Raised concentrations of glucose and adrenaline and increased in vivo platelet activation after myocardial infarction

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SUMMARY Plasma concentration of β thromboglobulin was used as an index of in vivo platelet activation in 36 patients after acute myocardial infarction. Twelve patients had diabetes, seven had pulmonary oedema or cardiogenic shock (pump failure) or both, and 17 had uncomplicated infarcts. On the first day of admission, concentrations of β thromboglobulin were higher in the patients with diabetes and those with pump failure than in those with uncomplicated infarcts. Concentrations of β thromboglobulin in the non-diabetic patients were studied by multiple regression analysis and were significantly associated with plasma concentrations of adrenaline, pump failure, and glucose but not with noradrenaline or infarct size. When all subjects were considered together, glucose, adrenaline, and pump failure were associated with the β thromboglobulin concentration but diabetes was without significant effect.

Hyperglycaemia and raised plasma adrenaline concentration after myocardial infarction may activate platelets, and this could contribute to poor outcome in such patients.

Case fatality rates are higher in diabetic patients admitted to hospital with acute myocardial infarction than in non-diabetic patients, with the principal causes of death being refractory heart failure or cardiogenic shock (pump failure) or both.12 The excess risk of pump failure in diabetic subjects does not result from more extensive necrosis,2-5 nor is there evidence that more widespread atheroma restricts the perfusion of non-infarcted myocardium in these patients.6 The role of hyperglycaemia remains controversial.7-11

The primary cause of myocardial infarction is thrombosis of a coronary vessel and the fate of this thrombus is an important determinant of outcome after myocardial infarction.12 Reperfusion of the infarcted myocardium preserves myocardial function and improves prognosis13 14 although the levels of enzyme release are no less.14 The process of recanalisation may result from fibrinolysis, and diminished thrombolytic activity is associated with several risk factors for poor outcome after myocardial infarction.15 There may be a dynamic equilibrium, however, between fibrinolysis, with consequent reperfusion, and continuing platelet aggregation and thrombosis,16 so that haemostatic variables may also influence the possibility of recanalisation.17

In patients with diabetes mellitus there is a hypercoagulable state with enhanced platelet activation and increased thrombogenesis.18 We have tested the hypothesis that in vivo platelet activation is increased both in diabetic patients and those with pump failure after acute myocardial infarction. We have also explored the relation between indices of platelet activation and metabolic and hormonal variables in such patients.

Patients and methods

We studied 36 patients admitted to hospital with acute myocardial infarction confirmed according to World Health Organisation criteria19: 12 consecutive
patients with known diabetes, one with pump failure; seven consecutive patients without known diabetes in whom pump failure developed; and 17 non-diabetic patients with uncomplicated infarcts. Pump failure was defined as a sustained systolic blood pressure of <90 mm Hg, associated with oliguria and signs of peripheral circulatory failure, with or without clinical or radiological evidence of pulmonary oedema. This classification corresponds to Killip grades C and D. For each patient with diabetes or pump failure that we studied, we also studied the next patient admitted without known diabetes with apparently uncomplicated myocardial infarction as a control. The results from three other non-diabetic patients, who were studied as controls, and one diabetic patient, were not analysed because clear evidence confirming myocardial infarction did not develop (fig 1). All patients who had taken drugs known to affect platelet function, including those on calcium channel blockers, were excluded from the study.

In all patients without known diabetes glycosylated haemoglobin (HbA1c) was measured on admission; none had concentrations of HbA1c indicative of undiagnosed diabetes. Infarct size was assessed by cumulative release of creatine kinase MB isoenzyme measured eight hourly for 48 hours and daily measurement of peak aspartate transaminase for 48 hours from onset of symptoms. We have previously reported a reasonable correlation between these two measures of infarct size ($r = 0.67$, $n = 28$, $p < 0.001$).

Blood samples were taken after adequate analgesia to measure catecholamines, the platelet specific proteins $\beta$ thromboglobulin and platelet factor 4, plasma glucose, and HbA1c shortly after admission to the coronary care unit and again on the second day of hospital admission. There was no significant difference in timing of the samples from the onset of symptoms between any of the three groups ($p > 0.3$, table 2). Blood was sampled from an antecubital vein through a 19 G needle without venous stasis. We took care to avoid aggregation of platelets in vitro and consequent spurious rises in concentration of $\beta$ thromboglobulin. We used commercial kits for radioimmunoassay of $\beta$ thromboglobulin (Amersham International) and platelet factor 4 (Abbott Laboratories). The within and between assay coefficients of variation for the $\beta$ thromboglobulin assay were 6.9% and 10.4%, and for platelet factor 4 they were 7.7% and 6.3%, respectively. Samples with $\beta$ thromboglobulin to platelet factor 4 ratios of less than 3:1 were excluded from analysis because such ratios reliably indicate in vitro platelet activation.

Blood for catecholamine assay was taken into cooled lithium heparin tubes and stored in an ice-water slurry before centrifugation at 4°C at 1500 g for five minutes. Plasma was stored at −20°C until assay for plasma adrenaline and plasma noradrenaline by high performance liquid chromatography with electrochemical detection, as previously described. The upper limits of normal by this method are 1.2 nmol/l for adrenaline and 2.6 nmol/l for noradrenaline and the within assay coefficients of variation are 10% and 6%, respectively. Glycosylated haemoglobin was measured by isoelectric focusing with within and between assay coefficients of variation of 4.9% and 5.3%. Plasma glucose was assayed by an automated glucose oxidase method. Aspartate transaminase was measured by a spectrophotometric method (AST-optimised, BCL, Lewes, Sussex) and creatine kinase MB isoenzyme by an immunological method (BCL). Figure 1 and table 1 show the number of subjects for whom each assay was satisfactory. Catecholamine concentrations were not known in two controls.

**Statistical Analysis**

Statistical analysis was performed by Student’s $t$ test and least squares regression analysis, on logarithmically transformed data if appropriate. Because the subgroups were small, these regression analyses were also repeated without the observation demonstrating the largest influence on the regression coefficient (Cook’s distance), to exclude the possibility that the results were dependent on a single observation. Data are presented as the mean (SD) for symmetrically distributed data and as median and range for skewed data. Multiple linear regression analysis was applied to the pooled data for all the patients and to that of the non-diabetic patients alone, with logarithmic trans-
formation as appropriate. We used the regression function of the SPSS-X program for the analysis, and we used dummy variables to explore group differences in slope and intercept. Alternative models were tested by use of sequential forced entry of the variables being tested, and the significance of F-change at each step is reported; however, the relations being tested by these models are not the only plausible explanation for the results. The appropriate F values are given for these analyses and the slopes of the fitted regression lines in the final model are presented with 95% confidence intervals. Probability values of p < 0.05 were regarded as statistically significant.

Power of the study
The numbers studied were adequate to demonstrate a 36% increase in plasma concentrations of β thromboglobulin in diabetic patients and a 40% increase in pump failure patients at the 5%, level with a power of 0.8. The total numbers of subjects studied were sufficient to permit the detection of significant effects of individual variables on plasma concentrations of β thromboglobulin at the 5%, level with a correlation coefficient of 0.36, implying that the variable determines 13% of the variance of β thromboglobulin. The regression analyses assume linearity, but there is a possibility that some significant effects may be a result of a non-linear relation. Non-significant results, in samples of this size, particularly in sub-groups, are not proof of non-association.

Results
INFARCT SIZE
We studied 36 patients with confirmed myocardial infarction (fig 1). One patient with diabetes and three without died after the development of pump failure. In addition, two with diabetes and two without diabetes and with apparent uncomplicated myocardial infarction developed serious dysrhythmias (complete heart block in three of the patients and one episode of ventricular fibrillation in a diabetic patient). There were no deaths from these complications. Table 1 shows data on all patients. There was no significant difference in ages between the groups (p > 0.2). Median peak serum concentration of aspartate transaminase and cumulative release of creatine kinase MB were significantly greater in the controls than in the diabetics (table 2). Infarct size

Table 1  Data for patients for whom valid results were available on day 1

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estimated by cumulative creatine kinase MB release was greater in the patients with pump failure than in the controls.

**PLASMA CONCENTRATIONS OF $\beta$ THROMBOGLOBULIN**

In seven samples (2 on day 1 and 5 on day 2) the ratio of $\beta$ thromboglobulin to platelet factor 4 was $< 3$, indicating possible in vitro platelet activation (fig 1). Plasma $\beta$ thromboglobulin was highest (202 ng/ml) in the diabetic patient with pump failure. This result was excluded from the statistical comparisons of diabetic and non-diabetic patients. The median $\beta$ thromboglobulin concentration on day 1 in the non-diabetic patients with pump failure was significantly greater than that in the control group of non-diabetic patients with uncomplicated myocardial infarction. The median $\beta$ thromboglobulin concentration was also significantly greater in the diabetic patients than in the control group. Although the concentration of blood urea was significantly higher in the patients with pump failure, there was no relation between blood urea and $\beta$ thromboglobulin concentration in any group ($r = -0.32$ to 0.20, $p > 0.2$). In the controls there was a weak relation between age and $\beta$ thromboglobulin concentration ($r = 0.28; p > 0.2$) and the mean age difference of seven years between the controls and pump failure group might explain a difference of only 3-1 ng/ml in $\beta$ thromboglobulin concentrations between the groups. On the second day after the onset of symptoms, the median $\beta$ thromboglobulin concentration in diabetic patients was no longer significantly different from that in controls ($p > 0.1$). The median $\beta$ thromboglobulin concentration in patients with pump failure remained high; however, three of the seven patients with pump failure had died before resampling (fig 1).

**DETERMINANTS OF $\beta$ THROMBOGLOBULIN CONCENTRATIONS IN NON-DIABETIC PATIENTS WITH OR WITHOUT PUMP FAILURE**

Concentrations of glucose, adrenaline, noradrenaline and cumulative creatine kinase MB release were significantly higher in patients with pump failure than in controls (table 2) (figs 2a and 3a). In the non-diabetic patients as a whole there were significant correlations between concentrations of $\beta$ thromboglobulin and adrenaline ($r = 0.71, p < 0.0002$), glucose ($r = 0.73, p < 0.0001$), cumulative creatine kinase MB release ($r = 0.57, p < 0.01$), and noradrenaline ($r = 0.47, p < 0.02$). All of these correlation coefficients were increased when the relations were reanalysed after omitting the observation with the largest Cook’s distance ($r = 0.84, 0.78, 0.80$, and 0.59 respectively). Because there are significant interrelations between these variables we used multiple regression analysis to test the hypothesis that adrenaline and glucose concentrations determine the concentrations of $\beta$ thromboglobulin.
Glucose, adrenaline, and in vivo platelet activation after myocardial infarction

Fig 2  The relation between plasma concentrations of β thromboglobulin and adrenaline in (a) non-diabetic and (b) diabetic patients after acute myocardial infarction. ●, non-diabetic patients with pump failure; ○, non-diabetic controls; ■, diabetic with pump failure; □, diabetics without pump failure. Correlation coefficients (r) are: non-diabetic patients with pump failure, 0.88 (p < 0.01); non-diabetic controls, 0.26 (p = 0.19); diabetic patients without pump failure, 0.04 (p > 0.4).

Fig 3  (a) The relation between plasma concentrations of β thromboglobulin and glucose in patients after acute myocardial infarction. ●, non-diabetic patients with pump failure; ○, non-diabetic controls; ■, diabetic with pump failure; □, diabetics without pump failure. (b) Regression lines for plasma concentrations of β thromboglobulin and glucose in all subjects (dotted line)—slope = 0.119 (95%CI 0.077 to 0.161); in non-diabetic patients with pump failure (P)—slope = 0.066 (95%CI 0.032 to 0.164); in non-diabetic controls (C)—slope = 0.020 (95%CI 0.012 to 0.119); in diabetic patients without pump failure (D)—slope = 0.072 (95%CI 0.038 to 0.182).
in these subjects. Adrenaline was the major catecholamine determinant of plasma concentrations of $\beta$ thromboglobulin (table 3a), with plasma glucose as an additional factor. In this model, pump failure still provided an additional significant contribution, but infarct size, estimated by cumulative creatine kinase MB isoenzyme release, and noradrenaline provided no additional contribution. In the final model, however, only pump failure remained as a significant variable.

**DETERMINANTS OF $\beta$ THROMBOGLOBULIN LEVELS IN NON-DIADEITIC AND DIABETIC PATIENTS (TABLE 3B)**

We also used multiple regression analysis to test the hypothesis that concentrations of glucose and adrenaline determine the raised plasma concentrations of $\beta$ thromboglobulin in all the patients we studied. Glucose and adrenaline were both significant determinants of $\beta$ thromboglobulin in this model, and each retained a significant effect in the presence of the other variable. When glucose was included in the analysis, forced entry of diabetes did not contribute significantly to $\beta$ thromboglobulin. The entry of pump failure to the analysis, however, made a significant additional contribution as a determinant of plasma $\beta$ thromboglobulin, even when glucose and adrenaline were included in the analysis. Infarct size, glycosylated haemoglobin $A_1C$, and noradrenaline were without significant effect. In the final model, glucose, pump failure, and diabetes were the only significant independent variables.

Figure 3 shows the relation between simultaneous concentrations of plasma glucose and $\beta$ thromboglobulin in diabetic and non-diabetic patients with and without pump failure. There is a significant relation between the concentrations of blood glucose and $\beta$ thromboglobulin in all subjects ($r = 0.73$, $p < 0.001$). The regression lines for all three groups did not have significantly different slopes, although multiple regression analysis showed that the intercept for subjects with pump failure was significantly higher than that for other subjects ($F = 11.88$, 27 df, $p < 0.002$). Reanalysis of the regression line without the observation showing the largest Cook's distance improved the relation ($r = 0.77$, $p < 0.001$) without markedly affecting the slope (0.128, 95% confidence interval 0.087 to 0.169).

**Discussion**

There are several difficulties in interpreting studies of platelet aggregation in patients with myocardial infarction. In vitro tests of platelet function may not
Glucose, adrenaline, and in vivo platelet activation after myocardial infarction

represent the situation in vivo, both because of artefacts implicit in the preparation of platelet rich plasma, and because metabolic changes in other blood components may also influence platelet aggregation. Some studies of platelet aggregation after myocardial infarction have demonstrated platelet hypoaggregability, which may result either from dissociation of circulating platelet aggregates during preparation of platelet rich plasma, or from in vivo consumption of the more active platelets. Because in vitro studies of platelet aggregation may not reflect the in vivo situation, circulating concentrations of α granule proteins have been used to indicate in vivo platelet activation. The likelihood of in vitro release of β thromboglobulin is increased on admission after myocardial infarction which means that such studies must be careful to exclude data in which there is evidence of in vitro platelet activation. Previous studies of plasma concentrations of β thromboglobulin after acute myocardial infarction have generally demonstrated an increase, which in one study was more pronounced in patients with left ventricular failure or cardiogenic shock, but the data have never been analysed after exclusion of subjects with evidence of in vitro activation. It is likely that in future the reference standard for evidence of in vivo platelet activation will be the concentration of the urinary thromboxane metabolite, 2,3-dinor-thromboxane B2. In one recent study in 14 patients, this did not correlate with infarct size.

We have demonstrated significant differences in plasma concentrations of β thromboglobulin between diabetic and non-diabetic patients in the first 24 hours after infarction. Moreover, plasma concentrations of β thromboglobulin were different in patients with uncomplicated myocardial infarction and those with pump failure. Although this study cannot establish whether this was a cause or an effect, the fall in concentrations of β thromboglobulin by the second day in diabetic patients suggests that the rise was secondary to the infarction. A recent report, which showed that radiolabelled platelets are incorporated into thrombus after myocardial infarction, has suggested that such a process may be responsible for thrombus proliferation and infarct extension. It is also possible that excess platelet activation might prevent recanalisation of a thrombosed vessel.

We studied the determinants of plasma concentrations of β thromboglobulin by multiple regression techniques. Using forced entry of different variables, we tested the hypothesis that concentrations of adrenaline and glucose were largely responsible for the variance of β thromboglobulin concentrations in patients in different subgroups. Nevertheless, we recognise that this cannot provide proof of causation, and that other models are also compatible with the observed relation.

In the non-diabetic patients concentrations of β thromboglobulin were highest in those with pump failure who sustained more extensive infarction and in whom adrenaline concentrations were high. Platelets have α adrenergic receptors and catecholamines can induce aggregation either directly or by increasing sensitivity to other agonists. Adrenaline has a more powerful effect than noradrenaline. The number of these α receptors may be reduced immediately after myocardial infarction, perhaps as a response to the raised concentrations of catecholamines found then. We have previously described a relation between plasma concentrations of adrenaline early in the course of infarction and the size of the myocardial infarction determined by enzyme release. In non-diabetic patients in whom pump failure develops, it is possible that extensive initial thrombosis is associated with high adrenaline concentrations which enhance platelet activation and thrombogenesis, thereby restricting reperfusion; the envisaged vicious circle might then only be broken by blocking adrenergic stimulation or platelet activation. A combination of pharmacological thrombolysis with blockade of platelet aggregation might therefore be a logical approach to the treatment in patients after myocardial infarction. This is currently being tested in the ISIS-2 trial. Our results do suggest, however, that the increase in platelet activation found in patients with pump failure cannot be totally explained on the basis of raised concentrations of adrenaline.

In diabetic patients platelet activation was increased after myocardial infarction even in the absence of pump failure. Increased concentrations of β thromboglobulin were reported in diabetic patients with or without microangiopathy, but similar studies have not been performed in patients after myocardial infarction. Patients with myocardial infarction in whom the occluded coronary artery does not recanalise have more residual impairment of myocardial function but have not been shown to have larger infarcts estimated by cumulative enzyme release. It is possible that the reports of a higher incidence of haemodynamic complications in diabetic patients at any given level of enzyme release are explicable on the basis of differing patterns of reperfusion, determined both by increased platelet activation and diminished fibrinolysis. Confirmation of this hypothesis depends on the patterns of coronary angiograms or enzyme release.

We have attempted to define the determinants of platelet activation in diabetic patients after myocardial infarction. Glucose concentrations seem to be
the major determinant of platelet activation without any additional contribution from diabetes per se. As in non-diabetic patients adrenaline concentrations and the presence of pump failure both contributed significantly to the concentration of β-thromboglobulin. We have shown that in the unstimulated state platelets from diabetic subjects release more noradrenaline than platelets from non-diabetic subjects, a finding which may parallel the additive effects of hyperglycaemia and adrenaline concentrations on platelet activation after myocardial infarction. The platelet α receptor may have an important role generally in stress induced aggregation in diabetic subjects; enhanced platelet aggregability after hypoglycaemia may be simulated in vitro by adding similar concentrations of adrenaline, and may be blocked by α blockade.

We have demonstrated that the relation between plasma concentrations of β-thromboglobulin and glucose is similar in diabetic and non-diabetic patients after myocardial infarction. There are two possible explanations for these findings. Most simply, higher plasma concentrations of glucose in diabetic patients after myocardial infarction may enhance platelet activation, in which case it might follow that tight control of blood glucose concentrations early in the course of myocardial infarction would reverse activation. The excess activation, however, may also result from an enhanced sensitivity of diabetic platelets to circulating catecholamines, which may mean that control of plasma glucose alone would not affect thrombogenesis. These hypotheses remain to be tested.

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References


Oswald, Smith, Delamothe, Betteridge, Yudkin

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