

# Effect of intravenous insulin infusion on mortality among diabetic patients after myocardial infarction

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**SUMMARY** A review of the records of 353 diabetic patients after a myocardial infarction confirmed the high mortality associated with the condition. The influence of improved diabetic control achieved by intravenous insulin was assessed in 64 patients and compared with earlier experience in a diabetic control group. The frequency of the major complications of myocardial infarction was unchanged and the death rate in both groups was identical (33%); even the patients with blood glucose concentrations >20 mmol/l on admission failed to benefit. Thus careful control of blood glucose concentrations after myocardial infarction in diabetic patients fails to improve the outcome of this high risk group.

Mortality in diabetic patients after myocardial infarction is almost twice that of patients without diabetes mellitus.<sup>1,2</sup> Improved metabolic control in the immediate period after infarction might reduce infarct size and influence survival. Insulin enhances the uptake of glucose, the major energy substrate of ischaemic myocardium,<sup>3</sup> and reduces non-esterified fatty acid concentrations,<sup>4</sup> which have been suggested to increase infarct size (by increasing myocardial oxygen consumption<sup>5,6</sup>), reduce myocardial contractility,<sup>5,7</sup> and be associated with postinfarction arrhythmias.<sup>8</sup>

The aim of this study, therefore, was to determine whether the use of intravenous insulin reduced mortality in diabetic patients after a myocardial infarction. A group of patients treated in this way was compared with a control group comprising all diabetic patients admitted from 1967 to the beginning of the insulin infusion regimen in 1981. To discover whether changes in management had appreciably altered mortality over this period the death rate in all non-diabetic patients was calculated.

## Patients and methods

A retrospective survey of all non-diabetic patients having a myocardial infarction admitted to hospital between 1967 and 1983 was performed to detect any

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changes in inpatient mortality during this period. The criterion for myocardial infarction was the presence of two of the following: (a) a typical history of cardiac ischaemic pain, (b) a rise in aspartate aminotransferase activity to greater than twice the normal value, or (c) electrocardiographic changes diagnostic of myocardial infarction.

## DIABETIC CONTROL GROUP

The records of all known diabetics admitted to this coronary care unit with a diagnosis of myocardial infarction between 1967 and 1981 (the onset of the insulin infusion regimen) were then reviewed; these patients comprised the diabetic control group. Previously undiagnosed diabetic patients were excluded from the survey (and also from the analysis of non-diabetic patients). The details sought were the age, sex, previous medical history, duration of diabetes, current diabetic treatment, site of infarct, maximum aspartate aminotransferase activity, blood glucose concentration on admission and at midday on the first two days, details of inpatient treatment, and complications of the infarction and survival.

## INSULIN INFUSED GROUP

The details of the insulin infusion regimen have been reported elsewhere.<sup>9</sup> Briefly 1 unit of insulin per hour is infused if the blood glucose concentration is between 0 and 8 mmol/l, 2 units of insulin per hour if the concentration is between 8 and 12 mmol/l, 4 units per hour if it is between 12 and 24 mmol/l, and if it is >24 mmol/l the infusion rate is adjusted to the needs



Table 2 Complications of myocardial infarction in the two groups of patients

	Diabetic control group		Insulin infused group		Significance
	No	%	No	%	
Haemodynamic complications	125	35	30	47	NS
Ventricular fibrillation	29	8	8	13	NS
Complete heart block	40	11	5	8	NS
Death	118	33	21	33	NS
No of patients	353		64		

NS, not significant

during these periods. The years 1967–81 were divided into periods of three years and the respective death rates were: 1967–9, 19.2%; 1970–2, 15.7%; 1973–5, 19.5%; 1976–8, 15.6%; and 1979–81, 18.7%, there being no statistical difference between any of these groups. Therefore, mortality was unchanged in non-diabetic patients over the study period.

#### DIABETIC PATIENTS

##### Clinical details

The age, sex distribution, diabetic history, and characteristics of myocardial infarction in the diabetic control and insulin infused groups are shown in Table 1 and the Figure. There was no significant difference between the groups in age, sex distribution, previous history (except for angina), prehospital diabetic treatment, duration of diabetes, site of infarct, or maximum recorded values of aminoaspartate transferase activity.

##### Blood glucose values

The blood glucose concentrations on admission were similar (the mean  $\pm$  1SD being 14.6  $\pm$  8.2 mmol/l in the control group and 16.1  $\pm$  10.3 mmol/l in the insulin infused group, the difference not being significant). By midday on the first full day after infarction the mean blood glucose concentration of the insulin infused group was 9.9  $\pm$  3.6 mmol/l compared with 12.4  $\pm$  5.9 mmol/l for the control group, a difference that was statistically significant ( $p < 0.01$ ).

##### Outcome

There was no significant difference between the conventionally treated (control group) and the insulin infused patients in terms of the major complications of myocardial infarction: haemodynamic response (ranging from cardiac failure to cardiogenic shock), complete heart block, or ventricular fibrillation (primary or secondary) (Table 2).

The death rate in the control group was 33% (118 out of 353 patients) and 33% (21 out of 64 patients) in the insulin infused group. Clearly, there is no difference between these values, and the 95% confidence levels are  $\pm 12\%$ . If the population mortality is 33% (based on the 353 control diabetic patients) then the

maximum reduction in mortality that might be missed by chance at the 2.5% level is 36%. Of the 118 deaths in the control group, 110 were due to cardiac failure and eight to some other cause (five to strokes, two to renal failure, and one to bronchopneumonia); in the insulin infused group 20 died in cardiac failure and one as a result of a stroke.

It was thought possible that the benefit of insulin infusion might be restricted to those with high blood glucose concentrations on admission, but no such advantage was shown when the patient population was stratified according to the concentrations on admission (Table 3).

The total experience of managing diabetes over 16 years shows that the death rate remained constant from 30 to 33% whatever the treatment used (Figure). For the insulin infused group, only the total death rate was computed, since the subsets divided according to prehospital treatment were too small for individual analysis.

#### Discussion

The death rate in diabetic patients who have a myocardial infarction is higher than for non-diabetics.<sup>1,2</sup> In part this may be due to changes that occur before infarction. Diabetic patients have more extensive coronary atheroma<sup>10–12</sup> and so might be expected to have more extensive infarcts. A specific cardiomyopathy<sup>13,14</sup> has been reported in diabetes, and this may impair left ventricular function, which adds to the damage induced by infarction. Furthermore, some patients have an autonomic neuropathy, and the changed pain perception may alter the time taken to contact a doctor; moreover, the tachycardia of autonomic neuropathy could increase myocardial oxygen consumption.

It is possible, however, that the metabolic changes induced at the time of infarction may also be of importance. The oxidation of non-esterified fatty acids is the major energy source of the normal myocardium, but ischaemic heart muscle depends largely on the anaerobic metabolism of glucose.<sup>3</sup> The supply of glucose is partly curtailed by the infarction,<sup>15</sup> such that in diabetic patients, with residual insulin secretion,

Table 3 Relation between death rate and blood glucose concentrations on admission in the two groups of patients

	Death rate (%)		Significance
	Diabetic control group	Insulin infused group	
Blood glucose concentration (mmol/l):			
0-10	18/74 (24)	5/19 (26)	NS
10-20	37/114 (32)	8/29 (28)	NS
>20	23/46 (50)	7/14 (50)	NS

NS, not significant

the increased output of adrenaline<sup>16</sup> may inhibit insulin release, while the raised concentrations of glucagon<sup>17</sup> and cortisol<sup>18</sup> may cause insulin resistance. Both mechanisms result in high blood glucose concentrations but a reduced cellular supply of glucose.

High concentrations of circulating non-esterified fatty acids are found after myocardial infarction.<sup>3,4,15</sup> It has been suggested that they increase myocardial oxygen consumption<sup>5,6</sup> and therefore may increase infarct size, compounding the effect of reduced glucose availability. Furthermore, high fatty acid concentrations may cause reduced contractility<sup>5,7</sup> and increased frequency of arrhythmias.<sup>8</sup> It would, therefore, seem possible that good metabolic control, by improving the glucose supply and reducing fatty acid concentrations, might reduce the mortality of myocardial infarction.

Little direct evidence exists to support this hypothesis, but a parallel is present with the use of glucose-insulin-potassium infusion. For many years it has been known that glucose and insulin can improve cardiac function,<sup>19,20</sup> and considerable interest arose from the suggestion of Sodi-Pallares *et al*, that glucose-insulin-potassium solutions reduce post-infarction arrhythmias.<sup>21</sup> More recent work has suggested that infarct size in animals may be reduced<sup>22,23</sup> and that pump function in man may be improved.<sup>4</sup> Translating this into the use of insulin for diabetic patients after infarction would suggest that intravenous insulin might be beneficial.

In this study the mortality of non-diabetic patients with myocardial infarction did not alter over the study period (1967-83), and it, therefore, seemed reasonable to take a historical group comprising all diabetic patients admitted from 1967 to 1981 to compare with the insulin group. When the insulin infused and control groups are assessed there is no reduction in the hospital death rate. Furthermore, when patients are subdivided according to their blood glucose concentration on admission (Table 3) even those with the highest concentrations, who presumably are most likely to benefit from insulin infusion, show no improvement in prognosis. When the total diabetic sample is reviewed (Figure) the mortality remains constant at about 33% irrespective of the method of

treatment used. Finally, the haemodynamic complication rate (Table 2), the major predictor of outcome, had remained unchanged by the introduction of intravenous insulin. All these observations point to the same conclusion: survival in diabetic patients after myocardial infarction is not dependent on the excellence (or otherwise) of diabetic control.

The confidence levels of the diabetic mortality results are such that a reduction in mortality of 36% might just be missed by chance (at the 2.5% level), but in view of all the other observations pointing to the lack of improvement with intravenous insulin the likely benefit that might be missed must be much less.

The inability of good control to alter survival may be due to a number of factors. Firstly, it is possible that if a coronary artery is occluded then insulin also will be unable to reach the infarcted area and so improve the influx of glucose into these cells. Secondly, lipolysis is extremely sensitive<sup>24</sup> to inhibition by insulin, and so, although non-esterified fatty acid concentrations will fall after insulin infusion, they may fall as quickly after subcutaneous insulin or the use of oral agents. Thirdly, it is probable that the high death rate in diabetic patients may be due to large myocardial infarcts, and then manipulation of cellular metabolism may have only a minor effect on outcome. It is also possible that our insulin regimen is still inadequate, as the mean blood glucose concentration in these patients does not fall within the normal non-diabetic range. Finally, the proportion of men in both diabetic groups was high, unlike the equal sex distribution usually seen in the diabetic population after a myocardial infarction,<sup>2,12</sup> raising the possibility that local referral patterns may differ from the norm and so influence outcome.

The management of the diabetic patient after infarction remains debatable. Although a reduction in mortality has not been shown with intravenous insulin, it is possible that less easily detectable benefits—such as reduction in infarct size—might occur; in addition, this insulin protocol provides a simple and effective way of controlling the inevitable dislocation of diabetic metabolism that occurs after myocardial infarction. For these reasons intravenous insulin infusion is used for the management of diabetic patients after coronary occlusion in our hospital.

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