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Prognosis of patients with different peak serum creatine kinase levels after first myocardial infarction

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The extent to which patients with low peak serum creatine kinase (CK) at their first myocardial infarction differ from patients with high CK levels in terms of risk for subsequent ischaemic events was investigated in 266 patients who survived the first 48 h from the onset of infarction. All patients were followed up for one year. Four groups were formed based on peak CK $\leqslant$ *200, 201–400, 401–800 and* $>$ *800 IU* l^{-1}. *During follow-up the incidence of mortality was 15% (N=39), non-fatal re-infarction 9% (N=23), and angina 53% (N=140). Hospital mortality was significantly higher (P<0·02) in the highest CK-group (16%), but the incidence of non-fatal re-infarction, angina pectoris and late mortality was similar in the four groups. In hospital survivors, ischaemic ST-changes during pre-discharge symptom limited bicycle stress test and multiple vessel disease were equally distributed in all four groups.*

We conclude that while hospital mortality is directly related to peak CK, there is no relationship between peak CK and late mortality, non-fatal re-infarctions, or recurrent angina. Accordingly, diagnostic and therapeutic procedures in the individual patients are not influenced by the amount of serum CK released during acute infarction.

Introduction

Serial measurements of serum creatine kinase (CK) in the first few days after acute myocardial infarction is a routine procedure for proving the existence of infarction and is also used to estimate the extent of myocardial damage[1]. It has been reported that this simple measurement also provides prognostic information since patients with high peak serum CK were found to have higher early mortality[2]. However, it is uncertain to what extent patients with low peak CK levels at their first infarction differ from those with high CK levels in terms of their risk for other ischaemic events, such as angina and recurrent infarction.

Small myocardial infarctions are more often 'non Q-wave' infarctions and some investigators have reported that these patients carry a worse prognosis than patients with Q-wave infarctions[3]. If this could be confirmed from enzyme studies, a more aggressive diagnostic and therapeutic approach would be justified in these patients. However, other authors have not found any clinical differences between the two forms of infarction and have also failed to demonstrate that the concept of Q-wave versus non Q-wave infarction implies a pathologic distinction[4].

To clarify the significance of the enzyme levels, we studied 266 consecutive patients with a first acute myocardial infarction and subdivided them into four subgroups with increasing peak serum CK levels. They were followed during the acute phase and during the year after recovery from the infarction.

The aims of this study were to determine the relation between peak serum CK and other clinical information reflecting infarct size, and to determine whether patients with a low peak serum CK have a different incidence of ischaemic events than those with larger infarctions, based on peak serum CK levels.

Patients and methods

The records of 361 consecutive patients

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admitted to the coronary care unit of the Thoraxcenter with a proven diagnosis of acute first myocardial infarction between 1 March 1981 and 31 December 1982 were considered for the study. The diagnosis of myocardial infarction was made in presence of at least 2 of the following criteria:

1. prolonged chest pain of at least 45 min;
2. dynamic electrocardiographic changes defined, in case of transmural infarctions, as evolving QR-complexes, Q-waves $>0{\cdot}04$ s or R>S in V_1–V_2 with ST–T wave changes, or in case of non-transmural infarction, as ST- and/or T-wave changes persisting for at least 24 h without loss of R-wave voltage or new Q-waves. Site of infarction was defined as undetermined in case of complete left bundle branch block;
3. a typical rise and fall of total serum CK with a peak level $>100\,\text{IU}\,\text{l}^{-1}$ (twice the upper limit of the normal range).

Patients were graded in 4 groups according to peak CK $<200\,\text{IU}\,\text{l}^{-1}$ ($N=71$, median 123, range 90–200), 201–400 $\text{IU}\,\text{l}^{-1}$ ($N=49$, median 290, range 220–400), 401–800 $\text{IU}\,\text{l}^{-1}$ ($N=84$, median 583, range 403–795) and $>800\,\text{IU}\,\text{l}^{-1}$ ($N=62$, median 1373, range 814–2994). Serial serum CK was sampled every 6 h during the first day of admission and thereafter once a day for seven days. The CK was measured both in our center and in the referring hospital with the same method[5]. The precision of the method is monitored by frequent analysis of commercially available control serum. Coefficients of variation in these lyophilized materials are in our laboratory 7–10%. When repeated analysis of fresh human serum is considered, variation coefficients are 3–6%.

Twenty three patients with a first myocardial infarction who died within 2 days from the onset of symptoms were excluded as the peak level of CK was possibly not reached. We also excluded from the study 19 patients admitted longer than two days from the beginning of symptoms and fifty three patients treated with intracoronary streptokinase, as part of an ongoing randomized clinical trial[6], since the treatment with streptokinase is known to modify the patterns of enzyme release. The treatment during hospital stay followed the guidelines recently described[7]. The data base therefore consisted of 266 patients.

At hospital discharge 188 patients were evaluated with a symptom limited bicycle stress test and 217 underwent a radionuclide ventriculography at rest[8]. Stress testing was not performed in 58 hospital survivors: in 14 because of recurrent angina, in 14 for persistent heart failure and in 30 for other limiting diseases or general disability. Eighty four patients underwent a coronary arteriography, elective in 58% of cases and in the others as part of a study protocol. After discharge patients were followed at the outpatient clinic. One year follow-up was complete. Mortality, recurrent infarction, persistent heart failure and typical angina pectoris were the end-points of the study.

Differences among groups of patients were assessed with analysis of variance for the continuous variables and with the Cochran modification of the chi square test for trend assessment of discrete variables.

Results

CK LEVELS, BASELINE CLINICAL DATA AND PRE-DISCHARGE EVALUATION (TABLES 1 AND 2)

Patients with a large infarction (CK>800) were slightly younger than those in the smaller infarction groups, but age was similar in the other groups. Sex and history of angina pectoris were evenly distributed. The percentage of patients referred from other hospitals for complications was 23% on average, being highest in patients with the largest infarcts (40%). As expected, the prevalence of non-transmural infarction was highest in the lowest CK-group (62%), while in the highest CK-group there was a prevalence of anterior infarctions (65%). Left ventricular ejection fraction progressively declined in the four CK-groups, and was on average 57, 56, 47 and 37%.

Stress testing could be performed in a similar fraction of each group — in 76% of patients on average. The maximal workload and the prevalence of ST-segment depression were equally distributed. Patients with the highest CK level had the lowest incidence of angina pectoris, but had the highest incidence of ST-segment elevation, the highest maximal heart rate and the lowest increment of systolic blood pressure, all indicators of impaired left ventricular function.

Coronary arteriography was performed in 37% of patients on average, and showed an even distribution of patients with multiple vessel disease in the four groups.

CLINICAL COURSE (TABLES 3 AND 4)

The incidence of mortality and severe heart failure during the hospital phase was significantly higher in patients with the highest peak CK-levels.

Table 1 Historical and clinical data in groups with different peak serum CK levels

Peak CK ($IU\,l^{-1}$):	⩽200	201–400	401–800	>800	*P* value
Number of patients	71	49	84	62	
Age (yrs; mean ± SD)	60 ± 11	57 ± 12	60 ± 11	53 ± 11	0·01
Males (%)	76	71	76	77	NS
Previous angina (%)	38	35	25	31	NS
Referred from other hospitals, (%)	14	18	18	40	0·01
Site of infarction					
anterior (%)	15	16	32	65	0·0001
inferior (%)	22	49	56	34	0·0001
non-transmural (%)	62	35	10	2	0·0001
unknown (%)	0	0	2	0	—
Peak *a*-HBDH ($IU\,l^{-1}$)	190 ± 96 ($N=64$)	360 ± 173 ($N=47$)	598 ± 254 ($N=78$)	1048 ± 430 $N=56$)	0·0001

If not specified, data are expressed by mean ± SD.

Table 2 Pre-discharge evaluation by radionuclide ventriculography, stress testing and coronary arteriography

Peak CK ($IU\,l^{-1}$):	⩽200	201–400	401–800	>800	*P* value
Ventriculograpy					
performed (%)	76	88	80	85	NS
LVEF (%)	57 ± 11	56 ± 11	47 ± 16	37 ± 17	0·001
Stress testing					
performed (%)	66	75	62	84	NS
max. workload (W)	119 ± 38	122 ± 43	112 ± 33	109 ± 28	NS
max. HR (bpm)	124 ± 25	133 ± 22	132 ± 21	141 ± 21	0·001
SAP rise (mmHg)	47 ± 25	45 ± 24	47 ± 27	34 ± 22	0·02
ST-depression (%)	40	52	48	25	NS
ST-elevation (%)	16	37	48	65	0·0001
angina (%)	28	40	19	3	0·002
Coronary angiography					
performed (%)	28	20	35	63	0·005
⩾2 VD (%)	65	80	72	64	NS

Abbreviations: LVEF = left ventricular ejection fraction; HR = heart rate; SAP = systolic arterial pressure. ST-depression and -elevation ⩾ 1 mm. If not specified, data are expressed as mean ± 1 SD.

Table 3 Hospital clinical course

Peak CK ($IU\,l^{-1}$):		⩽200	201–400	401–800	>800	*P* value
Mortality	*N*	1	2	7	10	
	%	1	4	8	16	0·02
Non-fatal re-infarctions	*N*	6	0	5	0	
	%	8	0	6	0	NS
Angina	*N*	18	11	16	10	
	%	25	22	19	16	NS
Killip class III–IV	*N*	2	2	9	17	
	%	3	4	11	27	0·0005

Table 4 Clinical course after hospital discharge during one year follow-up in 246 hospital survivors

Peak CK ($IU\,l^{-1}$)		⩽200	201–400	401–800	>800	*P* value
Number of patients		70	47	77	52	
Mortality	*N*	4	4	7	4	
	%	6	8	9	8	NS
Non-fatal re-infarctions	*N*	3	0	2	7	
	%	4	0	3	13	NS
Angina	*N*	25	17	23	15	
	%	36	36	30	29	NS
Heart failure	*N*	2	2	4	17	
	%	3	4	5	33	0·0001
CABG/PTCA	*N*	5/1	3/0	4/1	0/1	
	%	9	6	6	2	NS

CABG — coronary artery bypass grafting; PTCA — percutaneous transluminal coronary angioplasty.

Table 5 Treatment at hospital discharge

Peak CK ($IU\,l^{-1}$)		⩽200	201–400	401–800	>800	*P* value
Number of patients		70	47	77	52	
Beta blockers	*N*	45	27	31	10	
	%	64	57	40	19	0·0005
Nitrates	*N*	25	15	21	23	
	%	36	32	27	44	NS
Calcium blockers	*N*	21	12	15	6	
	%	30	26	19	46	NS
Digitalis	*N*	10	5	20	24	
	%	14	11	26	46	0·0005
Diuretics	*N*	19	10	30	30	
	%	27	21	39	58	0·005
Anticoagulants	*N*	5	2	16	23	
	%	7	4	21	31	0·0005
Antiarrhythmics	*N*	1	3	7	2	
	%	1	6	9	4	NS
No medication	*N*	10	9	11	3	
	%	14	19	14	6	NS
CABG/PTCA	*N*	7/3	1/1	3/2	2/0	
	%	17	4	6	4	NS

In contrast non-fatal re-infarctions and angina pectoris were similar in all groups. After hospital discharge, the follow-up data showed no differences in mortality, re-infarctions or angina pectoris during the first year. However, patients with the highest CK levels had the greatest incidence of persistent heart failure, which occurred in 33% of cases.

Discussion

Infarct size is well established as an important determinant of longterm outcome in patients who survive a first myocardial infarction[1,2,9,10]. Peak serum CK is a simple measurement related to the extent of myocardial damage, which is routinely carried out in most coronary care units[1].

Peak serum CK is a less accurate method to estimate the extension of myocardial necrosis than the calculation of total CK release[1]. However, total CK release is not practical for routine work and certainly more expensive. Furthermore, Thomson *et al.*[2]. found a fair correlation between the two methods.

We found that peak serum CK is inversely related to left ventricular function as detected by clinical variables, pre-discharge radionuclide ventriculography, and stress testing. Left ventricular ejection fraction at discharge was inversely correlated with peak CK. The extent of blood pressure rise during the bicycle ergometry test, an index of left ventricular function[8], was lowest in the highest CK-group. Also the incidence of ST-elevation during ergometry, an index of left ventricular dyskinesia, was highest in the highest CK-group. Therefore we confirm that peak CK, despite its limitations[1], is for practical purposes a reliable indicator of residual left ventricular function and early prognosis after acute first myocardial infarction.

Other serum enzymes like CK-MB or *a*-HBDH have been reported to provide more specific information on the amount of myocardial necrosis than total serum CK[11]. In the present study total CK was utilized since it was determined also in all referring hospitals. Furthermore, peak CK paralleled peak *a*-HBDH (Table 1), and therefore the use of total CK should not have invalidated our findings.

Hospital mortality and the incidence of advanced heart failure during the early phase was significantly higher in the highest CK-group (Table 3). In contrast, mortality after discharge during the first year follow-up was independent of peak CK, ranging from 5 to 8% in the four groups (Table 4). This is in partial agreement with the results of Thomson *et al.*[2]. who found that peak CK was more closely related to immediate than to late mortality. These investigators also found that the mode of death during follow-up was related to infarct size: patients with high peak CK died mostly from progressive heart failure while death was more often sudden in patients with a smaller infarction. In our series we could not confirm this last observation, since most of our patients who survived during follow-up died suddenly; however the incidence of heart failure was highest (25%) in the highest CK-group.

Another important issue is the relative incidence of angina pectoris and/or non-fatal re-infarctions since it is uncertain whether their incidence is higher in patients with small infarctions, which would justify more aggressive management of these patients. Our results indicate that the incidence of angina and re-infarction is not related to peak CK either during the acute phase or during late follow-up (Tables 3 and 4). This is consistent with the similar frequency of ischemic electrocardiographic changes during stress testing and that of multiple vessel disease in the different CK-groups (Table 2).

Our results could have been biased by the many patients referred to us from peripheral hospitals because of complications. This would overestimate the severity of the disease compared to an unselected population. In fact, the prevalence of patients with multiple vessel disease in our series was higher than that described by Abraham *et al.* in a consecutive series of unselected patients with a first myocardial infarction who underwent coronary arteriography[12]. This difference could also be due to the selection for coronary arteriography, mostly elective in our series.

The follow-up results could have been influenced by the treatment applied to the different CK-groups (Table 5). In particular, coronary artery bypass surgery and coronary angioplasty for the treatment of postinfarction angina were more frequently applied in the group of patients with a small CK rise. However, a recent study of our group[13], partially based on the population of the present study, showed that coronary artery bypass surgery early after myocardial infarction did not influence survival or re-infarctions compared to a matched group treated medically.

As expected, at the other end of the spectrum, patients with the largest infarctions (CK > $800\,IU^{-1}$) were more frequently treated with digitalis, diuretics and anticoagulants and less frequently with beta blockers, because of the higher incidence of heart failure. However, most of these differences disappeared by excluding from the comparison the group with CK greater than $800\,IU^{-1}$. It is therefore unlikely that treatment different influence on the clinical outcome in those patients with a small or intermediate CK rise.

In summary, we confirm that in patients with first myocardial infarction, residual left ventricular function is inversely correlated with peak serum CK. Accordingly, patients with highest CK levels have the highest incidence of hospital mortality and heart failure. On the coronary, late mortality, non-fatal re-infarctions and angina were not

related to peak CK levels. Therefore, in patients with a first myocardial infarction, the diagnostic procedures and therapeutic policy should not be influenced by peak serum CK. In particular, patients with a small enzyme rise, do not require a more aggressive approach, unless indicated by persistent symptoms. Our results also indicate that when interventions are planned during the acute phase of infarction to salvage myocardium, beneficial effects on survival can be expected during the early phase, but not during the subsequent year.

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