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(Accepted 11 July 1986)

Determinants and importance of stress hyperglycaemia in non-diabetic patients with myocardial infarction

G A OSWALD, C C T SMITH, D J BETTERIDGE, J S YUDKIN

Abstract

Determinants of plasma glucose concentrations were studied in patients on admission to hospital with confirmed acute myocardial infarction but without previous glucose intolerance as evidenced by raised concentrations of glycosylated haemoglobin (HbA_{1c}). Mortality in hospital increased significantly with increasing plasma concentrations of glucose in patients with both normal ($p<0{\cdot}0001$, n=311) and borderline ($p<0{\cdot}02$, n=70) concentrations of HbA_{1c}. There was a weak relation between plasma glucose concentrations and infarct size as estimated by peak aspartate transaminase activity in both HbA_{1c} groups ($r_s=0{\cdot}26$, n=101 and $r_s=0{\cdot}41$, n=35 respectively). A correlation was found between adrenaline and plasma glucose concentrations (r=0·47, n=27) and cortisol and plasma glucose concentrations (r=0·75, n=19), but the relation of plasma noradrenaline and plasma glucose suggested a threshold effect. Concentrations of adrenaline, but not those of noradrenaline or cortisol, correlated with infarct size as measured both by peak aspartate transaminase activity and cumulative release of creatine kinase MB isoenzyme. Multiple regression analysis showed that concentrations of cortisol, adrenaline, and noradrenaline (but not the concentration of HbA_{1c}, infarct size, or age) are the main determinants of plasma glucose concentration measured in non-diabetic patients when admitted to hospital after acute myocardial infarction.

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Introduction

The reasons for excessive mortality in diabetic patients with acute myocardial infarction remain undetermined. The potentially reversible metabolic disequilibriums that accompany acute myocardial infarction in diabetics may be responsible,[1] although this is a difficult hypothesis to test.[2] A relation has, however, been described in patients with acute myocardial infarction between hyperglycaemia on admission and the development of cardiogenic shock independent of the state of premorbid glucose tolerance.[3] Thus hyperglycaemia alone might possibly contribute to poor outcome in patients both with and without known diabetes. We tested this hypothesis in non-diabetic patients, in whom other factors peculiar to diabetes mellitus which may contribute to outcome after acute myocardial infarction, such as the existence of a specific diabetic heart muscle disease[4] or abnormal rheology,[5] are not present. The interrelations of hyperglycaemia on admission to hospital, infarct size, hormonal response to stress, and outcome in a group of patients with acute myocardial infarction, but without evidence of premorbid undiagnosed diabetes, were investigated.

Methods

The study group consisted of 397 patients, without known diabetes mellitus, admitted consecutively to the Whittington Hospital with acute myocardial infarction confirmed by the World Health Orgnisation's criteria.[6] Figure 1 shows the design of the study and composition of the patient subgroups. In all patients venous blood was taken immediately or shortly after their admission for determining concentrations of HbA_{1c}. Patients were classified as previously described[3] into clearly normal (group 1, $HbA_{1c}<6{\cdot}9\%$), borderline (group 2, HbA_{1c} 6·9-7·8%), or clearly abnormal (group 3, $HbA_{1c}>7{\cdot}8\%$) groups. Seventeen patients had concentrations of HbA_{1c} falling into group 3, which we have found to be indicative of undiagnosed diabetes,[3 6a] and were considered no further.

STUDY 1: RELATION BETWEEN PLASMA GLUCOSE AND HBA_{1c} CONCENTRATIONS AND OUTCOME

Of the 380 patients without diabetes, samples for plasma glucose measurement were taken from 236 on their admission to hospital before

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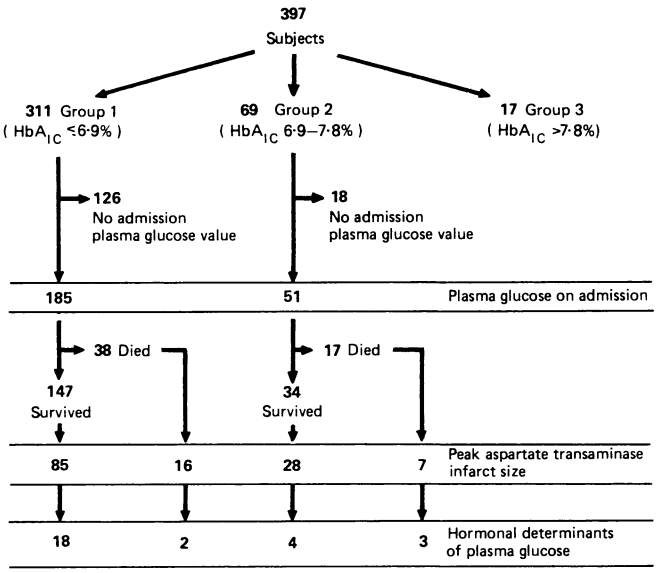

FIG 1—Patient numbers and study design.

α or β agonistic agents were administered or glucose infused. The median time of sampling from onset of symptoms was nine hours (range 1-24 hours). In this subgroup the relation between plasma glucose, HbA_{1c}, and outcome was studied.

STUDY 2: RELATION BETWEEN PLASMA GLUCOSE CONCENTRATION AND SIZE OF INFARCT

This relation was studied in a selected subgroup. Criteria for inclusion comprised, firstly, availability of a plasma glucose value taken on admission to hospital and, secondly, survival for at least 48 hours to allow assessment of the size of the infarct by peak aspartate transaminase activity. One hundred and one consecutive patients from group 1 and 35 consecutive patients from group 2 who fulfilled these criteria were included.

STUDY 3: HORMONAL DETERMINANTS OF HYPERGLYCAEMIA

The hormonal response to acute myocardial infarction was studied in a subgroup of 29 patients, not known to be diabetic, selected by virtue of admission to the coronary care unit (where the special arrangements for the collection and preparation of samples had been made), and satisfying the criteria outlined above. When patients arrived in the coronary care unit and they had been given adequate analgesia, venous blood was taken for determining HbA_{1c}, plasma glucose, cortisol, and catecholamine concentrations through a previously inserted cannula. Median time from onset of symptoms to sampling was 11 hours (range 1-23). Blood for catecholamine estimation was taken into tubes of cooled lithium heparin, which were subsequently transferred to an ice water slurry. The plasma was separated promptly at +4°C and frozen at −20°C until assay. Two of these patients died before the size of infarct could be determined by peak aspartate transaminase activity and were considered no further. None of the remaining 27 patients had concentrations of HbA_{1c} indicating undiagnosed diabetes,[3 6a] 20 having clearly normal concentrations and seven borderline concentrations. In total six patients developed cardiogenic shock, of whom five died. Results of cortisol concentrations were not available for seven patients of the total studied.

ASSAY METHODS

HbA_{1c} was determined, free of labile adducts, using an isoelectric focusing technique.[7] Size of infarct was calculated by two methods. In all patients studied the peak aspartate transaminase activity, measured on admission and daily for at least 48 hours after acute myocardial infarction, was taken as an estimate of myocardial necrosis. Aspartate transaminase activity was measured in the routine clinical chemistry laboratory of the Whittington Hospital, using a commercial kit (AST Optimised, BCL, Lewes, Sussex). Peak aspartate transaminase activity correlates well with more specific measures of infarct size,[8] as well as with both long term and short term mortality after acute myocardial infarction,[9] and as such is a reasonable estimate of the extent of myocardial necrosis. In 19 of the 27 patients in the study of hormone concentrations and outcome infarct size was further estimated by cumulative release of creatine kinase MB isoenzyme using the method of Sobel and Shell[10] as adapted by Boyle *et al.*[11] Sampling for creatine kinase MB was performed when patients were admitted and subsequently every eight hours for at least 48 hours. The creatine kinase MB isoenzyme activity was determined by an immunological method (BCL, Lewes, Sussex) that uses an antibody to inhibit the activity of the BB fraction. In 28 patients, both diabetic and non-diabetic, in whom estimates of both peak aspartate transaminase activity and cumulative creatine kinase MB isoenzyme were performed we found a moderate correlation between the estimates of infarct size ($r=0·67$, $p<0·001$), similar to the correlation previously described.[8]

Catecholamines (adrenaline and noradrenaline) were determined by high performance liquid chromatography with electrochemical detection.[12] Cortisol was estimated by radioimmunoassay using a commercial kit (Amerlex, Amersham International, United Kingdom).

STATISTICAL METHODS

Statistical analysis was by least squares regression, Spearman's rank correlation (r_s), Mann-Whitney U test, χ^2 test with Yates's correction where appropriate, Kendall τ c for trend, analysis of variance, logistic regression, and multiple linear regression analysis. The analysis was performed with a statistical package for the social sciences program. Logarithmic transformation was used when variables showed a positively skewed distribution, and a quadratic term was used for analysing exponential relations. Ninety five per cent confidence intervals are given for proportions, differences in means or proportions, and β or B values in logistic and multiple regression analyses, although in these latter cases it is recognised that the effects are not independent. For logistic regression analysis the 95% confidence interval is also presented as the upper and lower ends of the relative risk ratio for a certain change in the independent variable.

Results

SELECTION BIAS

There was no significant difference between the ages or gender of the patients in any of the three studies and those not included. Their mean age was 65·36 years (difference in mean ages 1·93 years, 95% confidence interval (CI) −0·45 to 4·31 years in study 1; 0·91 years, 95% CI −0·88 to 2·70 years in study 2; 0·51 years, 95% CI −4·06 to 5·08 years in study 3; $p>0·1$ in all cases). The proportion of women overall was 26·8% (the difference in proportion of women was 8·6%, 95% CI −1 to 18% in study 1; 4·0%, 95% CI −5 to 13% in study 2; 7·0%, 95% CI −11 to 25% in study 3; $p>0·1$ in all cases). The mortality of patients sampled for plasma glucose when admitted (22·8%) was similar to that of patients not sampled (27·3%) (difference in proportion 4·5%, 95% CI −4·5 to 13·5%, $p>0·3$). The mortality of patients without estimates of peak aspartate transaminase (29·1%) was, however, substantially greater than that of patients for whom such estimates were available (16·2%) (difference in proportion 12·9%, 95% CI 4·4 to 21·4%, $p<0·005$) because survival for 48 hours was a prerequisite for inclusion in this study.

STUDY 1: RELATION BETWEEN PLASMA GLUCOSE, HBA_{1c}, AND OUTCOME

Table I shows the distribution of mortality between normoglycaemic patients (plasma glucose <8 mmol/l (<144 mg/100 ml)), patients with moderate hyperglycaemia (plasma glucose 8-11 mmol/l (144-198 mg/100 ml)), and those with appreciable hyperglycaemia (plasma glucose >11 mmol/l (>198 mg/100 ml)). There was a highly significant ($\chi^2=29·27$, $p<0·001$; Kendall τ c 0·285, $p<0·001$) stepwise increase in mortality with increasing plasma glucose values in the patients with clearly normal concentrations of HbA_{1c} (group 1). In patients in group 2, no deaths were recorded among the 12 patients with plasma glucose concentrations less than 8 mmol/l (<144 mg/100 ml), but there was substantial mortality in the patients whose plasma glucose concentration exceeded 8 mmol/l ($\chi^2=8·04$, $p<0·01$; Kendall τ c 0·357, $p<0·01$). Analysis of the data using stepwise logistic regression with outcome as the dependent variable, and age, sex, plasma glucose, and peak aspartate transaminase activity as the independent variables, showed that the major determinants of mortality in group 1 were age ($\chi^2=16·6$, $p<0·001$, $\beta=0·139\pm0·039$; 95% CI for risk ratio for five year change 1·36-2·92) and plasma glucose ($\chi^2=13·6$, $p<0·002$, $\beta=0·303\pm0·099$; 95% CI for risk ratio for 5 mmol/l (90 mg/100 ml) change 1·71 to 12·03). Peak aspartate transaminase activity failed to reach significance in this model ($\chi^2=3·3$, $p=0·07$, $\beta=0·0026\pm0·0014$; 95% CI for risk ratio for 100 IU change

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0·98 to 1·73), probably because early death precluded estimation of this enzyme for 48 hours. In a similar analysis in patients in group 2 no variable reached standard levels of significance (95% CI in risk ratios for age 0·69 to 2·00; plasma glucose 0·11-3·37; aspartate transaminase activity 0·85-2·18; all p>0·1).

STUDY 2: INFARCT SIZE, PLASMA GLUCOSE, AND OUTCOME

Using non-parametric correlation analysis we found significant relations between plasma glucose concentrations on admission to hospital and peak aspartate transaminase activity in both groups (r_s=0·26, p<0·005, n=101 in group 1 (fig 2); r_s=0·41, p<0·01, n=35 in group 2). Figure 2 shows that despite this positive relation, there were several patients with appreciable hyperglycaemia and fairly low levels of enzyme release; seven patients had plasma glucose concentrations of more than 11 mmol/l but were in the lower half of distribution of aspartate transaminase activity. Similarly in group 2 three patients had plasma glucose concentrations greater than 11 mmol/l but were in the lower half of distribution of aspartate transaminase activity. Table II shows the characteristics of these 10 patients; eight of them either developed left ventricular failure or died, predominantly from cardiogenic shock. In case 5 (group 1) hyperglycaemia, measured when the patient was first admitted, may have been related to a cardiac arrest that occurred out of hospital; this patient never regained consciousness, and hyperglycaemia in these circumstances has been linked to poor prognosis for recovery of consciousness by an unknown mechanism.[13]

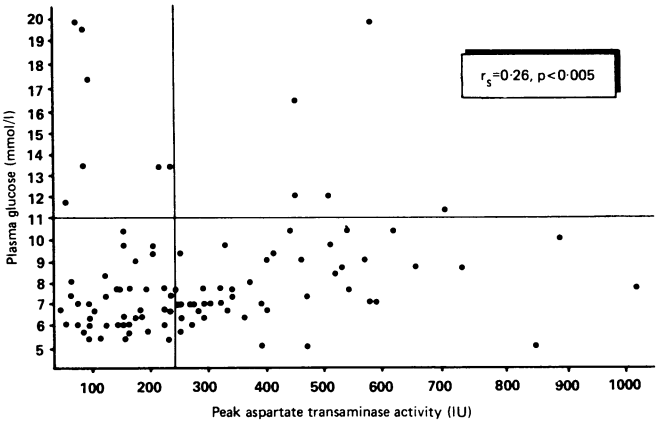

FIG 2—Plot of plasma glucose (on admission) and peak aspartate transaminase in 101 consecutive patients from group 1. Lines indicate the median for aspartate transaminase activity and a plasma concentration of glucose of 11 mmol/l.

TABLE I—*Patient details and mortality by HbA_{1c} group and by plasma glucose concentrations on admission*

	Group 1	Group 2
No	311	69
Age (SD)	64·9 (11·9)	67·6 (9·4)
No (%) of women	86 (27·7)	15 (21·8)
No (%) who died with plasma glucose concentrations (mmol/l) on admission of:		
<8	12/112 (10·7) CI 5·0 - 16·4%	0/12 (0)
8-11	13/52 (25·0) CI 12·2 - 36·8%	8/20 (40·0) CI 18·5 - 61·5%
>11	13/21 (61·9) CI 41·1 - 82·7%	9/19 (47·4) CI 25·0 - 69·8%
χ^2	29·27 p<0·001	8·04 p<0·02
Kendall τ -c	0·285 p<0·001	0·357 p<0·01
No (%) who died with no plasma glucose estimation	36/126 (28·6) CI 20·7-36·5%	3/18 (16·7%) CI 0-33·9%

Conversion: SI to traditional units—Glucose: 1 mmol/l≈18 mg/100 ml.

TABLE II—*Patients with severe hyperglycaemia and low peak aspartate transaminase activity*

Case No	Sex	Age (years)	Plasma glucose (mmol/l)	Peak aspartate transaminase (IU/l)	Course
			Group 1		
1	M	54	12·0	50	Uncomplicated
2	F	74	17·4	96	Left ventricular failure
3	F	78	13·6	230	Left ventricular failure
4	F	80	13·6	210	Died, cardiogenic shock
5	F	63	16·3	171	Died, ventricular fibrillation
6	F	75	13·4	81	Died, cardiogenic shock
7	F	68	19·7	84	Died, cardiogenic shock
			Group 2		
1	M	68	14·7	310	Died, cardiogenic shock
2	M	67	18·6	230	Left ventricular failure
3	M	78	16·3	102	Uncomplicated

STUDY 3: HORMONAL AND OTHER DETERMINANTS OF HYPERGLYCAEMIA

In 27 patients the relation between concentrations of cortisol and catecholamines and the size of the infarct were studied. Using logarithmically transformed data concentrations of plasma glucose correlated with the size of the infarct as measured by cumulative creatine kinase MB enzyme release, with cortisol, adrenaline, and noradrenaline (table III). Although the relation of both adrenaline and cortisol with plasma glucose concentrations appeared to be linear, that of noradrenaline with glucose appeared to be non-

TABLE III—*Correlation coefficient of hormones, glycosylated haemoglobin, cumulative creatine kinase MB isoenzyme, and plasma glucose. Data are logarithmically transformed except HbA_{1c} and age. Values shown are linear correlation coefficients (r) with their significance in parentheses*

	Plasma glucose on admission (n=27)	Cortisol (n=20)	Adrenaline (n=27)	Noradrenaline (n=27)	Cumulative isoenzyme release (n=19)	HbA_{1c} (n=27)	Age (n=27)
Cortisol	0·75 (<0·001)						
Adrenaline	0·47 (<0·01)	0·20 (0·20)					
Noradrenaline	0·54* (<0·002)	0·34 (0·07)	0·52 (<0·005)				
Cumulative isoenzyme release	0·65 (<0·001)	0·39 (0·051)	0·48 (<0·02)	−0·07 (0·38)			
HbA_{1c}	0·57 (<0·001)	0·53 (<0·01)	0·49 (<0·005)	0·44 (<0·02)	0·25 (0·15)		
Age	0·12 (0·27)	0·49 (<0·02)	0·07 (0·36)	0·08 (0·34)	−0·09 (0·35)	0·44 (<0·02)	

* The correlation between noradrenaline and plasma glucose uses a quadratic term (log noradrenaline)^2).

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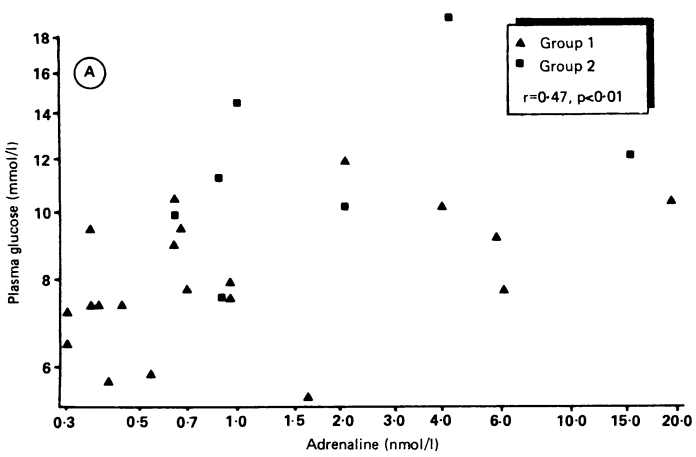

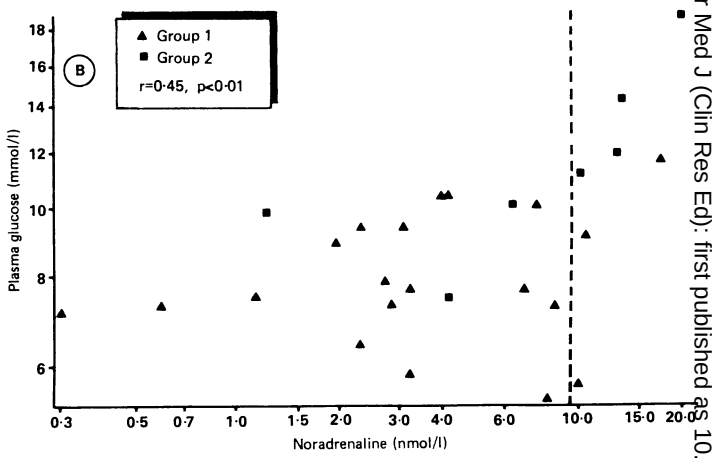

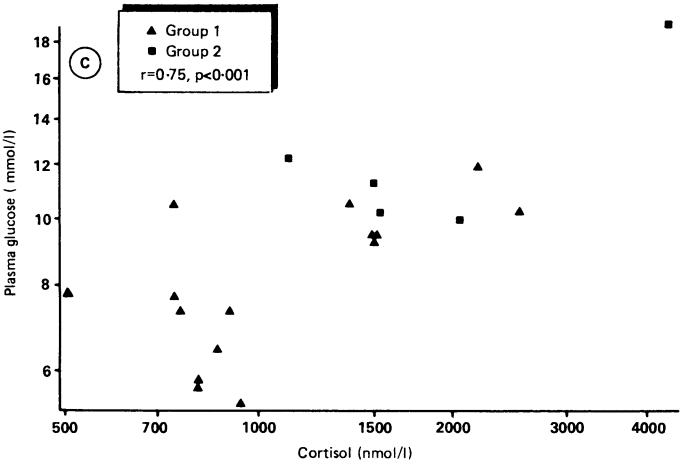

FIG 3—(*a*) Log/log plot of adrenaline and plasma glucose; (*b*) log/log plot of noradrenaline and plasma glucose. Vertical dotted lines=threshold concentration for metabolic effects of noradrenaline in the basal state[14]; (*c*) log/log plot of cortisol and plasma glucose.

linear and was compatible with a threshold effect (fig 3). When patients whose concentrations of noradrenaline exceeded 9 nmol/l (15·2 ng/100 ml) were excluded, this being the concentration at which noradrenaline has metabolic effects,[14] this relation disappeared. For this reason further analysis of the relation between noradrenaline and plasma glucose concentrations was performed using a quadratic term (logarithm of noradrenaline+(logarithm of noradrenaline)^2).

The determinants of released catecholamine and cortisol early in the course of acute myocardial infarction were sought. A correlation was found between adrenaline and the size of the infarct as assessed by cumulative creatine kinase isoenzyme MB values (fig 4), but no significant correlation was present between either noradrenaline or cortisol and the size of infarct assessed by cumulative creatine kinase MB. Analysis of variance showed that noradrenaline was significantly related to age ($p=0·04$) but not to cumulative creatine kinase MB values ($p=0·91$) or gender ($p=0·93$).

Six determinants of plasma glucose (noradrenaline, adrenaline, cortisol, age, cumulative creatine kinase MB, and HbA_{1c}) were then further assessed in a multiple linear regression analysis of patients in whom infarct size had been accurately assessed by determining cumulative creatine kinase MB activity. Cortisol ($F_{1,17}=22·86$, $B=0·415\pm0·084$, $p<0·001$) was the principal significant determinant of plasma glucose (multiple $r^2=0·56$) and both adrenaline ($F_{1,16}=6·21$, $B=0·086\pm0·028$, $p=0·03$, multiple $r^2=0·73$) and noradrenaline ($F_{2,15}=4·50$, $B=0·060\pm0·018$ for (log noradrenaline)^2, $p<0·05$, multiple $r^2=0·69$) provided similar contributions. There was no additional contribution from HbA_{1c} ($F_{1,13}=1·20$, $B=0·023\pm0·021$, $p>0·2$, multiple $r^2=0·76$). Moreover, adding cumulative creatine kinase MB did not significantly increase the explained proportion of the variance of plasma glucose ($F_{1,12}=2·95$, $B=0·250\pm0·145$, $p>0·1$, multiple $r^2=0·81$). Age was not a significant determinant of plasma glucose concentration in this model ($F_{1,11}=0·03$, $B=0·003\pm0·007$, $p>0·8$).

Figure 5 shows the distribution of the concentrations of catecholamines and cortisol on admission in all 27 patients studied. The patients with plasma glucose concentrations over 11 mmol/l are indicated in the figure. These five patients had the highest concentrations of noradrenaline, but concentrations of cortisol and adrenaline were more widely distributed. Four of these patients developed cardiogenic shock.

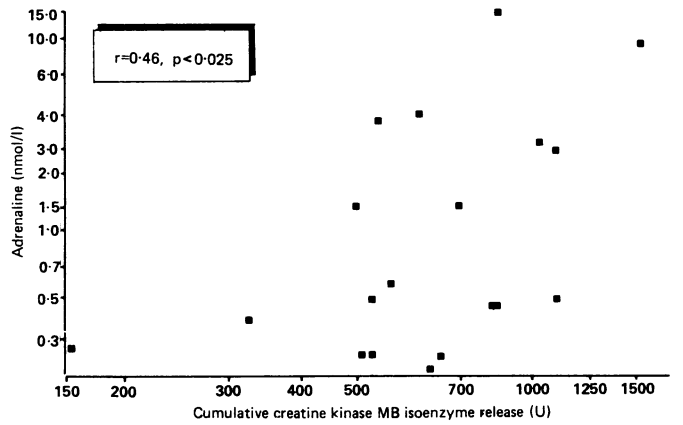

FIG 4—Log/log plot of adrenaline against size of infarct assessed by cumulative release of creatine kinase MB isoenzyme.

Discussion

Hyperglycaemia on admission to hospital, independent of the state of premorbid glucose tolerance, has been shown to be linked to the development of cardiogenic shock in non-diabetic patients with acute myocardial infarction.[3] In this study we have shown a further relation between increasing plasma glucose concentration and death in hospital from acute myocardial infarction in patients highly unlikely to have undiagnosed diabetes mellitus. Indeed, over half the patients with normal or borderline HbA_{1c} and plasma glucose concentrations greater than 11 mmol/l died in hospital from their acute myocardial infarction.

The relation between enzymatically determined infarct size and plasma glucose concentration confirms that stress hyperglycaemia is a real phenomenon in non-diabetic patients with acute myocardial infarction, and that poor outcome in such patients predominantly

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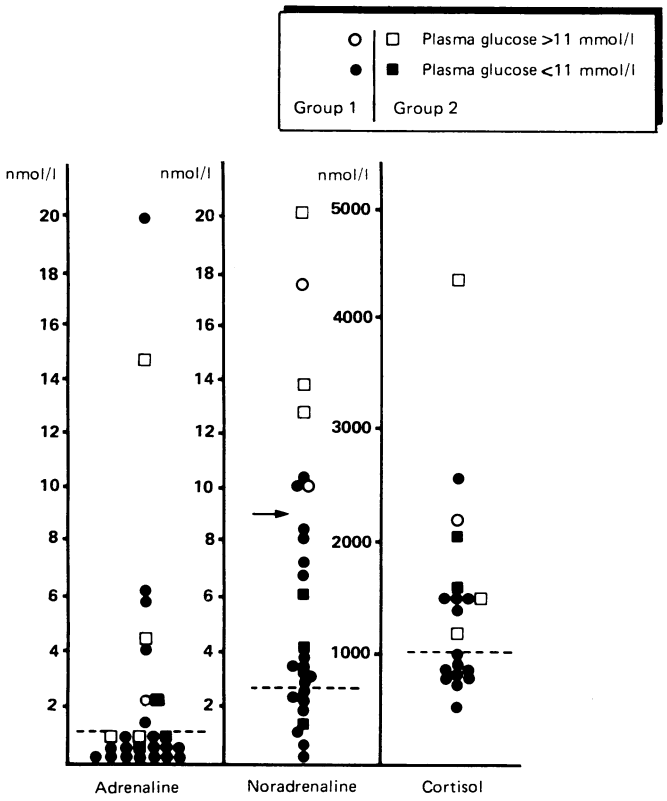

FIG 5—Distribution of hormone results obtained on admission in 27 patients surviving to have the size of their infarct assessed by peak aspartate transaminase activity. Dotted lines=upper limits of normal, arrow=level beyond which noradrenaline has measurable metabolic changes in the basal state.[14]

Conversion: SI to traditional units—Adrenaline: 1 nmol/l≈18·3 ng/100 ml. Noradrenaline: 1 nmol/l≈16·92 ng/100 ml. Cortisol: 1 μmol/l≈35·71 μg/100 ml. Glucose: 1 mmol/l≈18 mg/100 ml.

reflects the clinical course of the extent of underlying infarction.[9] We showed a correlation between plasma concentrations of adrenaline in the early stages of infarction and the size of the infarct. Hyperglycaemia measured on admission in most non-diabetic patients with acute myocardial infarction is determined both by the extent of infarction, mainly through the secretion of adrenaline, and through secretion of other stress hormones that are independent of infarct size. In experimental myocardial infarction it has been suggested that the stimulus to adrenaline release is a reflex arising from receptors at the site and boundary of the infarct.[15] The relation of plasma concentrations of adrenaline early in the course of infarction to infarct size in the patients we studied is compatible with a similar mechanism existing in man.

Hyperglycaemia is associated with poor outcome even when age and size of infarct are taken into consideration. Several patients were identified as having an infarct of moderate size, as estimated by peak aspartate transaminase activity, but with appreciable hyperglycaemia, and these subjects had a poor prognosis, with their cause of death being mainly pump failure. Such patients probably do not have undiagnosed diabetes, but possibly hyperglycaemia may be contributing to, rather than consequent on, their poor outcome. Patients with plasma concentrations of glucose over 11 mmol/l who were further investigated in study 3, however, showed high concentrations of both noradrenaline and cortisol early in the course of acute myocardial infarction, but no relation between these hormone concentrations and infarct size was found. Thus in some patients hyperglycaemia appears related to an excess stress hormone response, independent of the extent of infarction.

In patients with chronic stable heart failure noradrenaline concentrations have been found to be a sensitive and specific indicator of the degree of myocardial dysfunction.[16 17] Severe myocardial dysfunction in the presence of acute myocardial infarction of apparent modest extent may have been precipitated by infarction superimposed on an already diseased myocardium, perhaps resulting from previous acute myocardial infarction or from diffuse ischaemia.

Although plasma catecholamine concentrations fluctuate in the period after admission to hospital,[18] these concentrations generally remain raised for up to 48 hours.[19] We have shown, using multiple regression analysis, that despite the range of times between onset of symptoms and sampling in this study, adrenaline, noradrenaline, and cortisol concentrations, together with HbA_{1c} values and the size of the infarct, account for roughly 80% of the variation in plasma glucose values.

Other workers have found relations between the extent of infarction and the catecholamine response early in the course of acute myocardial infarction.[20 21] Our results, however, differ from those of Benedict and Grahame-Smith,[20] who found relations between concentrations of noradrenaline, but not of adrenaline, and the size of infarcts. Previous studies concerning the relations between the size of infarcts and plasma cortisol concentrations have also shown good correlations, which we have not confirmed.[22-24] These discrepancies may arise from the different subject populations; in the quoted studies most patients developed cardiogenic shock and were found to have both extensive infarction and very high concentrations of noradrenaline and cortisol, whereas in our study most patients had uncomplicated acute myocardial infarction.

Several groups have attempted to define the cause of hyperglycaemia after acute myocardial infarction. A recent study found that plasma glucose in subjects after acute myocardial infarction was related to concentrations of adrenaline but not noradrenaline.[25] A previous study described a relation between noradrenaline concentrations and fasting plasma glucose concentrations taken shortly after infarction,[26] but this is perhaps surprising in view of the concentrations of noradrenaline in that study, which were well below those at which metabolic effects become apparent.[14] One study has also shown a relation between plasma cortisol concentrations and those of fasting blood glucose.[24] The mechanism of stress hyperglycaemia in patients after acute myocardial infarction may be similar to that shown in dogs,[27] where different hormones relating to stress have been found to act synergistically both to increase glucose production and to reduce clearance. In our study the contribution of infarct size to plasma glucose concentration on admission was insignificant after allowing for the effects of cortisol and catecholamines, but other workers have suggested that glucagon may also contribute to hyperglycaemia.[28]

In conclusion, hyperglycaemia seen on admission in non-diabetic patients with acute myocardial infarction is an important prognostic indicator, and is mainly determined by raised concentrations of catecholamines and cortisol. These in turn are either a response to extensive infarction or associated with severe myocardial dysfunction. We found no evidence in our study to suggest that hyperglycaemia was contributory to, rather than purely resultant on, poor outcome. By inference, perhaps hyperglycaemia in diabetic patients with acute myocardial infarction may also not be causally associated with poor outcome, although studies of the effect of induction of normoglycaemia on the clinical course of diabetic patients with acute myocardial infarction[2 29 30] would be necessary to test this hypothesis.

We thank the medical and nursing staff of the admission ward and coronary care unit, without whose help this study would not have been possible. We are grateful to Dr Brian Newman, department of statistics, University College London, for statistical advice, and we also wish to thank Dan Wilsher for help with the statistical analyses and Gill Brown for expert secretarial help. GAO was supported by Novo Laboratories Ltd.

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(Accepted 16 July 1986)

SHORT REPORTS

Thrombotic microangiopathy and acute renal failure associated with arteriography

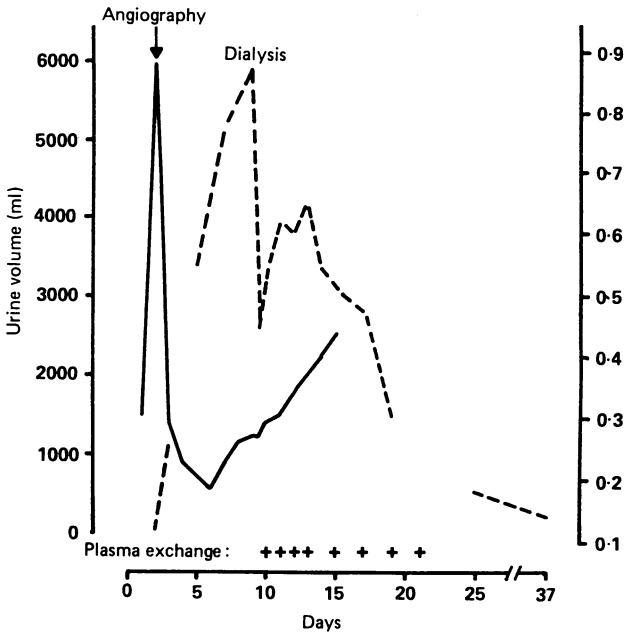
Acute renal failure after administration of contrast media has been well documented. In the late 1950s a change from earlier contrast media to salts of diatrizoate was thought to have curtailed this problem, but a review in 1978 reported 75 well documented cases of acute renal failure after use of newer contrast media.[1] We report on a man with a well functioning renal transplant in whom thrombotic microangiopathy caused acute renal failure after aortofemoral angiography. This form of acute renal failure induced by a radiocontrast agent has not been recognised previously.

Case report

A 59 year old man with renal failure due to analgesic nephropathy started haemodialysis in 1973. In 1979 he underwent successful cadaveric renal transplantation, and the serum creatinine concentration remained normal (0·10-0·12 mmol/l (1·1-1·3 mg/100 ml)) for six years. In March 1985 he presented with severe bilateral intermittent claudication and underwent angiography before a left femoral-popliteal bypass operation. After angiography, in which he was given 70 ml of 65% meglumine diatrizoate intravenously, his renal function deteriorated acutely, the serum creatinine concentration rising from 0·12 to 0·22 mmol/l (1·3 to 2·4 mg/100 ml) and falling again to 0·11-0·12 mmol/l. His urine output remained normal during this episode.

He was readmitted in June for angiography on the right side because of worsening symptoms and distal ulceration. On admission creatinine concentration was 0·11 mmol/l (1·1 mg/100 ml). He was well hydrated on the day of angiography. The next day, however, the serum creatinine concentration rose to 0·27 mmol/l (3·0 mg/100 ml), and it continued to rise until the seventh day after angiography, when he required haemodialysis because of uraemic symptoms. Over the same period the haemoglobin concentration fell from 127 g/l to 86 g/l and the platelet count from 314 × 10^9/l to 73 × 10^9/l. A blood film showed spherocytes and fragmented red blood cells. The bilirubin concentration peaked at 36 μmol/l (2·1 mg/100 ml) (normal <19 μmol/l (<1·1 mg/100 ml)). Urine output fell from 5950 ml on the day of angiography to 540 ml four days later (figure). Urine microscopy showed 10 × 10^9 glomerular red cells/l and numerous renal tubular epithelial cells. Renal biopsy on day 6 showed occlusion of many glomerular capillaries by fibrin thrombi, while others contained polymorphs. The appearances were those of thrombotic microangiopathy. Acute tubular necrosis and some mild features of chronic vascular rejection were also evident.

Plasma exchange with four litres of reconstituted plasma protein precipitate was begun as soon as the result of the biopsy was known and was continued daily for four days and then on alternate days for three weeks. The serum creatinine concentration fell rapidly to 0·14 mmol/l (1·5 mg/100 ml), and urine volumes returned to normal. In spite of the good initial response to plasma exchange renal function deteriorated gradually and three months later biopsy showed diffuse double contours in glomerular capillaries and continuing activity resembling chronic microangiopathy on electron microscopy.



Urine volume (——) and serum creatinine concentrations (----) after angiography.

Comment

The mechanism of acute renal failure after administration of contrast media was initially ascribed to acute tubular necrosis[2] or acute interstitial nephritis.[3] To our knowledge we report a previously unrecognised mechanism of acute renal failure after arteriography—namely, thrombotic microangiopathy. The outlook for patients with acute renal failure resulting from thrombotic microangiopathy is poor without treatment.

Although thrombotic microangiopathy can result from acute graft rejection, this is unlikely to occur so long after transplantation. Fluid loading and high urine output, which are recommended to prevent acute renal failure after administration of contrast media, were not effective in this patient. Two mechanisms might have led to the diffuse thrombi in glomeruli in this case. In our view the most likely is that atheromatous emboli were dislodged into the renal artery during angiography. Atheromatous material has been shown to activate complement in vitro,[4] and infusion of atheromatous material into the carotid artery in rats leads to diffuse fibrin thrombi in glomeruli. Alternatively, the activation of complement by contrast medium[5] could have precipitated the thrombotic microangiopathy.

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