Evaluation of evolution of myocardial infarction by serial determinations of serum creatine kinase activity

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In order to investigate the relation between the release of creatine kinase (CK) in acute myocardial infarction and the evolution of infarction, the appearance functions of CK (release of CK from the heart into the circulation) were calculated by the modified method of Sobel and associates from the serial determinations of serum CK activity in 50 patients with acute myocardial infarction. The relation of the time between the onset of infarction and the peak value of the appearance function to the duration of the evolution of abnormal Q waves in 14 patients with inferior infarction and to the duration of pain in all patients was investigated.

The duration of CK release from the heart averaged 37.2 ± 2.4 hours and correlated well with the total CK released ($r=0.665$) which represents the infarct size. The mean per cent of the total CK eventually released by the time of maximum ΣQ (sum of the amplitude of Q wave in leads II, III, and aVF) was 80.0 ± 6.4 per cent and that of CK released while pain persisted was 72.0 ± 3.9 per cent. These results strongly suggest that the appearance function of CK reflects the evolution of myocardial infarction.

In myocardial infarction the incidence of cardiogenic shock and heart failure is related to the extent of myocardial damage (Harnarayan *et al.*, 1970), and various treatments which improve the balance of oxygen supply in relation to the demand of the ischaemic myocardium are used to try to limit the injury to the myocardium (Maroko *et al.*, 1972a, b; Pelides *et al.*, 1972). Thus, it is important to assess the time course of the evolution of myocardial infarction as well as the ultimate infarct size, in order to decide upon the effectiveness of such treatments.

Recently a method for assessing the infarct size from serial determinations of serum creatine kinase (CK) activity was reported by Sobel and associates (1972). Though the 'appearance function' of myocardial CK (the rate of release of CK from the infarcted myocardium into the circulation) can be calculated by this method and should indicate the evolution of myocardial infarction as a function of time (Norris *et al.*, 1975; Witteveen *et al.*, 1975), its clinical significance has not been extensively studied (Mathey *et al.*, 1975). The present study, in patients with acute myocardial infarction, was undertaken

to investigate the relation of this 'appearance function' to the duration of chest pain. We wanted to evaluate this function as a clinical guide in assessing the evolution of myocardial infarction.

Subjects and methods

Fifty patients with acute myocardial infarction were included in this study. They were between the ages of 43 and 78 years (average 60.2) and were admitted to the Coronary Care Unit of Sakurabashi Watanabe Hospital within 12 hours after the onset of chest pain and survived for more than 4 days. Patients with reinfarction within a few days after the onset, those who were given morphine, or those whose onset was not clear were not included. Twenty-three patients had anterior infarction (including septal and lateral infarction) and 27 patients had inferior infarction (including pure posterior and inferolateral infarction). From past history and electrocardiograms before this admission, 16 patients were judged to have had previous myocardial infarction. Patients were divided into two groups: group A included 30 patients without heart failure and group B included 20 patients with heart failure.

SERUM ENZYME DETERMINATIONS

Samples of peripheral venous blood were obtained from the patients every 4 hours during the first 24 hours after admission and thereafter every 6 hours until serum CK activity returned to normal. The sample was allowed to clot at room temperature, the serum was separated, and stored immediately at 4°C. The determinations were made within 15 hours after sampling. As intramuscular injections can cause a release of CK (Meltzer *et al.*, 1970), all injections were given either intravenously or subcutaneously.

MATHEMATICAL ANALYSIS OF DATA

The appearance function of CK released from the infarcted myocardium was calculated according to the method of Sobel *et al.* (1972), modified by Norris *et al.* (1975). The principle underlying the calculation is that the instantaneous rate change of serum CK activity ($dE(t)/dt$) is determined by the release rate of myocardial CK from the heart ($f(t)$) and its disappearance rate from the serum (k). Thus:

$$dE(t)/dt = f(t) - kE(t)$$

Where $E(t)$ represents the instantaneous serum CK activity subtracting the individual basal value. By this formula, the appearance function ($f(t)$) of CK released from the infarcted myocardium is calculated as follows:

$$f(t) = dE(t)/dt + kE(t)$$

Accordingly total CK released can be calculated by integrating the appearance function as follows:

$$\int_0^t f(t) dt = E(t) + \int_0^t kE(t) dt$$

DURATION OF PAIN

Patients' complaints of chest pain were recorded at least four times a day by investigators who did not know the enzyme values. In this study, we included as cardiac pain not only typical chest pain but also any oppressive feeling in the chest, back pain, and, in inferior infarction, epigastric pain, but we excluded low back pain which could have been the result of continued bed rest. In our series, only the duration of pain was studied. The severity of pain, which involves a subjective assessment, was not investigated. In no patient was the pain completely relieved after the administration of analgesic agents, though its severity was effectively reduced.

EVOLUTION OF ABNORMAL Q WAVES IN ELECTROCARDIOGRAMS

Standard 12-lead electrocardiograms were recorded at least three times a day for the first several days and once daily thereafter. In 14 of the 27 patients with inferior infarction, the amplitudes of newly developed Q waves in leads II, III, and aVF were

measured serially. Thirteen patients were excluded as follows:

- (1) Patients with bundle-branch block in the electrocardiogram.
- (2) Patients with previous inferior infarction.
- (3) Patients with significant changes of the electrical axis.

In patients with bundle-branch block or those with previous inferior infarction, determination of the amplitudes of the new Q waves in leads II, III, and aVF proved difficult. Patients with anterior infarction were also excluded from the electrocardiographic analysis since in almost all such cases quantitative measurements were impossible in praecordial leads because the new Q waves were masked by the QS complex.

As an index of evolution of infarction (ΣQ), we obtained the sum of the amplitudes of Q waves in leads II, III, and aVF divided by the sum of the amplitudes R_I , S_{aVR} , and R_{aVL} to correct for transient low voltage. Though the duration of the Q wave is believed to be more valuable than its amplitude in the evaluation of a transmural infarction, we measured serial changes of the amplitude of Q waves as ΣQ , since the measurement of their duration in a standard record (paper speed of 2.5 cm/s) was very difficult.

Individual appearance functions of released CK were calculated from the serial changes of serum CK activity for each of the 50 patients, and the relation of this function to the duration of pain, as well as to the evolution of abnormal Q waves in electrocardiograms was studied.

Results

(1) APPEARANCE FUNCTION OF RELEASE OF CK ($f(t)$)

The appearance functions calculated by the modified method of Sobel *et al.* in 4 representative cases are illustrated in Fig. 1a to 1d. In case 6 (Fig. 1a), the release rate of CK (shown by the solid line $f(t)$) increased rapidly to a peak 9 hours after the onset and decreased gradually to zero 36 hours after the onset, while the serum CK activity (dotted line $E(t)$) showed a peak value at 24 hours and fell to normal 72 hours after the onset. This shows that the release of CK from the heart into the circulation ceased long before the serum CK activity returned to normal.

Fig. 1b shows another case representative of early reinfarction which was excluded from the 50 patients of this study. The appearance function of this patient clearly shows the second attack of infarction after the conclusion of evolution of the first attack. This, however, could not have been clearly

Fig. 1 Serial serum CK activities ($E(t)$, subtracting individual basal value), the appearance function of CK ($f(t)$), and the cumulated CK released ($\int_0^t f(t) dt$) in 4 representative cases.

shown by the serum CK activity alone, since it never returned to a normal level. Electrocardiograms of this patient confirmed the anterior infarction corresponding to the second rise of the appearance function. Fig. 1c illustrates a case whose appearance function indicates that the major release of CK was completed within 18 hours, while Fig. 1d shows a case whose release rate of CK decreased much more slowly.

The duration of the release of CK in the 50 patients ranged from 12 to 87 hours, averaging 37.2 ± 2.4 (mean $\pm$ SE) hours (see Table 1), and Fig. 2 shows the relatively high correlation ($r = 0.665$) between the duration of release of CK and total CK released ($\int_0^t f(t) dt$). This indicates that infarct size determines not only the total CK released as has been established, but also the duration of its release.

The mean peak time of the release of CK was 12.4 ± 0.9 hours from the onset. In fact in 22 of 50 patients, the release rate reached a peak within 10 hours. An average of 62.2 per cent of total CK re-

leased appeared in the circulation in the first half of the duration of release, which indicates that the major part of the evolution of infarction occurred in that time.

The mean duration of CK release in 30 patients without heart failure (group A) was significantly shorter than that in 20 patients with heart failure (group B) ($P < 0.01$, see Table 1). There was, however, no significant difference in the ratio of CK released by the time of peak release rate to total CK released, between groups A and B. However, the mean ratio of CK released within the first 24 hours after the onset to the total CK released of group A ($87.1 \pm 2.6\%$) was significantly greater than that of group B ($71.4 \pm 4.3\%$). Since group B (with heart failure) includes the cases with the clinically more severe involvement, it is reasonable to conclude that the longer duration of CK release in this group is the result of larger infarct size. This is further confirmed by the finding that the mean total CK released in group B was significantly greater than in group A ($P < 0.005$, see Table 2).

Table 1 CK release and duration of pain

	No. of subjects	Duration of release of CK (h)	Total CK released ($\int f(t)dt$) (IU/ml)	Duration of pain (h)	Release ratio† (pain) (%)
Without prior myocardial infarction	34	39.5 $\pm$ 2.8	939.0 $\pm$ 99.5	27.3 $\pm$ 2.3	77.2 $\pm$ 4.2
With prior myocardial infarction	16	32.4 $\pm$ 4.4	497.6 $\pm$ 113.1	18.7 $\pm$ 3.5	61.0 $\pm$ 7.3
Anterior myocardial infarction	23	35.7 $\pm$ 4.1	719.7 $\pm$ 122.1	18.9 $\pm$ 2.6	66.9 $\pm$ 7.3
without prior myocardial infarction	14	39.5 $\pm$ 5.5	952.7 $\pm$ 166.4	23.7 $\pm$ 3.4	77.6 $\pm$ 6.9
with prior myocardial infarction	9	29.9 $\pm$ 5.4	357.1 $\pm$ 80.1	11.4 $\pm$ 2.4	49.5 $\pm$ 10.6
Inferior myocardial infarction	27	38.4 $\pm$ 2.8	864.3 $\pm$ 109.1	29.3 $\pm$ 2.6	76.2 $\pm$ 4.4
without prior myocardial infarction	20	39.5 $\pm$ 2.7	929.4 $\pm$ 122.5	29.8 $\pm$ 2.9	76.9 $\pm$ 5.4
with prior myocardial infarction	7	35.6 $\pm$ 7.2	678.3 $\pm$ 219.1	28.0 $\pm$ 5.6	74.2 $\pm$ 7.1
Group A	30	31.2 $\pm$ 1.9	664.3 $\pm$ 72.6	22.8 $\pm$ 2.2	73.3 $\pm$ 5.1
without prior myocardial infarction	24	33.0 $\pm$ 2.2	735.3 $\pm$ 83.6	23.9 $\pm$ 2.4	74.5 $\pm$ 5.6
with prior myocardial infarction	6	23.8 $\pm$ 2.6	380.5 $\pm$ 54.7	18.5 $\pm$ 4.9	69.0 $\pm$ 11.6
Group B	20	46.2 $\pm$ 4.6	998.0 $\pm$ 164.0	27.2 $\pm$ 3.6	79.2 $\pm$ 5.9
without prior myocardial infarction	10	54.9 $\pm$ 5.4	1428.0 $\pm$ 200.4	35.5 $\pm$ 3.9	83.2 $\pm$ 5.1
with prior myocardial infarction	10	37.5 $\pm$ 6.4	567.9 $\pm$ 174.3	18.8 $\pm$ 4.7	55.7 $\pm$ 8.9
Total	50	37.2 $\pm$ 2.4	797.8 $\pm$ 82.0	24.5 $\pm$ 2.0	72.0 $\pm$ 3.9

*P < 0.05.

**P < 0.01.

†Ratio of released CK from onset until pain disappears to total CK released.

(2) APPEARANCE FUNCTION AND DEVELOPMENT OF Q WAVES

The appearance function and the serial changes of $\Sigma Q((Q_{II} + Q_{III} + Q_{aVF})/(R_I + S_{aVR} + R_{aVL}))$ in 3 representative cases are shown in Fig. 3. In case 2 (Fig. 3a), ΣQ increased to a maximum 45 hours after the onset (making a plateau thereafter), when 88.2 per cent of the total CK released had already appeared in the circulation. In 2 other cases (cases 24 and 35 in Fig. 3b, 3c), most of the total CK released had been released by the time of maximum ΣQ . In the 14 patients studied, the ratio of cumulated CK released by the time of maximum ΣQ to total CK released was 80.0 ± 6.4 per cent. This shows that the release of CK calculated from the serial determinations of serum CK activity cor-

responds to the amplitude development of abnormal Q waves. The mean period from the onset to the point of maximum ΣQ in group B with heart failure was 35.5 ± 3.9 hours, which was longer than in group A without heart failure (23.9 ± 2.4 hours, $P < 0.05$).

(3) DURATION OF APPEARANCE FUNCTION AND DURATION OF PAIN

The appearance function of CK and the duration of pain in representative cases are shown in Fig. 1. The mean duration of pain was 24.5 ± 2.0 (3 to 56) hours in the 50 patients. Though this value was 16.4 hours shorter than the mean duration of release of CK, the major release ($72.0 \pm 3.9\%$ of total CK released) occurred during the period of chest pain. Indeed, in 28 of 50 patients (56%), the difference between the duration of pain and CK release was less than 12 hours.

In the patients with previous myocardial infarction, a smaller per cent of CK ($61.0 \pm 7.3\%$) had been released before chest pain disappeared, than in the patients without previous myocardial infar-

Fig. 2 Relation between duration of release of CK and total CK released. Closed and open circles represent patients with and without prior myocardial infarction, respectively.

Table 2 Release ratio of CK in groups A and B

	Sample size	Release ratio (peak)† (%)	Release ratio (24 h)‡ (%)
Group A	30	36.5 $\pm$ 3.3	87.1 $\pm$ 2.6***
Group B	20	36.4 $\pm$ 3.9	71.4 $\pm$ 4.3***
Total	50	36.5 $\pm$ 2.5	76.7 $\pm$ 2.3

***P < 0.005

†Ratio of released CK until release rate reaches peak to total CK released.

‡Ratio of released CK within 24 hours after onset to total CK released.

Fig. 3 Relation between ΣQ and appearance function of CK ($f(t)$) and cumulated CK released ($\int_0^t f(t) dt$) in representative cases.

tion ($77.2 \pm 4.2\%$ of total CK released). This agrees with the clinical findings that pain stopped earlier in patients with a history of previous myocardial infarction.

The mean duration of pain was shorter in the patients with anterior infarction than in those with inferior infarction in our series. However, if we exclude the patients with previous myocardial infarction, there was no significant difference in the duration of pain between these groups. The mean duration of pain in group B with heart failure was 35.5 ± 3.9 hours which was substantially longer than in group A without heart failure.

Discussion

Attempts to achieve reduction of infarct size by pharmacological and physiological interventions

have recently been made (Braunwald *et al.*, 1974; Flaherty *et al.*, 1975). To assess these treatments, however, it is necessary to be able to follow the evolution of myocardial infarction as well as to estimate the infarct size. Though Maroko *et al.* (1972a, b) reported the multi-lead electrocardiographic mapping method of assessing the infarct size, individual variations in ST elevation have been shown to be significantly large (Norris *et al.*, 1976). On the other hand, the method of Sobel *et al.* (1972) modified by Norris *et al.* (1975) is very useful in estimating the infarct size from the serial changes of serum CK activity. Though the appearance function calculated by this method represents the evolution of myocardial infarction, there have been few reports relating the appearance function to the clinical course (Mathey *et al.*, 1975).

In the present study, a close relation was ob-

served between the appearance function of CK and chest pain and development of Q waves in the electrocardiogram. This indicates that the evolution of myocardial infarction can be followed by the appearance function of CK.

(1) DURATION OF RELEASE OF CK

The duration of release of CK, calculated by the modified method of Sobel *et al.* (1972), in our series, ranging from 12 to 87 hours, was in good agreement with the report by Sobel *et al.* (1972) and Norris *et al.* (1975). Though the pathological sequential study of the evolution of myocardial infarction in man is impractical, it has been done in dogs. In these experiments there was good agreement between the histochemical findings on the evolution of the infarct (Cox *et al.*, 1968), and the appearance function of CK (Shell *et al.*, 1971). Therefore, the appearance function calculated from the serial serum CK levels should represent the evolution of infarction in man also.

As shown in Fig. 2, the duration of the release of CK correlated well with the total CK released which we know represents the infarct size. This suggests that the larger the infarct, the longer its development requires. This, however, does not agree with the report of Mathey *et al.* (1975) which indicated no significant difference in total CK released between patients with and without prolonged CK release.

(2) DEVELOPMENT OF ABNORMAL Q WAVES

It has been established that the development of abnormal Q waves, initially reported by Pardee (1930), indicates transmural infarction (Myers *et al.*, 1949). In this study serial changes in the amplitude of the pathological Q waves were used as an index of extension of transmural infarction and compared with the appearance function of CK in each case studied. For reliability of measurement of Q waves, patients with anterior infarction, a previous history of myocardial infarction, bundle-branch block, and/or a significant change in electrical axis were excluded from this study. At the time of peak ΣQ (see Method), an average 80 per cent of total CK released had appeared in the circulation (in 13 of the 14 patients, omitting one case with apparently discrepant findings, this was 86%). A pronounced increase in ΣQ was seen in this early phase, corresponding well to the greater release of CK in the first half of the duration of release. Thus, the appearance function of CK can be considered to be in good agreement with the development of the abnormal Q waves. Errors in the peak time of ΣQ were at most 8 hours, since the recording of electro-

cardiograms was done at least three times a day. However, in one case, ΣQ reached the maximum 6 hours after the onset, while the duration of the release of CK was 36 hours. This may be the result of the gradual extension of nontransmural infarction. In 2 cases, ΣQ curve rose again on the 4th and 5th day after the onset following the initial plateau phase. The late rises in these cases corresponded to changes in the pathological T wave in leads II, III, and aVF, strongly suggesting reinfarction. Poliwoda (1966) found that the amplitude of abnormal Q waves reached a maximum within one week in only about 25 per cent of his patients. In our study, however, ΣQ reached the maximum within 3 days after the onset in 12 of 14 patients. This discrepancy may be the result of the fact that we excluded cases with obvious reinfarction in the acute stage, and also because our ΣQ was obtained by the sum of the amplitudes of Q waves in leads II, III, and aVF corrected by dividing the sum of R_I , S_{aVR} , and R_{aVL} . Indeed without this standardisation, in some cases, the maximum of ΣQ was seen a few days later.

(3) DURATION OF PAIN AND APPEARANCE FUNCTION

In this study, it is suggested that there is a correlation between the duration of pain and that of the release of CK. This agrees with the results reported by Mathey *et al.* (1975), indicating a longer duration of chest pain in patients with prolonged CK release. Though the mechanism of cardiac pain has not been established, pain-producing substances, such as kinin, released by ischaemia are believed to stimulate the nerve endings to cause pain (Gorlin, 1965). Since pain disappears when the ischaemic region has died, the persistence of pain indicates that the extension of the ischaemic zone is continuing (Friedberg, 1966). In 22 of 50 patients, the mean difference between the duration of pain and the release of CK was less than 12 hours, and for all 50 patients an average of 72.0 ± 3.1 per cent of the total CK released had appeared in the circulation by the time the pain disappeared. This relation between the duration of pain and the release of CK showed no significant difference between anterior and inferior infarction. However, the duration of pain was shorter in the patients with previous infarction than in those without earlier infarction. Evans and Sutton (1956) also reported that a silent infarction is often seen in patients who have a history of myocardial infarction and/or heart failure. They considered that this may be the result of the slower evolution of infarction in such patients. The fact that there was no difference in the duration of

the release of CK between the patients with and without earlier myocardial infarction, in spite of the finding that the mean total CK released in the patients with prior infarction was significantly less than in those without prior infarction, confirms their conclusion. In some cases, the duration of pain was remarkably short showing great discrepancies between it and duration of release of CK. Though this could have been caused by the administration of analgesia, reduction of sensitivity by ageing, and individual subjective variations in complaints of pain, the fact that the mean duration of pain and the maximum time of ΣQ from the onset were shorter than that of the release of CK suggests that the evolution of infarction might be completed a little earlier than the appearance function of CK returning to zero.

(4) VALIDITY OF MATHEMATICAL CALCULATION

Although the method of Sobel and associates which was used in this study is a unique and valuable method, it is based on some assumptions, e.g. that the total amount of CK appearing in the circulation is directly related to the amount lost from myocardium; that the kinetics of enzyme clearance are first order; that the volume of distribution is constant during the evolution of infarction; and that variable inactivation of CK does not occur. These assumptions are open to criticism which if valid would mean that the mathematical model to estimate myocardial enzyme release from the serum CK activities, used in this study, is inaccurate (Roe and Starmer, 1975). While recognising this possibility the correlations observed are none the less significant and potentially useful empirically.

In our study, in order to avoid the effect of extra-cardiac CK release which would be from traumatised skeletal muscle, all injections were given either intravenously or subcutaneously. Patients with profound haemodynamic alterations, such as cardiogenic shock which could cause a release of non-cardiac CK were also excluded. Except in these conditions in which serum CK increases without increasing serum MB-CK activity, the relation between the calculated infarct size from total CK and MB-CK appears to be consistent (Roberts *et al.*, 1975) and the calculated total CK released in this study should reflect the CK released from the myocardium.

In fact, the decrease of serum CK levels after intravenous injection of partially purified CK shows a biphasic curve; the fast and slow components represent the diffusion of CK into a distribution space, and the decaying of total CK, respectively

(Shell *et al.*, 1971). In the present method the fractional disappearance rate was calculated from the slope of the monoexponential portion (slow component) of the curve because we cannot obtain the diffusion rate in humans. However, we believe that if the ratio of these two decaying constants are not variable, the ratio of the released CK to the estimated CK released, assuming the first order kinetic, is constant (unpublished data). Therefore, it is reasonable that the actual total CK released can be obtained from the estimated total CK released by multiplying with a correcting factor. In contrast to errors caused by neglecting the fast component of decaying curve in estimating the infarct size, the pattern and duration of the appearance function do not change significantly.

However, the estimated release rate of CK can be affected if the distribution volume changes during the release of CK since the release rate is expressed as the amount of CK which appears in a unit volume (ml) of distribution space in one hour. Recently Witteveen *et al.* (1976) reported the influence of plasma volume change on calculated infarct size, suggesting that the changes in plasma volume have to be taken into account when infarct size is calculated on the basis of serum enzyme levels. Fortunately, however, the characteristics of pattern and duration of the appearance function of CK are not greatly affected by the small change of plasma volume, though the correction of the calculated release rate of CK by haematocrit changes will improve the accuracy of the estimation.

Concerning the invariability of the disappearance rate, Roberts *et al.* (1975) showed that haemodynamic perturbations profoundly affecting cardiac output, heart rate, renal blood flow, or hepatic blood flow in conscious dogs did not much affect the disappearance rate of CK activity, though a wide variation in this measure was observed from person to person. Norris *et al.* (1975) have found that successive determinations of the appearance function are quite constant in the same patient.

Despite the above assumptions which may interfere with the validity of the mathematics of a method, a close relation was observed between the calculated appearance function of CK and the duration of chest pain and the development of Q waves in electrocardiograms which indicate the development of myocardial infarction. Thus, we believe that the estimation of the appearance function of CK is valuable in assessing the development of myocardial infarction and deserves further study.

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