Myocardial infarct size and mortality in diabetic patients

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SUMMARY The mortality rate from myocardial infarction is disproportionately high in diabetic patients. One explanation for this may be that diabetic patients incur more extensive myocardial necrosis. This possibility was examined in a three part study. Firstly, peak serum aspartate aminotransferase concentrations of all diabetic and non-diabetic patients admitted with myocardial infarction over a 16 year period were compared retrospectively. Secondly, peak aspartate aminotransferase concentrations in a series of diabetic patients and controls matched by age and sex were examined retrospectively. Thirdly, creatine kinase MB release and electrocardiographic measures of infarct size were investigated prospectively in a case/control study. Although cardiac failure and death were more common in the diabetic groups, there were no significant differences in estimates of infarct size between diabetic and non-diabetic patients in any of the studies.

Therefore, the high case fatality rate amongst diabetic patients is not caused by increased myocardial damage. Presumably survival is prejudiced by factors operating before the infarction.

Diabetic patients are at increased risk of death from myocardial infarction.^{1,2} Not only is there a higher incidence of infarction³ but the case fatality rate is about 1.5 to 2.0 times higher than it is in non-diabetic patients.^{4,5}

In general, the major determinant of mortality once the patient has reached hospital is the degree of myocardial necrosis,^{6,7} and, therefore, one explanation of the diabetic death rate could be more extensive infarction. There are theoretical reasons why this might be so—diabetic patients may have more extensive coronary disease⁸; local tissue oxygenation may be disproportionately impaired by a combination of basement membrane thickening,⁹ decreased deformability of red cells,¹⁰ increased viscosity,¹¹ and hypercoagulability of blood¹²; also a relative insufficiency of insulin¹³ is likely to lead to impairment of glycolysis (the only source of high energy phosphate in ischaemia¹⁴) and to an undue increase in non-esterified fatty acids which may further increase infarct size.¹⁵

Therefore, in trying to unravel the cause of the high mortality from myocardial infarction in diabetic patients it is important to determine whether

infarct size is greater in these patients. We have evaluated infarct size in three separate surveys in an attempt to explore the possible causes of increased mortality from myocardial infarction in diabetic patients.

Patients and methods

We conducted three separate surveys.

SURVEY 1967-83

All patients known before admission to be diabetic who were admitted to the coronary care unit between January 1967 and December 1983 with myocardial infarction were studied retrospectively. Myocardial infarction was diagnosed by the presence of two out of three of the following criteria: ischaemic pain lasting more than 30 minutes; development of new Q waves of longer than 30 ms duration; and a rise in serum aspartate aminotransferase concentrations to greater than twice the upper limit of normal.

For convenience only half of the non-diabetic patients were evaluated. Four periods of two years (1967-68, 1972-73, 1977-78, and August 1981 to December 1983) were selected and all non-diabetic patients admitted to the coronary care unit with myocardial infarction during these years were identified. Patients in whom diabetes was diagnosed

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only after admission were excluded from the study and patients who were re-admitted were treated statistically as a second patient. Peak serum aspartate aminotransferase and hospital mortality were determined from hospital records. The assay for aspartate aminotransferase has not altered over the past 16 years.

SURVEY 1979-83

In a second retrospective study all diabetic patients admitted from January 1979 to December 1983 with myocardial infarction were matched by age (± 5 years) and sex with the next appropriate non-diabetic patient who was admitted. For these patients peak aspartate aminotransferase, hospital course, and mortality were determined. To be sure that peak aspartate aminotransferase concentration had been measured we excluded patients admitted more than 48 hours after the onset of pain and those who died less than 24 hours after the onset of pain.

SURVEY 1982-84

In a prospective study, all diabetic patients admitted from July 1982 to May 1984 suspected of having a myocardial infarction were paired with the next non-diabetic patient, matched by age (± 5 years), sex, and presence or absence of a previous history of myocardial infarction (irrespective of the number of infarcts). Patients were excluded if the onset of pain occurred more than 12 hours before admission to the coronary care unit. Blood was sampled on admission and every eight hours for 72 hours. All patients suspected of having an infarction were studied, but patients were later excluded if they did not meet the diagnostic criteria. Results from those who died within 72 hours (before the blood sampling was completed) were also excluded.

All patients had electrocardiographic monitoring for 24 hours with access to immediate write-out. We noted arrhythmias that were unlikely to be overlooked: complete heart block, ventricular fibrillation and atrial fibrillation. Left ventricular failure (diagnosed on the basis of the following—a third heart sound, widespread crepitations, or a chest x ray film showing pulmonary oedema) and cardiogenic shock (hypotension, poor perfusion, and low urine output) were also noted.

Analysis of creatine kinase MB

Plasma concentrations of creatine kinase MB isoenzyme activity were determined by an immunoinhibition method (kit no 300691; Boehringer Mannheim) at 340 nm and expressed as U/l at 37°C. Plasma specimens treated with edetic acid were used and a plasma blank correction was determined and applied to each specimen.

Calculation of infarct size

The mean plasma concentration of creatine kinase MB in a series of 30 hospital patients without myocardial infarction was 20 U/l and this was subtracted from all values of creatine kinase MB. The disappearance coefficient (kd) was calculated by application of exponential regression analysis to the descending portions of the creatine kinase MB time curve (using a Super-Brain Computer and Stats-pak programme). The infarct size was calculated by the formulas of Shell *et al.*¹⁶ as modified by Norris *et al.*¹⁷ For small infarcts, where there is a degree of inaccuracy in the determination of kd, we made the arbitrary rule that if the correlation coefficient of the regression line was less than 0.95 that value of kd was rejected and the mean of the pooled values of kd was used.

Comparison of creatine kinase MB kinetics

We analysed the release of creatine kinase MB in the diabetic and non-diabetic patients by comparing the disappearance coefficient and the time to peak creatine kinase MB in the two groups. In addition, the creatine kinase MB released was found for each patient at 6, 12, 18, and 24 hours by extrapolation of each curve and this was then expressed as a percentage of total creatine kinase MB released, these percentage values were averaged for the two groups so that accumulation curves for diabetic or non-diabetic patients could be compared.

Electrocardiographic analysis

To support the enzyme data we also used two simple electrocardiographic analyses of infarct size—QRS scoring¹⁸ and the presence or absence of reciprocal ST depression.¹⁹ For the QRS score the 12 lead electrocardiogram was recorded daily at a standard speed (25 mm/s) and sensitivity (1 mV/cm); the last available electrocardiogram up to and including the seventh day after infarction was analysed for this purpose. Patients with previous infarction, left ventricular hypertrophy, or conduction abnormalities were excluded from the QRS scoring study. Reciprocal depression was defined as ST depression of 1 mm or more in at least two leads remote from the infarct site and was scored as being present if seen on any electrocardiogram. Patients with electrocardiographic defects were also excluded from this study.

Study size

From our initial study of aspartate aminotransferase and mortality in non-diabetic patients, it was evident that if the excess mortality in our hospital were solely the result of increased infarct size, then the diabetic population would be expected to have 50% more myocardial necrosis than the non-diabetic pa-

tients. Using this figure, a power of 90%, the standard deviation of a pilot study on creatine kinase MB sizing of infarcts, and looking for significance at the 5% level we calculated that data from 25 matched pairs were needed to exclude a positive result²⁰ (in the end we recruited 38 pairs).

STATISTICS

Groups were compared by Student's *t* tests and by χ^2 tests with the Yates's correction as appropriate.

Results

RETROSPECTIVE STUDY 1967-83

From 1967 to 1983, the 456 diabetic patients admitted with myocardial infarction had a hospital mortality of 33.6%, in contrast to the 18.3% mortality ($p < 0.001$) in 1951 non-diabetic patients admitted over the four two year periods of the study. Serum aspartate aminotransferase levels and mortality data were available for 1516 (78%) of the non-diabetic patients and 328 (72%) of the diabetic group. The distributions of serum aspartate aminotransferase concentrations are almost identical in the two groups (Fig. 1). Mortality increased with peak aspartate aminotransferase in both groups (Fig. 2), but at any aspartate aminotransferase concentration mortality in the diabetics exceeded that in the non-diabetics ($p < 0.001$), suggesting that the excess mortality is not solely due to infarct size.

CASE MATCHED STUDY 1979-83

Over the period of this study 167 diabetic patients were admitted with infarction; 50 died (30%). During the same period 228 (18.6%, $p < 0.001$) of 1224 non-diabetic patients died. We studied 120 pairs of

Fig. 1 Distribution of peak serum aspartate aminotransferase concentrations in retrospective analysis of 1967-83 data from diabetic and non-diabetic patients with myocardial infarction.

Fig. 2 Mortality of peak serum aspartate aminotransferase concentrations in 1967-83 retrospective analysis of diabetic and non-diabetic patients with myocardial infarction. Numbers above the bars are the number of patients.

patients from these groups; the two age and sex matched groups were similar (Table 1) for prevalence of hypertension, previous myocardial infarction, and renal dysfunction (as judged by admission creatinine concentrations). Arrhythmias were not more common in the diabetic group but haemodynamic problems (cardiogenic shock plus left ventricular failure) were (49% compared with 28% in the non-diabetics, $p < 0.01$), and Killip and Kimball grading was also significantly different in the two groups.²¹ In the diabetic group there was a statistically significant increase in the frequency of cardiogenic shock and an increase (but not a significant one) in left ventricular failure. To test for bias in our clinical haemodynamic assessment we looked at the death rate for each heart disease category. For cardiac failure, 27% of the diabetic and 23% of the non-diabetic patients died and for cardiogenic shock 94% of diabetic and 100% of non-diabetics died. These values are so similar that diagnostic bias seems unlikely. The death rate in the diabetic group was higher than that in the non-diabetic group (23% *vs* 9%, $p < 0.01$); the overall death rate was lower than that in the 1967-83 survey because of the exclusion criteria used. But despite the higher frequency of haemodynamic failure and death in the diabetics serum aspartate aminotransferase concentrations were almost identical in the two groups (mean diabetic concentration 366 U/l, mean non-diabetic 357 U/l, Fig. 3). This accords with the conclusions of the previous study that excess mortality in diabetic patients is not simply due to infarct size.

PROSPECTIVE CREATINE KINASE MB CASE CONTROL STUDY (1982-84)

Sixty five diabetics were admitted to hospital in this study period and 24 were excluded (10 died before

Table 1 Survey 1979-83

Patients	Diabetic	Non-diabetic	Significance
No	120	120	
Age in years	62.4 (9.2)	62.2 (9.0)	NS
Sex	91 male	91 male	NS
Previous history			
Hypertension	15 (13%)	19 (16%)	NS
Myocardial infarction	27 (23%)	15 (13%)	NS
Serum creatinine > 125 μ mol/l	28 (25%)	18 (17%)	NS
Serum creatinine > 300 μ mol/l	1 (1%)	2 (2%)	NS
Complications			
Atrial fibrillation	19 (16%)	18 (15%)	NS
Complete heart block	16 (13%)	8 (7%)	NS
Ventricular fibrillation	10 (8%)	14 (12%)	NS
Left ventricular failure	41 (34%)	31 (26%)	NS
Cardiogenic shock	18 (15%)	3 (3%)	p < 0.01
Left ventricular failure and shock	59 (49%)	34 (28%)	p < 0.01
Killip grades			
1	75	98	p < 0.001
2	23	19	
3	10	2	
4	12	1	
Death			
Enzymes	28 (23)	11 (9)	p < 0.01
Serum aspartate aminotransferase (U/l)	366 (322)	357 (236)	NS

Figures are means (1 SD) and percentages. Serum creatinine was measured at admission in only 110 diabetics and 106 non-diabetic patients.

Fig. 3 Distribution of peak serum aspartate aminotransferase concentrations in 1979-83 survey of diabetic and non-diabetic patients with myocardial infarction. Horizontal lines indicate mean values.

completion of enzyme sampling, 11 arrived 12 hours or more after the onset of pain, and three were excluded at the request of their own physician). Of the 41 remaining patients two could not be matched by the end of the study and one had a reinfarction 24 hours after admission. These patients were not included.

The 38 study patients (Table 2) had been diagnosed as diabetic a mean of 11.2 years ago; seven were being treated by diet, 20 with oral agents, and 11 with insulin; five had some degree of retinopathy, three had proteinuria, and three had peripheral vascular disease. The histories of diabetic and non-diabetic patients were similar but fewer diabetic patients were current smokers. The frequency of arrhythmias was similar in the two groups. There was a trend to more haemodynamic complications but the numbers are too small for valid statistical analysis. Because of the exclusion criteria the death rate was low in both groups.

Whatever the method of assessment used diabetic patients did not have larger infarcts than non-diabetic patients (Table 3). The 95% confidence limits of the sum of creatine kinase MB release are such that infarct size in diabetic patients might have exceeded by up to 33 U/l that in non-diabetics, but the chance that a larger excess could have been missed is less than 2.5%. If the non-diabetic sample is assumed to be identical with the non-diabetic population, the maximum excess diabetic infarct size that could be missed by chance (at the 2.5% level) would be 6% of the infarct size in

Table 2 Survey 1982-84

Patients	Diabetic	Non-diabetic	Significance
No	38	38	
Age in years	60.7 (9.4)	60.7 (9.0)	NS
Sex	27 male	27 male	NS
Previous history			
Hypertension	11 (29%)	13 (34%)	NS
Myocardial infarction	10 (26%)	10 (26%)	NS
Angina	4 (11%)	5 (13%)	NS
Current smoker	9 (24%)	21 (55%)	p < 0.01
Electrocardiogram abnormality			
Anterior infarct	17	15	NS
Inferior infarct	19	22	
Right bundle branch block	1	1	
Left bundle branch block	1	0	
Complications			
Atrial fibrillation	6 (16%)	5 (13%)	NS
Complete heart block	3 (8%)	4 (11%)	NS
Ventricular fibrillation	3 (8%)	4 (11%)	NS
Left ventricular failure	17 (45%)	10 (26%)	NS
Cardiogenic shock	3 (8%)	2 (5%)	NS
Left ventricular failure and shock	20 (53%)	12 (32%)	NS
Killip			
1	31	33	NS
2	5	4	
3	2	0	
4	0	1	
Death			
	3	2	NS

Figures are means (1 SD) and percentages.

Table 3 Estimation of infarct size

	Diabetic	Non-diabetic	Significance
By enzyme			
Peak aspartate aminotransferase (U/l)	472 (402)	421 (321)	NS
Peak creatine kinase MB (U/l)	240 (129)	297 (174)	NS
Sum of creatine kinase MB (U/l)	414 (241)	525 (382)	NS
Creatine kinase MB (gram equivalent)	24.0 (14.3)	31.7 (25.4)	NS
Creatine kinase MB (g/m ²)	13.3 (7.9)	17.1 (13.1)	NS
By electrocardiogram			
Reciprocal depression	22 (61%)*	21 (57%)†	NS
QRS Score	5.7 (3.2)‡	6.9 (3.5)‡	NS

*36 patients available for analysis. †37 patients available for analysis. ‡23 patients available for analysis. NS, not significant. Figures are means (1 SD) and percentages.

Table 4 Creatine kinase MB kinetics in diabetic and non-diabetic patients with myocardial infarction

	Diabetic	Non-diabetic	Significance
Disappearance coefficient (kd)	-0.071	-0.068	NS
Time to peak creatine kinase MB (h)	20.7	22.8	NS
Percentage of total creatine kinase MB released by			
6 h	13	10	NS
12 h	40	41	NS
18 h	68	71	NS
24 h	85	90	NS

NS, not significant.

non-diabetic patients. The creatine kinase MB kinetics of diabetic and non-diabetic patients were compared (Table 4). The coefficient of disappearance (kd), time to peak creatine kinase MB concentration, and the rate of release of creatine

kinase MB expressed as a percentage of total creatine kinase MB release were identical in the diabetic and non-diabetic groups.

The 12 lead electrocardiographic data were examined for the two semiquantitative indices of

infarct size—reciprocal ST depression and QRS score—and results in the diabetic and non-diabetic patients were almost identical. Therefore, it is very unlikely that diabetic patients have bigger infarcts than non-diabetic patients.

Hyaluronidase

For some years this hospital has been assessing the effect of treatment with hyaluronidase (GL enzyme) on myocardial infarction.²² Twenty three per cent of patients in the 1979–83 survey and 20% of those in the 1982–84 survey were given the drug. This is unlikely, however, to have altered our conclusions because in our experience²² and that of others²³ hyaluronidase does not reduce infarct size in man as judged by cardiac enzyme release (aspartate aminotransferase or creatine kinase MB). Also it could not alter the significance of the observation that there is disparity between enzyme concentrations and mortality in the two groups; and, finally, the results are unchanged by exclusion from the analysis of all patients receiving hyaluronidase.

Discussion

The frequency of diabetes among all patients studied may have been underestimated because many were seen before haemoglobin A₁ estimation had become common practice.²⁴ Even so, approximately 2% of the apparently non-diabetic population was found to be diabetic on admission to hospital and these patients have been excluded from the study. The remainder of the non-diabetic population may have contained a further 2–3% of diabetic patients²⁵ who could now be detected by measurement of haemoglobin A₁ but this is too small a figure significantly to influence the results.

To our knowledge no one has examined the validity of creatine kinase MB kinetics as an estimate of infarct size in the diabetic patient. This requires a parallel necropsy study which we did not perform, nor were sufficient patients available for such a study. But the disappearance coefficients, the time to peak creatine kinase MB concentrations, and the rates of accumulation of creatine kinase MB are all so similar in the two groups (Table 4) that it seems very unlikely that creatine kinase MB kinetics differ in diabetic patients.

Among those diabetic patients reaching hospital, the majority of deaths (80–85%) are due to pump failure.²⁶ In this respect they are no different from non-diabetic patients (and this study shows that arrhythmias are not more prevalent in diabetics and previous work from this hospital also indicates that ketoacidosis is a rare (3%) complication of infarction in diabetic patients²⁷). An alternative explanation of

the high mortality in diabetic patients could be that they have a greater degree of myocardial necrosis which in turn might be due to more extensive coronary atheroma in diabetes; poor tissue oxygenation due to abnormalities of the micro-circulation^{9–12}; or the pronounced impairment of glycolysis¹⁴ and raised non-esterified fatty acid concentrations¹⁵ that would be expected in the diabetic patient after infarction.

We have examined the possibility of a systematic increase in infarct size in diabetics by using three complementary sets of observations—a retrospective 16 year study of all diabetics with a relatively non-specific enzyme method of estimating infarct size, a matched series in which aspartate aminotransferase was measured, and a study which excluded some of the more seriously ill patients but which used a more specific and precise enzyme technique (creatine kinase MB) reinforced by analysis of the 12 lead electrocardiogram. In none of these three sets of patients did the diabetic patients have larger infarcts than the non-diabetic ones. This accords with the results of Jaffe *et al* who showed that although diabetic patients have increased rates of cardiac failure after myocardial infarction, infarct size in these patients is less than that of the non-diabetic patients.²⁸

Thus, although in theory there are mechanisms by which the diabetic might be at risk of more extensive infarction, these do not appear to be important in practice. We have also found that careful metabolic control after infarction has little effect on mortality.²⁹ Therefore, the unknown cause of the excess death rate may well operate before the fatal infarction occurs. The most likely explanation appears to be previous left ventricular disease, possibly vascular in origin or possibly related to some other aspect of diabetes. Attempts to improve survival among diabetic patients should be instituted before the onset of infarction.

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