Creatine kinase release in acute myocardial infarction: correlation with clinical, electrocardiographic, and pathological findings¹

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Creatine kinase (CK) release curves were analysed in 40 patients with acute myocardial infarction. Three groups could be identified. Group A (duration of CK release < 30 hours) comprised 15 patients whose CK release was completed within 22.8 hours. In these patients chest pain was noted on the first hospital day and necropsy in three showed a homogeneous myocardial infarction. Group B (duration of CK release > 30 hours) comprised 16 patients who had a significantly longer CK release time of 42.2 hours ($P \leq 0.05$). Their chest pain persisted for two to three days and pathological examination in five patients showed a heterogeneous composition of the infarcted myocardium. Group C comprised nine patients who had a second rise of serum CK. This was always associated with chest pain. It reflected an extension of the infarct which accounted on average for 24 per cent of the size of the final infarct.

We conclude that a CK release of short duration indicated infarction without extension, CK release of longer duration indicated a gradual extension of infarction, and a repeated CK release resulted from a sudden extension of an infarct. According to these criteria an extension of the infarct occurred in 62 per cent of our patients.

Serial determinations of serum creatine kinase (CK) activity to assess the immediate and long-term prognosis were performed in all patients with acute myocardial infarction admitted to hospital during 1974. Unexpectedly the curves showed striking variability. In a few cases the curve was similar to that seen in dogs after experimental coronary occlusion, with a steep rise and an early discrete peak (Shell, Kjekshus, and Sobel, 1971). In most cases, however, significant deviations from this 'typical' shape were found. In order to find out if these deviations were related to the time-pattern of myocardial necrosis the measurements of CK activity were correlated with the clinical, electrocardiographic, and pathological findings.

Patients and methods

Forty patients with acute myocardial infarction were included in the study. The diagnosis of acute myocardial infarction was based on a typical history, the electro-

cardiogram, and serum enzyme changes. Initially serum CK activity in all patients was still within the normal range (< 40 mU/ml). Patients who had had intramuscular injections, direct current shock, or other possible cause of increase in serum CK activity were excluded from the study.

Blood for CK determinations was taken at one-, two-, or three-hourly intervals from the time of admission until CK activity had either returned to normal or, in patients who died, was decreasing. CK activity was measured with Boehringer CK activated test sets (Boehringer, Mannheim) at 25°C, with an upper normal value of 40 mU/ml (Szasz, Busch, and Farohs, 1970). A 12-lead standard electrocardiogram was recorded on the day of admission and on the following three days. Daily ST segment changes were measured according to the criteria suggested by Reid *et al.* (1974) and expressed as a percentage of the initial ST segment height. Blood pressure, heart rate, arrhythmias, and clinical events were carefully monitored. The incidence and severity of recurrent chest pain were estimated by the patient's consumption of morphine or its derivatives.

A post-mortem examination was performed in 12 patients. For macroscopic observation the heart was cut into slices 0.5 cm thick, which were stained with Nitro-BT (Nachlas and Shnitka, 1963). As the result of a

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FIG. 1 CK serum and release curves in a representative case (Case 14) from group A. Serum CK activity rises steeply, has early single peak, and a mono-exponential decline thereafter. With the early decline of the serum curve the release curve flattens 16 hours after the serum curve exceeds 40 mU/ml, indicating that no further release of myocardial CK occurred. Post-mortem examination showed a large, homogeneous infarction, suggesting that the CK release was from myocardial cells that had all died at the same time.

Nitro-BT-dehydrogenase reaction non-infarcted myocardium turned blue while the area of infarction remained unstained. Tissue from infarcted and non-infarcted myocardium was examined by light microscopy.

Data analysis

Serum CK activity after an acute myocardial infarction is mainly governed by two contrary mechanisms – release of CK from the myocardial infarct and elimination of CK from the serum. If there were no elimination of CK from the serum then CK activity would be the result only of CK release. A CK release curve may be calculated from the serum curve by adding to it the product of the area limited by the serum curve and the rate constant of elimination (Shell *et al.*, 1971; Sobel *et al.*, 1972; Mathey *et al.*, 1974). In this study CK release curves were calculated by means of a computer programme,¹ which was also utilized to plot serum and release curves as a function of time.

CK release is terminated when the release curve is at its maximum. The period between a serum CK activity of 40 mU/ml and the maximum of the release curve was defined as the CK release time (Fig. 1). The maximal value of the release curve represents the total amount of CK that is released from the infarcted myocardium into 1 ml of the distribution space. From this value the size of the infarct can be determined (Shell *et al.*, 1971;

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TABLE 1 Clinical details of 15 patients in group A

Case No.	Age	Site of infarct	Preinfarction angina	Interval between onset of pain and CK of 40 mU/ml (h)	CK release time (h)	Infarct size (g)	Rate constant of CK elimination (h ⁻¹)
1	76	A	—	?	16.4	29	0.06
2	45	I	—	4.5	27.4	50	0.06
3	53	I	+	3.5	26.0	83	0.07
4	59	A	—	3.8	28.0	91	0.07
5	46	I	—	6.5	25.0	27	0.07
6	56	A	—	5.0	21.8	27	—
7	75	I	+	3.3	20.0	23	0.06
8	59	I	—	4.2	23.0	27	0.06
9	58	I	+	3.5	27.0	78	0.06
10	65	I	+	4.0	29.0	37	0.07
11	67	A	—	3.5	17.0	13	0.12
12	67	A	—	1.5	18.2	76	—
13	59	I, A	—	1.2	27.0	184	—
14	79	I	+	6.0	16.0	63	0.06
15	61	A	—	2.8	20.0	86	0.06
Mean ± SEM				3.8 ± 0.5*	22.8 ± 5.5*	59.6 ± 11.2†	0.07 ± 0.02

* Significant difference between groups A and B.

† Significant difference between groups A and C.

I = Infarct of inferior wall; A = Infarct of anterior wall.

Sobel *et al.*, 1972) with an accuracy of ± 10 g (Bleifeld *et al.*, 1974) using the formula:

$$\text{Infarct size (g)} = \frac{\text{max. value rel. curve (U/ml)} \times \text{body weight (g)} \times 0.0005 \left(\frac{\text{ml}}{\text{U}}\right)}{\text{The constant used in this equation is derived as follows:}}$$

The constant used in this equation is derived as follows:

$\frac{0.074}{0.3 \times 500} = 0.0005$ where 0.074 represents the ratio of the CK distribution volume on the whole body weight (Bleifeld *et al.*, 1974); 0.3 is the proportion of depleted myocardial CK appearing in the serum; 500 is the amount of CK (U/ml) depleted from myocardium undergoing necrosis (B.E. Sobel, 1974, personal communication).

The rate constant of CK elimination was obtained from the slope of the terminal portion of the serum curve if the latter was plotted semi-logarithmically.

Results

Three groups of patients could be identified from the duration of CK release. Group A consisted of 15 patients with a CK release time of less than 30 hours, group B of 16 patients with a CK release time of more than 30 hours, and group C of nine patients who had a further release of CK. More detailed analysis of the three groups showed that they were largely homogeneous in relation to clinical and pathological findings. The arbitrary 30 hours' limit between groups A and B was chosen because it is compatible with the experimental finding that the minimum residual CK activity in

ST segment change (%)		Chest pain hospital day			Died
Day 1-2	Day 2-3	1	2	3	
-55	-35	+	-	-	-
-45	-5	+	-	-	-
-71	0	+	-	-	-
-59	-35	+	+	-	-
?	?	+	-	-	-
-24	-40	+	-	-	-
?	?	+	-	-	-
-	-	+	-	-	-
-	-	+	-	-	-
-44	-12	+	-	-	-
-	-	+	-	-	-
ventricular pacing		+	-	-	+
-74	?	+	-	-	-
-52	-13	+	-	-	+
-52	-13	+	-	-	-
-53 $\pm$ 5.9		-19 $\pm$ 5.3

FIG. 2 CK serum and release curves in the representative case (Case 14) from group B. The serum CK curve rises slowly and the CK release time is prolonged to 50 hours. Post-mortem examination showed a laminar type of infarction.

infarcted myocardium occurs 24 hours after coronary occlusion (Kjekshus and Sobel, 1970). Since CK enters the circulation after a mean delay of four hours CK release from a uniform necrosis should be completed within 30 hours.

Group A

The course of the serum CK curve in these 15 (38% of the whole series) patients, whose clinical

FIG. 3 Changes in CK serum and release curves in a representative case (Case 8) in group C. 60 hours after onset of pain there is a second peak in the still raised serum CK activity. This was associated with severe chest pain, and a following rise in the release curve reflects an increase of the infarction.

TABLE 2 Post-mortem findings in 3 patients in group A

Case No.*	Macroscopical findings	Microscopical findings
12	Full thickness infarct of IV septum and LV anterior wall	Homogeneous necrosis with peripheral neutrophilic infiltration
13	Extensive infarct of entire thickness of IV septum and LV inferior wall; laminar necrosis of LV anterior wall	Extensive homogeneous necrosis
14	Large infarct of IV septum and LV inferior wall	Homogeneous necrosis with neutrophilic infiltration and focal haemorrhages

*See Table 1.

TABLE 3 Clinical details of 16 patients in group B

Case No.	Age	Site of infarct	Preinfarction angina	Interval between onset of pain and CK of 40 mU/ml (h)	CK release time (h)	Infarct size (g)	Rate constant of CK elimination (h ⁻¹)
1	35	I	?	?	44.4	55	0.07
2	57	I	+	4.5	43.0	85	0.04
3	52	I	+	?	40.0	68	0.07
4	69	A	+	5.0	30.4	106	0.05
5	65	A	—	3.0	59.8	78	0.06
6	60	A	+	4.0	40.0	43	0.07
7	52	A	+	10.0	39.0	40	0.06
8	62	A	+	9.0	41.4	60	0.06
9	47	I	—	5.0	36.0	54	0.07
10	30	I	—	4.3	31.0	93	0.06
11	62	I	—	2.0	55.0	152	0.06
12	69	A	+	5.0	33.2	21	0.06
13	67	I	+	10.5	41.4	36	0.08
14	72	A	+	?	50.0	59	0.07
15	73	A	+	9.0	56.0	100	0.07
16	64	I	+	3.8	34.5	90	0.06
Mean ± SEM				5.8* ± 0.8	42.2† ± 2.2	71.3* ± 8.2	0.06 ± 0.009

* Significant difference between groups A and B.

† Significant difference between groups B and C.

I = Infarct of inferior wall; A = Infarct of anterior wall.

TABLE 4 Post-mortem findings in 5 patients in group B

Case No.*	Macroscopical findings	Microscopical findings
12	Laminar and in some parts disseminated necrosis of IV septum and LV anterior wall	Old fibrous scars; early necrosis of surrounding muscle fibre bundles; granulation tissue, estimated age about 12 days
13	Disseminated necrosis in old scar of LV inferior wall	Small areas of early necrosis surrounded by living injured and scarred tissue
14	Laminar necrosis of subendocardial layers of LV anterior wall	Necrotic muscle fibres separated by granulation tissue of different age (Fig. 3)
15	Not available	Areas of early necrosis without leucocytic infiltration cells; surrounded by granulation tissue, scars, and partially removed necrotic muscle; large area with fragmentation and swelling of the sarcoplasm of the heart muscle cells
16	Large, non-uniform infarction of LV inferior wall and IV septum	Early focal necrosis separated by living muscle fibres; beginning neutrophilic infiltration

* See Table 3.

data are summarized in Table 1, showed a steep rise, an early peak, and a mono-exponential decline thereafter. According to the early fall of the serum curve CK release was completed after a mean of 22.8 hours. A representative example of this type of CK release is shown in Fig. 1. Of the 15 patients in the group 14 complained of chest pain only on their first hospital day. The onset was sudden and unexpected in 10 of the 15 patients with a mean delay of 3.8 hours before the serum CK activity was

exceeded 40 mU/ml averaged 5.8 hours, which was significantly more than in group A ($P < 0.05$). The infarcts in patients in group B were of heterogeneous composition. Three showed a laminar or disseminated necrosis and in one case (Case 16) there was a large, non-uniform infarction. Histological examination in five cases revealed an infarction area composed of dead, viable, and variously injured tissue. Dead tissue was found in different stages of repair (Table 4). Daily ST segment changes in the standard electrocardiogram did not differ significantly between group A and B.

Group C

In the 9 patients (22% of the whole series) in group C (Table 5) a second or third peak in a persistently raised serum CK activity was seen 20–40 hours after the onset of chest pain. As can be seen (Fig. 3), the second peak of the serum CK curve was followed by a corresponding rise in the release curve, reflecting an increase in the infarct size. Including all peaks of the serum curve the mean final infarct size in cases in group C was 89 g, of which 22 g – that is, 24 per cent – may be attributed to the second peak in the serum CK curve. In six of the cases the standard electrocardiogram failed to indicate the extension of the infarct. In two patients the second peak of serum CK activity was accompanied by a rise in previously isoelectric ST segments. This was found in one patient (Case 4) when rapid atrial fibrillation occurred. Five of the patients in group C died, four of acute left heart failure and one of cardiac rupture. The post-mortem examination (Table 6) of the hearts showed an extensive, homogeneous necrosis in three patients similar to that seen in the patients in group A. In one patient (Case 8) there was evidence of repeated infarction.

Discussion

CK activity in infarcted rabbit myocardium was found to be at a minimum 24 hours after the coronary occlusion (Kjekshus and Sobel, 1970). Within this period CK is released from the infarcted myocardium and enters the serum. This process is called CK release and its duration was defined by us as CK release time. In the present study the CK release time ranged from 16 to 60 hours. The mean short CK release time of 22.8 hours in the patients in group A corresponds well with the duration of CK release found in the animal experiments referred to above. This finding, the short duration of chest pain, and the homogeneous composition of the infarction found at necropsy in three patients support the idea that, as in infarction after experimental acute coronary occlusion, all the

raised to 40 mU/ml. In three patients who died necropsy showed a homogeneous, sharply demarcated necrosis (Table 2).

Group B

In the 16 (40% of the whole series) patients in group B the mean CK release time was prolonged to 42.2 hours, which was nearly twice that of group A ($P < 0.05$). In contrast to group A, the serum CK curve showed a slow rise and a flat single peak (Fig. 2). Eleven patients complained of chest pain persisting for the first two to three hospital days. The onset of severe chest pain was preceded by preinfarction angina (Yu, 1973) in 11 patients (Table 3). The delay between the onset of severe chest pain and the time when serum CK activity

ST segment change (%)		Chest pain hospital day			Died
Day 1–2	Day 2–3	1	2	3	
+30	–5	+	–	–	–
–20	0	+	+	–	–
?	?	+	+	+	–
?	?	+	+	–	–
–65	+10	+	–	+	–
–33	–10	+	+	–	–
+38	+9	+	+	+	–
–44	–16	+	+	–	–
–74	+6	+	+	–	–
–65	–20	+	+	–	–
–31	–9	+	+	–	–
–38	–27	+	–	–	+
?	?	+	–	–	+
?	?	–	–	–	+
+3	0	+	+	+	(pericarditis) +
–40	?	+	+	–	+
–28 ± 10.3		–6 ± 4			

TABLE 5 Clinical details of 9 patients in group C

Case No.	Age	Site of infarct	Preinfarction angina	Interval between onset of pain and CK of 40 mU/ml (h)	CK release time (h)		Infarct size (g)		Third	Final
					First	Second	First	Second		
1	71	I	?	?	25.6	48.0	59	5	—	64
2	42	A	—	5.3	27.0	—	82	28	—	110
3	68	A	—	?	—	47.0	65	20	—	85
4	59	I	—	4.2	34.5	47.0	43	3	—	46
5	70	A	+	1.5	12.0	40.0	40	62	20	122
6	53	I	+	4.3	24.0	44.0	101	11	—	112
7	64	I	+	5.5	32.0	41.0	60	14	—	74
8	72	A	—	?	20.0	40.0	59	41	—	100
9	66	I	+	5.0	—	30.0	51	11	28	90
Mean $\pm$ SEM				4.3 $\pm$ 0.6	25.0 $\pm$ 2.8†	41.6 $\pm$ 2.0	62.2 $\pm$ 6.4	21.7 $\pm$ 6.4	24.0 $\pm$ 4.0	89.2 $\pm$ 8.2‡

* Pericarditis.

† Significant difference between groups B and C.

‡ Significant difference between groups A and C.

I = Infarct of inferior wall; A = Infarct of anterior wall.

myocardial necrosis developed at the same time without further extension of the infarct. As the increase in serum CK activity is usually noted four hours after infarction has occurred it may be concluded from the time interval of 3.8 hours between the onset of chest pain and a serum CK activity of 40 mU/ml that in group A chest pain and the onset of infarction generally coincided.

Patients in group B had a mean CK release time of 42.2 hours, which was significantly longer than that of patients in group A. Several factors must be considered in the interpretation of this difference in CK release time. The infarct size and the rate of CK elimination can be excluded, because there was no significant difference between group A and B in these two values. A delay of CK release or a grad-

ual extension of the infarct could account for the prolonged CK release period in group B. Though a delay in CK release cannot be definitely rejected, the persistence of severe chest pain during two to three hospital days is more consistent with an extension of infarction. This is supported by the pathological studies. They showed typical findings of incomplete infarction, which is characterized by a mixed composition of dead, living, and variously injured tissue (Wartman, 1963). Dead tissue was found in different phases of repair, indicating that cellular damage had occurred over a period. The myocardial cells that die later are supposed to be the source of the CK that appears later, thus resulting in a prolonged CK release time. As a further difference between groups A and B the interval

TABLE 6 Post-mortem findings in 4 of the 5 patients in group C who died

Case No.*	Macroscopical findings	Microscopical findings
5	Full thickness infarct of IV septum and LV anterior wall	Diffuse, dense neutrophilic infiltrate in association with necrotic muscle cells of which nuclei had completely disappeared. Focal necrosis with pyknotic nuclei and less dense infiltration
7	Full thickness infarct of LV inferior wall; sub-endocardial laminar necrosis of LV anterior wall	Early homogeneous necrosis
8	Large infarct involving more than half of thickness of LV anterior wall; laminar necrosis of the inner layers at base	Early homogeneous necrosis with small foci of necrotic tissue partially removed by dense granulation tissue
9	Full thickness necrosis of LV inferior wall and IV septum; second separate infarct area is seen in LV lateral wall	Early homogeneous necrosis; beginning leucocytic infiltration

* See Table 5.

Rate constant of CK elimination (h ⁻¹)	ST segment change (%)		Infarct extension detected by ECG	Chest pain hospital day			Died
	Day 1-2	Day 2-3		1	2	3	
0.05	-39	-29	+	+	+	-	-
0.07	-20	+8	-	+	+	+	-
0.07	-16	-21	-	+	+	-	-
0.06	-14	-24	+	+	+	-	-
—	-33	-5	+	+	+	+	+
0.05	-79	+26	-	+	+	-	+
—	-82	-9	-	+	+	-	+
0.06	-61	-25	-	+	+	-	+
—	-25	-60	-	+	+	+	+
0.06 ± 0.009	-41 ± 8.9	-15.4 ± 13					

from the onset of chest pain until the rise of serum CK activity to 40 mU/ml was significantly longer in group B, suggesting that the beginning of severe chest pain preceded the onset of infarction.

Further rises in serum CK activity associated with severe chest pain were seen in 22 per cent of the patients (group C). In experimental infarction it has been shown that a second rise in serum CK activity represented a sudden extension of the infarct (Shell *et al.*, 1971). It is reasonable to assume that this was also the case in the patients in group C. An extension of infarction accounted for 24 per cent of the final infarct size and may be regarded as a major factor in the poor prognosis in this group.

In conclusion, analysis of CK serum and release curves showed three modes of CK release: short, long, and repeated release. Comparison with clinical and pathological data showed that these three modes probably reflect a different mechanism of infarct development. CK release of short duration occurs in an infarction without extension, a long duration of CK release occurs in patients with gradual infarct extension, and repeated CK release occurs with sudden infarct extension. According to these criteria there was an extension of infarct in 78 per cent of our patients. This high incidence again emphasizes the potential value of treatment designed to limit the final infarct size (Reid *et al.*, 1974; Maroko, 1974). Serial CK determinations may be an appropriate way of evaluating the effectiveness of such a therapy. Isoenzyme estimations may be of more value for this purpose, but the accuracy of the methods of measuring them is still a matter of controversy.

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