 8](https://circ.ahajournals.org/content/circulation/65/4/762/F8)

**Figure 8.** (top) Correlation between the myocardial infarct size estimated by serum CK-MB (U/l) and the myocardial necrosis measured (p < 0.001), quadratic equation y = \(-1.395 \times 10^{-5}x^2 + 8.452 \times 10^{-2}x + 14.2\), linear equation r = 0.83, SEE = 28%, y = 0.039x + 38. (bottom) Correlation between the myocardial infarct size estimated by serum CK and the myocardial necrosis measured (p < 0.01), quadratic equation y = \(-5 \times 10^{-7}x^2 + 1.43 \times 10^{-2}x + 26.1\), linear equation r = 0.63, SEE = 38%, y = 0.0058x + 49.

### Table 4. Coefficients of Correlation and Standard Errors of Estimate Between Estimated and Measured Infarct Size

<table>
<thead>
<tr>
<th>Method of estimation of infarct size</th>
<th>Measured vs estimated infarct size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equation</td>
<td>Unit</td>
</tr>
<tr>
<td>AUC (log norm.) × kₚᵢ *</td>
<td>U/l</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (log norm.) × kᵢ</td>
<td>U/l</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (comp.) × kᵢᵢ</td>
<td>U/l</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (comp.) × kᵢᵢ × plasma volume</td>
<td>U</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (comp.) × kᵢᵢ × body surface</td>
<td>U/m² × 1</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC (comp.) × kᵢᵢ × plasma volume</td>
<td>g-Eq</td>
</tr>
</tbody>
</table>

*Not corrected for changes in plasma volume.
†Depletion is calculated from figure 7 and the mean recovery was used.

Abbreviations: AUC = area below plasma CK-MB curve; Comp. = compartment model; kᵢ = elimination constant; kᵢᵢ = mean elimination constant; kᵢᵢᵢ = mean kᵢ if so of the kᵢ curve fit was > 0.021 hour⁻¹ and individual kᵢ if sd was < 0.021 hour⁻¹; log norm. = log normal model.
farcts. To overcome this, the equation in figure 7 could be applied for estimating the CK-MB depletion in survivors. The individual variation in the amount of CK-MB depletion, and the fact that this equation is based on some assumptions (fig. 2) do, however, limit its usefulness. Although the reliability of calculating the total CK-MB depletion seems satisfactory, when controlled by whole heart homogenates, further research is needed to estimate the enzyme depletion in human myocardial infarcts.

An experimental study in dogs has shown a negative linear relationship between IS and $k$, in homogeneous infarcts, but in the present study, $k_\omega$ was independent of IS. However, a significantly higher $k$, in subendocardial infarcts than in the transmural infarcts was observed. We assumed that the enzyme leakage in the subendocardial infarcts is drained mainly by the small veins into the ventricular cavity. CK-MB is transported from the transmural infarcts over a longer distance and probably to a higher degree by the lymphatic capillaries, resulting in a more marked inactivation before reaching the systemic circulation. Furthermore, experimental studies have shown that the half-life of CK is higher in lymph than in blood.

Clinically, it is often difficult to distinguish between subendocardial and transmural infarcts. This implies that the difference in $k$, is of minor importance. The difference in $k_\omega$ is negligible compared with $(1 - k)$, i.e., the amount of depleted CK-MB that does not reach the plasma. Furthermore, the estimate of $k$, might be too great. In fresh myocardial tissue, extracts of CK and CK-MB content are a few percent above the activity obtained by measurement in samples from autopsies. Since, however, the inactivation of myocardial enzymes is only 1–6% during the first 10 hours after death, and we have shown a similar inactivation in normal and infarcted tissue, the present finding for $k_\omega$ seem reliable. Since the fraction of 0.29 is independent of IS, a small overestimation of is of minor importance.

Theoretically, the optimal calculation of the IS is equation 1, where AUC, $k_\omega$, plasma volume, depletion and $k_\omega$ are all taken into account. However, when a satisfactory estimate of enzyme depletion in survivors cannot be obtained, only the intraindividual difference in plasma volume needs to be corrected by corresponding serum protein determinations. Further corrections are of doubtful value (table 4). 

Acknowledgment

We thank Asger Pedersen, M.D., chief physician, Department of Cardiology, for excellent working conditions, Hanne Køhn for technical assistance, Jytte Jensen for secretarial help, the staff at the coronary care unit, the Department of Clinical Chemistry, and the Department of Pathology, Glostrup Hospital, for their collaboration.

References

26. Erhardt LR: Clinical and Pathological Observations in
Intravenous Hyaluronidase Therapy for Myocardial Infarction in Man: Double-blind Trial to Assess Infarct Size Limitation

JOHN A. CAIRNS, M.D., DOUGLAS A. HOLDER, M.D., PAUL TANSER, M.D., AND ELEFTHERIA MISSIRLIS, M.Sc.

SUMMARY Patients with their first myocardial infarction not initially complicated by severe atrio-ventricular block or power failure were given a skin test and then randomized to receive either hyaluronidase or placebo in double-blind fashion. Hyaluronidase, 500 IU/kg i.v., was given every 6 hours for 42 hours.

Of the 48 eligible patients, 26 received hyaluronidase and 22 received placebo. The mean CK serum entry was 3140 ± 2111 mIU/ml (mean ± SD) in hyaluronidase patients and 3574 ± 1476 mIU/ml in placebo patients (p < 0.21). The mean infarct size was 54.6 ± 35.8 CK gram-equivalents in the hyaluronidase patients and 64.0 ± 31.1 CK gram-equivalents in the placebo patients (p < 0.20). Among the 21 patients treated within 6 hours of the onset of infarction, the difference in infarct size was greater (p < 0.15). There was no significant difference in the incidence of power failure, ventricular arrhythmias, recurrence of ischemic pain, infarct extension or mortality. No benefit of hyaluronidase was demonstrated in this study, which was designed to detect a 50% reduction of infarct size. However, to detect a 20% reduction in infarct size would require a much larger study population.

THE CONCEPT that the extent of myocardial necrosis developing during the course of a myocardial infarction can be influenced by many factors independent of the underlying coronary pathology and collateral blood supply has been the focus of extensive investigation. The importance of infarct size is attested to by evidence of positive correlations between infarct size and the incidence of cardiogenic shock, frequency of ventricular arrhythmias, the severity of hemodynamic abnormalities, and prognosis in the hospital and after discharge. It is presumed that a zone of ischemic tissue surrounds an area of necrosis, and that the fate of this border zone depends on various influences on the infarcted ventricle, but this concept is controversial.

Attempts to limit human infarct size are based on evidence from animal studies that certain inter-ventions may limit the extent of myocardial necrosis after experimental coronary artery occlusion. Although many interventions appear to limit infarct size in animals, only a few have been documented in humans, among them propranolol, practolol, nitroglycerin, trimethaphan and hyaluronidase. Quantitation of infarct size in the living patient is difficult. The two principal techniques are ECG mapping and the serial CK technique. Both have
Estimation of acute myocardial infarct size in man by serum CK-MB measurements.
P Grande, B F Hansen, C Christiansen and J Naestoft

Circulation. 1982;65:756-764
doi: 10.1161/01.CIR.65.4.756
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1982 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/65/4/756

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/