QUANTITATIVE ASSESSMENT OF MYOCARDIAL INFARCT SIZE
FROM SERIAL DETERMINATIONS
OF SERUM CREATINE PHOSPHOKINASE ACTIVITY:
Significance of Previous Infarction for the Cardiac Function and Prognosis

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In 50 patients with acute myocardial infarction (16 patients with previous infarction and 34 patients without), total creatine phosphokinase (CPK) released which represents infarct size was calculated from the serial change of serum CPK activity by the method of Sobel improved by Norris, and related it to the presence or absence of heart failure, the ejection fraction and one-year-mortality.

If the patients with previous myocardial infarction were excluded, mean total CPK released in 10 patients with heart failure (1428 ± 200.4 IU/ml in Group II) was significantly larger ($P < 0.01$) than that in 24 patients without heart failure (735.3 ± 83.6 IU/ml in Group I).

However, in patients with previous myocardial infarction there was no significant difference in infarct size between these two groups (Groups I and II) indicating that the complication of heart failure does not directly relate to the size of the recent infarction but in large extent to the presence of prior infarction.

The ejection fraction was obtained in 15 patients who had left ventriculography. Both of two patients with prior myocardial infarction in these 15 patients showed smaller ejection fraction than the predicted values from the total CPK released. This also indicates that the previous myocardial infarction could contribute to impaired cardiac function as well as the recently occurred infarction.

One-year-mortality in Group II (37.5%) was higher than that of Group I (7.4%). In four patients with prior infarction who died within one year after the onset, mean total CPK released (275.3 IU/ml) was significantly smaller than that in three patients without prior infarction (899.0 IU/ml).

These results strongly suggest that the patients with previous myocardial infarction are often complicated with heart failure and have poor prognosis even with comparatively small infarction and also demonstrate the substantially large contribution of the reduced contractility resulting from the previous myocardial infarction to the impaired cardiac function.

Key Words:

Acute myocardial infarction
Creatine phosphokinase (CPK)
Infarct size
Heart failure
Ejection fraction

ALTHOUGH the mortality rate of acute myocardial infarction due to arrhythmia has been reduced by monitoring and prompt treatment in coronary care unit, the death rate following pump failure and/or cardiogenic shock

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TABLE I THE PERTINENT DATA IN SUBJECTS STUDIED

Patient	Age	Sex	Site of Infarct	Past History	$\int_0^t f(t) dt$ (IU/ml)
<i>Group I</i>					
1. K.T.	77	F	I	MI	550
2. S.A.	55	M	IL	AP	680
3. H.M.	74	M	IL	HT	650
4. K.K.	46	M	AL	MI	365
5. S.T.	48	M	I	HT	1100
6. T.H.	57	M	I	HT, DM	675
7. F.S.	46	M	AS	MI, HT	440
8. D.B.	50	M	I	AP	278
9. H.T.	70	M	I	MI	460
10. I.S.	60	M	AS	HT	570
11. T.T.	56	F	AL	HT	645
12. K.K.	62	M	AL	CVA, DM	1220
13. M.Y.	62	M	S	AP, DM	267
14. F.H.	46	M	AS	AP, DM	300
15. K.S.	45	M	I	(-)	1310
16. O.K.	43	M	AS	(-)	1500
17. T.Y.	57	M	I	CVA	340
18. Y.M.	48	M	AS	MI	348
19. M.M.	52	M	I	(-)	690
20. S.M.	65	M	PL	(-)	1390
21. M.H.	66	F	I	HT	930
22. S.K.	54	M	AS	(-)	373
23. M.K.	45	M	AL	HT	800
24. H.T.	60	M	IP	HT	1523
25. M.K.	68	M	IP	(-)	775
26. I.M.	48	F	A	HT	138
27. T.K.	65	F	I	AP, DM	482
28. S.M.	68	M	AS	AP, DM	795
29. K.H.	57	M	P	AP, HT	215
30. F.T.	47	M	A	MI, HT	120
<i>Group II</i>					
31. O.K.	71	M	I	MI, AP, DM	860
32. I.G.	63	M	IL	AP, HT	605
33. K.T.	69	M	AS	MI	124
34. S.N.	67	M	I	MI	160
35. M.S.	63	M	I	HT	2320
36. S.T.	73	M	I	MI, HT, DM	60
37. A.Y.	49	M	I	HT	1110
38. S.N.	68	F	IL	(-)	1200
39. S.H.	62	M	AS	HT	1745
40. K.H.	53	M	AL	(-)	1740
41. S.N.	69	F	A	MI	151
42. K.A.	78	M	AL	MI	370
43. S.K.	69	M	AS	MI, AP, DM	340
44. I.K.	61	M	I	HT	1500

45.	T.Y.	76	F	A	MI, HT	956
46.	N.S.	66	F	AL	(-)	1442
47.	S.Y.	50	M	I	MI, HT	1944
48.	Y.S.	74	M	P	MI	714
49.	K.N.	64	M	AS	(-)	2348
50.	M.C.	71	F	IP	AP	270

Abbreviations: Sex; M: Male, F: Female

Site of Infarct; I: Inferior, A: Anterior, AS: Anteroseptal, AL: Anterolateral, P: Posterior, S: Septal, IP: Infero-posterior, IL: Inferolateral, PL: Posterolateral

Past History; MI: Myocardial Infarction, AP: Angina Pectoris, HT: Hypertension, DM: Diabetes Mellitus, CVA: Cerebral Vascular Accident.

remains excessive.¹

In 1972 Sobel et al² demonstrated a close correlation between the prognosis of patients with acute myocardial infarction and the infarct size calculated from the serial serum creatine phosphokinase (CPK) activities. Norris et al³ also reported that patients who had larger infarct were more frequently complicated with pulmonary congestion than those with smaller infarct.

However, we have often observed the patients with heart failure and poor prognosis, although they had only small infarct judging from their electrocardiographic changes. We noticed that such a patient frequently has had previous myocardial infarction.

In our study, we attempted to estimate the infarct size of the patients with or without previous myocardial infarction by the method of Sobel² improved by Norris³ and relate it to the presence or absence of heart failure. The ejection fraction obtained by left ventriculography and one-year-mortality were also investigated to analyze the effect of the previous myocardial infarction on cardiac function and prognosis.

MATERIALS AND METHODS

I. Patients studied

Fifty patients with acute myocardial infarction admitted to the Coronary Care Unit of Sakurabashi Watanabe Hospital within 12 hours after the onset of infarct and surviving for more than four days, with serum CPK activity returning to normal by that time, were studied.

Patients with cardiogenic shock or severe arrhythmias were excluded in this study. Patients who had right heart catheterization using Swan-Ganz catheter in acute phase of infarction were

included, since we noticed that right heart catheterization could not be a cause of a release of CPK.⁴ The average age of the patients was 60.2 years (range 43 to 78 years); 40 were male and 10 female. Pertinent clinical data are presented in Table I.

The diagnosis of acute myocardial infarction was based on a history of chest pain, development of pathologic Q waves, the typical evolution of serum enzyme activity [CPK, glutamic oxaloacetic transaminase (GOT), lactic dehydrogenase (LDH), and α -hydroxybutyrate dehydrogenase (HBD)].

(i) Complication of heart failure

The patients were divided into two groups according to the presence or absence of heart failure (Table 1). Group I included 30 patients with no evidence of heart failure and Group II consisted of 20 patients with heart failure. Diagnosis of heart failure is based on the following criteria: A. No heart failure; no clinical signs of cardiac decompensation, B. Heart failure; pulmonary rales or pulmonary edema in chest X-ray and S3 gallop.

(ii) Correlation of total CPK released to ejection fraction

In order to investigate the relationship between infarct size and cardiac function as a pump, ejection fraction was obtained in 15 patients who had left ventriculography within six months after the onset of infarction. In our study, single plane left ventriculogram was obtained in the right anterior oblique position (100 frames/sec) before the selective coronary arteriogram using 40–50 ml of sodium diatrizoate. Ejection fraction was obtained as the ratio of ventricular stroke volume to end-diastolic volume and the relationship between the ejection fraction and

the total CPK released (see below) was investigated.

(iii) Total CPK released and one-year-mortality

In order to investigate the relationship between the infarct size and the prognosis, 42 out of 50 patients were followed up for a year after the onset of infarction and one-year-mortality and cause of death were studied in relation to the total CPK released. Seven patients who are still followed were excluded from this study since it has not been one year after the onset and one patient was dropped from our follow-up study.

II. Serum enzyme determination and analysis of data

Peripheral venous blood samples were obtained every 4 hours during the first 24 hours following admission, and every 6–8 hours thereafter until serum CPK activity returning to normal. The sample was allowed to clot at room temperature and serum stored at 4°C immediately after separation. The determinations were made within 15 hours after sampling by the modified method of Nuttal-Wedin with a normal range of less than 40 IU/ml⁵. As intramuscular injections can cause a release of CPK, all injections were given either intravenously or subcutaneously.

The appearance function of CPK released from the injured heart muscle was calculated according to the method of Sobel and associates² modified by Norris et al.³ The principle of this method is that the instantaneous rate change in

serum CPK activity ($dE(t)/dt$) reflects the rate of appearance ($f(t)$) of enzyme released from the circulation in monoexponential fashion as represented by the disappearance rate (K) multiplied by the instantaneous serum CPK activity ($E(t)$).

$$\frac{dE(t)}{dt} = f(t) - K \cdot E(t)$$

Thus, the appearance function is obtained as follows:

$$f(t) = \frac{dE(t)}{dt} + K \cdot E(t)$$

Where $E(t)$ represents the instantaneous serum CPK activity after subtracting the individual basal serum CPK activity (average 15 IU/ml).

The CPK disappearance rate (K) was estimated in each patient from the terminal portion of the disappearance curve ($E(t)$) graphed in a semilogarithmic plot on the assumption that additional myocardial CPK release into the circulation had not continued in the terminal monoexponential portion. The average disappearance rate of serum CPK was 0.046 ± 0.002 (mean $\pm$ S.E.) hours⁻¹.

Integration of the appearance function ($\int_0^t f(t)dt$) theoretically should give the total amount of CPK released per unit of blood volume which has been shown by Shell et al.⁶ to be closely correlated to infarct size.

In practice, we used the computer (NEAC-2200/500, TSS) of Osaka University to calcu-

Fig.1. Serum CPK activity ($E(t)$), appearance function of CPK ($f(t)$) and total CPK released ($\int_0^t f(t)dt$) in a representative case without heart failure.

Fig.2. Serum CPK activity ($E(t)$), appearance function of CPK ($f(t)$) and total CPK released ($\int_0^t f(t)dt$) in a representative case with heart failure.

late $f(t)$ and its integration. Statistical evaluation of the data was done by the t-test.

RESULTS

Appearance function of CPK ($f(t)$) and the total CPK released ($\int_0^t f(t)dt$)

Fig. 1 shows serial changes in the serum CPK activity ($E(t)$) and in the appearance function ($f(t)$), and also the integration of the appearance function ($\int_0^t f(t)dt$) in a representative case of acute myocardial infarction without heart failure (Case 6). As can be seen, serum CPK activity reached a peak 24 hours after the onset and its peak value was 311 IU/ml. The appearance function of CPK ($f(t)$) increased rapidly and reached a maximum 9 hours after the onset, and returned to zero by 36 hours after the onset. Total CPK released ($\int_0^t f(t)dt$) increased rapidly and reached a maximum level of 675 IU/ml 36

hours after the onset at the same time as termination of enzyme release.

Fig. 2 also shows serial changes in serum CPK activity ($E(t)$), in its appearance function ($f(t)$) as well as the integration of the appearance function ($\int_0^t f(t)dt$) in a patient complicated with heart failure (Case 38). The peak value of serum CPK activity was 395 IU/ml at 24 hours after the onset of infarction, and the release of CPK from the myocardium continued markedly longer than that in Case 6 terminating by 72 hours after the onset. Total amount of CPK released from the myocardium was 1200 IU/ml in this case, indicating a substantially large infarct.

Relationship between the total CPK released and the complication of heart failure

Table II shows the total CPK released in Groups I and II which correspond to the infarct size. In 30 patients without heart failure (Group

TABLE II TOTAL CPK RELEASED IN THE PATIENTS WITH ACUTE MYOCARDIAL INFARCTION ($\int_0^t f(t)dt$)

(Mean $\pm$ SE, IU/ml)

	Prior MI (—)	Prior MI (+)	Total
Group I	735.3 $\pm$ 83.6 (24)	380.5 $\pm$ 54.7 (6)	664.3 $\pm$ 72.6 (30)
Group II	1428.0 $\pm$ 200.4 (10)	567.9 $\pm$ 174.3 (10)	998.0 $\pm$ 164.0 (20)
Anterior MI	952.7 $\pm$ 166.4 (14)	357.1 $\pm$ 80.1 (9)	719.7 $\pm$ 122.1 (23)
Inferior MI	929.4 $\pm$ 122.5 (20)	678.3 $\pm$ 219.1 (7)	864.3 $\pm$ 109.1 (27)
Total	939.0 $\pm$ 99.5 (34)	497.6 $\pm$ 113.1 (16)	797.8 $\pm$ 82.0 (50)

The number of cases is shown in parenthesis. ** $p < 0.01$, * $p < 0.05$

I), the mean total CPK released (664.3 ± 72.6 IU/ml) was significantly smaller ($P < 0.05$) than that (998.0 ± 164.0 IU/ml) of 20 patients with

Fig.3. Comparison of total CPK released ($\int_0^t f(t)dt$) between patients without heart failure (Group I) and those with heart failure (Group II). A closed circle and open circle represent a patient without and with prior myocardial infarction, respectively.

heart failure (Group II, see Fig. 3). Furthermore, if the patients with previous myocardial infarction are excluded, a great difference was observed between the remaining 24 patients of Group I (735.3 ± 83.6 IU/ml) and 10 patients of Group II (1428.0 ± 200.4 IU/ml, see Fig. 3).

There was no significant difference in total CPK released between the patients with anterior infarction including septal and lateral infarction (average 719.7 ± 122.1 IU/ml) and those with inferior infarction (average 864.3 ± 109.1 IU/ml).

In contrast to the great difference in infarct size in the patients without previous myocardial infarction between with and without heart failure, in those with previous myocardial infarction there was no significant difference in infarct size between these two groups, indicating the patients with previous myocardial infarction are frequently complicated with heart failure with comparatively small infarct. Actually a much greater percent (50%) of patients with prior myocardial infarction was in Group II and the mean total CPK released of these patients (567.9 ± 174.3 IU/ml) was significantly smaller than that of patients without prior myocardial infarction (1428.0 ± 200.4 IU/ml) (see Table II).

The relationship between the total CPK released and ejection fraction

Fig. 4 shows the relationship between the total CPK released and ejection fraction which was obtained in 15 patients who had left ventriculography. These two parameters correlated

Fig.4. Relationship between the total CPK released and ejection fraction in seven patients with anterior infarction and eight patients with inferior infarction. Straight lines show linear regression in each group excluding two patients with previous infarction. (○: Anterior infarction, ▲: Inferior infarction without prior myocardial infarction, ●: Anterior infarction with previous myocardial infarction).

TABLE III THE CAUSE OF DEATH, SURVIVAL INTERVAL AND THE TOTAL CPK RELEASED IN THE PATIENTS WHO DIED WITHIN A YEAR AFTER THE ONSET

Patient No.	Age	Sex	Prior MI	Cause of Death	Survival Interval	Total CPK Released ($\int_0^t f(t) dt$, IU/ml)
<i>Group I</i>						
1. K.T.	77	F	+	Complete A-V Block	6 Days	550
3. H.M.	74	M	—	Sudden Cardiac Arrest	7 Days	650
<i>Group II</i>						
32. I.G.	63	M	—	Uncontrollable Heart Failure	9 Months	605
36. S.T.	73	M	+	Gastric Cancer	7 Months	60
41. S.N.	69	F	+	Uncontrollable Heart Failure	3 Months	151
43. S.K.	69	M	+	Sudden Death	12 Months	340
46. N.S.	66	F	—	Uncontrollable Heart Failure	1 Month	1442

well in 5 patients with anterior infarction excluding 2 patients with previous myocardial infarction (coefficient of correlation is -0.93) and also in 8 patients with inferior infarction (coefficient of correlation is -0.91), indicating that the infarct size is directly related to the ejection fraction. However, two patients with previous myocardial infarction (both with anterior infarction) demonstrated the comparatively small ejection fraction for their infarct size (see Fig. 4).

This strongly suggests that the reduced contractility in previously infarcted myocardium could be added to the recent myocardial damage, resulting a severe impairment of cardiac contraction.

Relationship between the total CPK released and one-year-mortality

In 42 patients who were followed at least for a year, seven patients died during the first one year. Table III shows the cause of death, survival interval after the onset of infarction and the total CPK released. Two out of seven patients were included in Group I (without heart failure) and they both died from arrhythmia; one from sudden cardiac arrest and the other from complete A-V block. In contrast to these two patients in Group I, three of the remaining five patients in Group II (with heart failure) died from uncontrollable heart failure. One of these three patients was complicated with severe heart failure after the attack of reinfarction. One of the remaining two patients died suddenly after discharge from the hospital, probably due to cardiac arrhythmia and another one died from gastric cancer. This difference in mortality rate

between these two groups (Groups I and II) strongly suggests that heart failure due to infarction mainly contribute to poor prognosis.

It should be noticed, however, that in seven patients who had died within first one year, the mean total CPK released in four patients with prior myocardial infarction (275.3 IU/ml) was significantly smaller than that in three patients without prior myocardial infarction (899.0 IU/ml), indicating a patient with previous myocardial infarction has a high risk even with comparatively small infarction.

DISCUSSION

Now that the mortality rate of acute myocardial infarction has been reduced by the aggressive and prophylactic use of newer anti-arrhythmic agents and the application of external counter-shock and of pacemakers in the coronary care unit⁷⁻⁹ the most important problem is to reduce the residual incidence of mortality resulting primarily from cardiac pump failure.¹⁰ Recently therapeutic interventions to reduce the infarct size have been tried on patients in the early phase of acute myocardial infarction.^{11,12} Although the patients with previous myocardial infarction sometimes have poor prognosis even with small infarction, no studies have reported to investigate the quantitative relationship between infarct size and cardiac function and/or prognosis in patients with previous myocardial infarction. The present study demonstrates that the contribution of previous myocardial infarction to impairment of cardiac function is substantially large and the prognosis of the patients with

previous myocardial infarction is poor even with small infarction which is assessed from the serial serum CPK activities.

1) *Total CPK released and complication of heart failure*

The mean total CPK released in Group II (with heart failure) was significantly greater than that of Group I (without heart failure). This difference was more prominently demonstrated when the patients with previous myocardial infarction were excluded.

In a study by Norris et al.³ they arrived at comparable results, although their analysis technique was different from ours. They report a basal CPK value of 40 mIU/ml which we assume to be comparable to our basal value 15 IU/ml. This factor of 375 (15 IU/ml divided by 40 mIU/ml) converts their results to values approximating ours. In their series, the mean total CPK released was 3.4 IU/ml (corresponding to 1,275 IU/ml in our technique) in 14 patients with transmural infarction complicated with pulmonary congestion, which was significantly greater than that in 17 uncomplicated patients (1.7 IU/ml which corresponds to 637.5 IU/ml in our technique). In our series, the mean total CPK released was 998.0 IU/ml in patients with heart failure and was 664.3 IU/ml in patients without heart failure. This shows a good agreement between our results and theirs, indicating that the infarct size is a major determinant factor of the complication of heart failure in patients without previous myocardial infarction.

However, this is not a case in patients with previous myocardial infarction. In our series, 16 patients had the previous history of myocardial infarction, 6 of 30 patients of Group I (20%) and 10 of 20 patients of Group II (50%). It was particularly interesting that the patients with prior myocardial infarction were more often complicated with heart failure, although the average infarct size in these 10 patients of Group II (average 567.9 ± 174.3 IU/ml) was significantly smaller than that in the remaining 10 patients without prior myocardial infarction (average 1428.0 ± 200.4 IU/ml, $P < 0.01$). This suggests that the residual viable myocardium which would function as a pump had been reduced in patients with previous myocardial infarction and its inadequacy resulted in heart failure. Furthermore, the reduction in viability of remaining myocardium also appears to contribute to heart failure. Actually the mean age in 10 patients with previous myocardial infarction in Group II (69.5

y.o.) was higher than that in 6 patients in Group I (55.7 y.o.). Although there is one young patient (Case 47, 50 y.o.) in Group II, he had the myocardial deterioration factor such as hypertension while two aged patients (Case 1, 77 y.o. and Case 9, 70 y.o.) in Group I had no such history.

2) *Total CPK released and ejection fraction*

Although ejection fraction has been believed to be a good index for cardiac performance in ischemic heart disease,¹³ no studies have been reported to investigate the quantitative relationship between infarct size and ejection fraction. It was surprising that our results demonstrated a close correlation between these two parameters in patients without previous myocardial infarction. However, higher ejection fraction was obtained in patients with inferior infarction than in patients with anterior infarction. This may be due to the underestimation of the reduced movement of the inferior wall by a single plane left ventriculogram and/or comparatively small contribution of the contraction of the inferior wall to the ejection fraction.

It should be noticed, however, two patients with previous myocardial infarction showed lower ejection fraction than the predicted value from the total CPK released in patients without prior myocardial infarction (see Fig. 4). This difference shows that the previous myocardial infarction would influence the cardiac function greatly and may be a cause of heart failure which is often observed in patients with prior myocardial infarction.

3) *Total CPK released and one-year-mortality*

Seven of 42 patients died during the first one year, mortality rate being 16.7%. In Group I (without heart failure), mortality rate being 7.4%; only two patients died both from cardiac arrhythmia. In contrast to Group I, four out of 15 patients of Group II died from cardiac events within one year excluding one patient who died from gastric cancer (mortality rate is 28.6%); three patients died from uncontrollable heart failure and one had sudden death. These results confirmed the previous reports which demonstrated that the patients with the complication of heart failure have unfavourable prognosis.¹⁴ Our results also showed that the patient with previous myocardial infarction would have poor prognosis even with small myocardial infarct.

Although a history of myocardial infarction has been considered to influence greatly the cardiac function and prognosis, our results

strongly suggest that the previous myocardial infarction is one of the major risk factors as well as the size of recently occurred infarction.

4) *Validity of the mathematical calculation*

Although the method of Sobel and associates² 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 CPK appearing in the circulation is directly related to the amount lost from myocardium; that the volume of distribution is constant during the evolution of infarction; and that variable inactivation of CPK does not occur. These assumptions are subjects to criticisms which could invalidate the mathematical model to estimate myocardial enzyme release from the serum CPK activities.¹⁵

In our study, in order to avoid the effect of extracardiac CPK release which would be from traumatized skeletal muscle, all injections were given either intravenously or subcutaneously. Patients with profound hemodynamic alterations such as cardiogenic shock which could cause a release of noncardiac CPK were also excluded. Except in these conditions in which serum CPK increases without increasing serum MB-CPK activity, the relationship between the calculated infarct size from total CPK and MB-CPK appears to be consistent¹⁶ and the calculated total CPK released in this study should reflect the CPK released from the myocardium.

However, the estimated release rate of CPK can be affected if the distribution volume changes during the release of CPK since the release rate is expressed as the amount of CPK which appears in an unit volume (ml) of distribution space in one hour. Witteveen et al.¹⁷ reported recently the influence of plasma volume change on calculated infarct size, suggesting that the changes of plasma volume have to be taken into account when infarct size is calculated on the basis of serum levels. Fortunately, however, if the patients with cardiogenic shock or with large amount of infusion are excluded, the total CPK released is not greatly affected by the small change of plasma volume, although the correction of the calculated release rate of CPK by hematocrit changes will improve the accuracy of the estimation.

Concerning the invariability of the disappearance rate, Roberts et al.¹⁶ demonstrated that hemodynamic perturbations profoundly affecting cardiac output, heart rate, renal blood flow in conscious dog did not markedly affect the disappearance rate of CPK activity, although a wide

variation in this parameter was observed from person to person. Norris et al.³ also 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 this method, a close relationship was observed between the calculated total CPK released and the total depletion of myocardial CPK in the canine experiments.⁶ Thus, we believe that the estimation of the integrated appearance function of CPK is reliable to assess the infarct size.

The present study demonstrated the clinical importance of history of previous myocardial infarction as well as an encouraging correlation between total CPK released and the clinical indices of severity of infarction in the patients without previous myocardial infarction. Work is now proceeding on relationship between the appearance function of CPK and other clinical parameters such as symptoms and electrocardiographic changes in acute myocardial infarction.

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