Haemostatic function in myocardial infarction

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SUMMARY Coagulation factor VIII, von Willebrand factor, antithrombin, fibrinogen, plasminogen activator capacity, and inhibitors of fibrinolysis, including a recently discovered fast inhibitor of tissue plasminogen activator, were measured three to six months after myocardial infarction in 116 male and 32 female patients aged <45 and in 136 age and sex matched random controls. Plasma concentrations of fibrinogen and the fast inhibitor of tissue plasminogen activator were raised in male patients (with or without correction for orosomucoid levels, blood group distribution, tobacco and alcohol consumption, and weight/height index) and plasminogen activator capacity was reduced. In female patients the concentrations of factor VIII, von Willebrand factor, the fast inhibitor of tissue plasminogen activator, α_2 -antiplasmin, and C1 inhibitor were significantly increased. The increase in factor VIII concentrations depended strongly on a persisting inflammatory response. Multivariate analysis indicated that a combination of fibrinogen and tissue plasminogen activator inhibitor concentrations gave the best independent discrimination between male patients and controls. For female patients the best combination was von Willebrand factor and tissue plasminogen activator inhibitor. Male patients with multiple vessel atheromatosis at coronary angiography had higher fibrinogen concentrations than those with atheromatosis of a single vessel. Atheromatosis was defined as sharp-edged, plaque-like, or irregular indentations, often multiple, into the vessel lumen without features suggesting fibromuscular hyperplasia.

Several mechanisms have been suggested to explain the pathogenesis of ischaemic heart disease. According to the thrombogenic theory of atherogenesis,¹ hypercoagulability may be a prerequisite not only for the development of thrombotic complications but also for the pathogenesis of atherosclerosis. Impaired fibrinolysis at the onset and during the course of myocardial infarction is viewed mainly as a reduction in defensive capacity while coronary occlusion and fibrin formation are under way.

Most studies of haemostatic function in patients with previous myocardial infarction have focused on platelet function. In general, studies including tests of blood coagulation and fibrinolysis²⁻⁷ have been

conducted in the acute phase and the patients studied have been heterogeneous with regard to age, medication, and coexisting disorders. Furthermore, the presence and extent of coronary atherosclerosis has not been assessed by angiography.

Young adults with ischaemic heart disease constitute an ideal group in which to study the factors operating early in atherogenesis and arterial thromboembolism. We therefore performed a comprehensive investigation of blood coagulation and fibrinolysis in consecutive patients who had survived a definite myocardial infarction before the age of 45 and in whom coronary angiography had been performed. We measured various coagulation variables including factor VIII, von Willebrand factor, antithrombin, and fibrinogen. Fibrinolytic function was studied by determination of plasminogen activator capacity and possible inhibitors of fibrinolysis, including the recently discovered fast inhibitor of tissue plasminogen activator.

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Patients and methods

STUDY GROUPS

Between May 1980 and September 1982, 163 patients aged <45 were admitted with definite myocardial infarction⁸ to the eleven hospitals in Stockholm County with intensive care units. Of these, 137 were male and 26 were female. Six male patients had a history of recurrent infarctions. Fifteen patients died during the stay in hospital. The 148 consecutive survivors were subsequently referred to the Department of Medicine, Danderyd Hospital, for haemostatic, metabolic, and cardiological investigations. Two further patients died shortly after discharge from hospital. Eight patients declined the investigation and for other reasons a complete evaluation was not performed in two patients. To enlarge the female patient group, twelve more women who had myocardial infarction between October 1982 and December 1983 were also included in the study. Thus we studied 116 male patients (92% of male survivors) and 32 female patients (94% of female survivors). All patients were investigated as outpatients 3–6 months after infarction. Clinical data were abstracted from the medical records acquired on admission to the intensive care units. In addition, a medical history was obtained by a structured interview and questionnaires at the time of this study.

Most (127 cases) patients had no angina or only mild angina (New York Heart Association classes I–II) during the early post-infarction period. Severe peripheral atherosclerosis with incapacitating intermittent claudication was present in two patients and manifest diabetes in fourteen. Coronary bypass surgery was not performed in any of the patients in the period between onset of infarction and this study. One patient had been operated upon six years before the study. There were no signs of cardiac decompensation in any of the patients at the time of the haemostatic evaluation.

Two patients were initially receiving anticoagulants because of thromboembolic complications during the acute phase. They were investigated at least two months after the end of the treatment. Oral contraception had been discontinued upon admission to hospital in five women. One woman in the control group was taking oral contraceptives at the time of the study.

For each patient a control subject from the same neighbourhood was randomly selected from a general register of all residents in the county after matching for age and sex. Previous medical history and risk factors were established in the controls in the same way as they were in the patients. None of the controls had a history suggestive of angina or

electrocardiographic signs indicative of ischaemic heart disease during a maximal exercise stress test (Minnesota codes 4·1 and 4·2).

BLOOD SAMPLING

Blood samples for evaluation of the haemostatic system were drawn three to six months (mean (SD) 3·5 (1·2); range 2·5–12 months) after the onset of myocardial infarction, at which time the patients were considered to be in a stable clinical and metabolic state. Matched controls were investigated simultaneously with the patients to avoid any influence of seasonal variations on group comparisons. In both patients and controls blood sampling was evenly distributed over the year. Participants had been given written instructions to avoid platelet inhibiting treatment in the 10 days before blood sampling. All subjects were free from symptoms of infectious disease at the time of blood sampling and they had been fasting for 12 hours. Antecubital vein puncture with a 1·4 mm Wassermann needle (TSK Laboratories, Japan, Size DIM 1·4 × 45 mm) was performed between 8.00 and 9.30 am after 10 minutes' rest in the supine position. The first 5 ml of blood was discarded, then 9 ml venous blood was taken into 1 ml trisodium citrate (0·13 mol/l) pH 7·5, and was immediately and thoroughly mixed. After centrifugation at room temperature for 20 min at 4000 *g*, plasma was dispensed into plastic tubes and kept frozen at –70°C until it was tested.

LABORATORY METHODS

Factor VIII was determined by a two stage thrombin generation assay⁹ and von Willebrand factor by quantitative electroimmunoassay.¹⁰ Antithrombin antigen and activity were measured by radial immunodiffusion¹¹ and a chromogenic peptide substrate method.¹² Fibrinogen was analysed by a polymerisation test.¹³ Plasminogen activator activity was determined by the fibrin plate method¹⁴ with euglobulin precipitates. Urokinase (Loevens, Ballerup, Denmark) was used as an internal standard and the results were expressed in Plough units (PU). Plasminogen activator release was provoked by venous stasis obtained by a tourniquet applied to the upper arm at 100 mm Hg for 10 minutes. The difference in plasminogen activator activity between samples drawn before and after venous stasis was used as a measure of plasminogen activator capacity. This method primarily measures tissue plasminogen activator activity. The fast inhibitor of tissue plasminogen activator,¹⁵ α_2 -antiplasmin,¹⁶ prekallikrein,¹⁷ kallikrein inhibiting activity,¹⁷ and C1 inhibitor¹⁸ were measured by methods that use chromogenic peptide substrates.

In addition we calculated the ratio of von

Willebrand factor to factor VIII, which has been suggested as being a useful index of hypercoagulability,¹⁹ and the ratio of antithrombin activity to antigen. The acute phase reactant orosomucoid was determined by electroimmunoassay.¹⁰ For technical reasons analyses of kallikrein inhibiting activity and C1 inhibitor were only performed in every second male subject.

UNITS FOR VARIABLES

Assays of all haemostatic variables except the fast inhibitor of tissue plasminogen activator were calibrated against an internal plasma pool obtained from 20 healthy men (aged 54.6 (5.3), range 44–61 years). The results were expressed as percentages of the internal standard, which is deemed to contain 100%. Internal standards for factor VIII and von Willebrand factor were calibrated against the 1st and 8th British plasma standards (66/335 and 78/506, National Institute for Biological Standards and Controls, London). Results from analysis of the fast inhibitor of tissue plasminogen activator were expressed as previously described.¹⁵

CORONARY ANGIOGRAPHY

Coronary angiography was performed by the percutaneous transfemoral technique in 133 patients (107 men and 26 women) three to six months after myocardial infarction (mean (SD) 4.4 (1.5), range 1–12). Angiograms were routinely obtained both before and five minutes after the administration of sublingual glyceryl trinitrate.

The coronary angiograms were allocated to one of the following four groups: 1, normal coronary angiogram; 2, occlusion or stenosis of a single vessel—no other definite angiographic abnormalities; 3, atheromatosis in a single vessel with or without occlusion or stenosis in the same or any other vessel; 4, atheromatosis of multiple vessels with or without occlusion or stenosis of any vessel.

Atheromatosis was defined as sharp-edged, plaque-like, or irregular, indentations, often multiple, into the vessel lumen without features suggesting fibromuscular hyperplasia. One single stenosis with smooth contours or a single occlusion, in the absence of additional changes, was not classified as atheromatosis, whereas multiple lesions always were. In addition to this classification patients were divided into traditional coronary artery disease categories, according to the number of major coronary arteries with haemodynamically important lesions.²⁰ All angiograms were interpreted by one of us (AS) without knowledge of the clinical history or haemostatic profile of the patient.

ADDITIONAL RISK INDICATORS

For calculation of the average tobacco consumption, one cigarette was considered to be equivalent to one gram, one cigarillo to two grams, and one cigar to five grams of tobacco. The tobacco consumption of pipe smokers was calculated by dividing by seven the weekly consumption in grams. Cumulative tobacco consumption before myocardial infarction was estimated as cigarette-years. Figures on alcohol consumption were based on a structured interview and questionnaires and expressed as grams of absolute alcohol consumed during one month. Body weight was measured with subjects dressed in ordinary indoor clothing without jacket or shoes. Blood pressure was measured in the supine position after five minutes' rest. Hyperlipoproteinaemias were defined according to the World Health Organisation classification.²¹ All subjects had been evaluated by preparative lipoprotein ultracentrifugation²² and agarose lipoprotein electrophoresis.²³ The cut-off limits for the different lipoprotein phenotypes were set to the 90th percentile of the very low density lipoprotein triglyceride and low density lipoprotein cholesterol values in age and sex matched random controls. Manifest diabetes mellitus was defined as being present when fasting hyperglycemia (whole blood) exceeded 7.0 mmol/l. Blood glucose was measured by a glucose oxidase method.²⁴ Oral glucose tolerance had been assessed in all patients after ingestion of 1.75 g glucose/kg body weight and the criteria for reduced glucose tolerance suggested by Efendic *et al*²⁵ were applied.

STATISTICAL METHODS

The statistical methods used were those recommended by Snedecor and Cochran.²⁶ Proportions were compared by the χ^2 test with Yates's correction. Statistical significance for differences in haemostatic variables between groups was tested by one-way analysis of variance and two-tailed *t* tests. Significance testing of selected pairs of values after analysis of variance was performed by the Tukey studentised range method. Coefficients of skewness and kurtosis were used to test deviations from a normal distribution, and logarithmic transformation of the individual values of skewed variables was performed before statistical analysis and testing for significance. Differences between groups were further studied by analysis of covariance which enabled us to control for concomitant group differences in other variables which may have influenced blood coagulation or fibrinolysis. Stepwise multiple discriminant analysis was performed to evaluate the independent discriminant value of the haemostatic variables. Variables reflecting smoking habits,

Table 1 Characteristics of patients and controls (mean (SD))

	Male		p value	Female		p value
	Patients (n=116)	Controls (n=116)		Patients (n=32)	Controls (n=17)	
Age (yr)	39.8 (3.9)	39.9 (3.9)	NS	38.7 (4.6)	39.1 (4.4)	NS
Blood groups (n) A/AB/B/O	52/8/18/38	48/10/15/43	NS	16/2/5/9	9/0/2/6	NS
Orosomucoid (g/l)	0.46 (0.17)	0.39 (0.10)	<0.001	0.53 (0.21)	0.36 (0.09)	<0.001
Smoking habits (n):						
Present smoker	46	45	<0.001	13	6	<0.001
Former smoker	63*	30		13†	0	
Non-smoker	7	41		6	11	
Tobacco consumption:						
Present (g/day)	6.5 (10.1)	8.0 (12.5)	NS	3.6 (5.5)	4.4 (7.4)	NS
Cumulative (cigarette-years)	411 (226)	198 (218)	<0.001	310 (176)	107 (154)	<0.001
Alcohol consumption (g/month)	415 (381)	623 (388)	<0.001	274 (289)	209 (135)	NS
Hypertension (n)	29	12	<0.001	12	1	<0.001
Hyperlipoproteinaemia (n):						
IIa	31	10	<0.001	2	3	<0.001
IIb	8	2		18	0	
III	3	0		3	0	
IV	33	7		7	1	
Diabetes (n):						
Type I	2	0	<0.001	7	0	<0.001
Type II	4	0		1	0	
Decreased oral glucose tolerance (n)	35	10		2	0	
Weight/height index weight/ (height-100) (kg/cm)	1.06 (0.13)	0.99 (0.12)	<0.001	0.97 (0.1)	0.91 (0.15)	NS

*55 and †11 patients stopped smoking at the time of the infarction.
NS, not significant.

alcohol consumption, and stature, as well as ABO blood groups were entered as forced variables.

ETHICAL CONSIDERATIONS

All subjects gave their informed consent to the study. The study protocol was approved by the regional ethical committee.

Results

CLINICAL CHARACTERISTICS AND RISK INDICATORS

Table 1 gives clinical characteristics and conventional risk indicators in patients and controls. Orosomucoid concentrations were significantly increased in both patient groups. Blood group distribution was similar in patients and controls. Smoking habits were identical in the two groups at the time of the haemostatic evaluation. There was a pronounced overrepresentation of former smokers in the patient groups, however, most of whom had stopped smoking at the time of infarction. Accordingly, cumulative lifetime tobacco consumption was much higher in patients. Alcohol consumption was higher in male controls than in male patients, whereas no differences were seen between the female study groups. More patients than controls were found to have hyperlipoproteinaemia, manifest diabetes, or reduced oral glucose tolerance. In addition, the weight/height index was higher in the young male post-infarction patients.

As shown in Table 2 a markedly higher propor-

tion of female patients (16/26) than male patients (27/107) had no definite angiographic signs of coronary atheromatosis ($\chi^2=10.997$, $p<0.001$). Similarly the distribution of the female patients in coronary artery disease categories differed from that of the male patients, with a higher proportion of female patients having insignificant or single vessel disease ($\chi^2=6.486$, $p<0.05$).

HAEMOSTATIC VARIABLES IN PATIENTS AND CONTROLS

Table 3 gives the plasma concentrations of the haemostatic variables in patients and controls. Because sex differences were found in the plasma concentrations of some haemostatic variables male and female subjects were compared separately. Differences between patients and controls were also evaluated by analysis of covariance with orosomucoid concentration alone and with tobacco consumption, alcohol consumption, weight/height index, and ABO blood group as covariates.

The fibrinogen concentration was higher in male patients than in male controls. The difference in fibrinogen concentration between male subjects persisted when the analysis was performed with all selected covariates (mean (SD)) (3.42 (0.08) vs 3.16 (0.08) g/l, $p<0.05$), but was lost when orosomucoid level alone was used as a covariate. Mean fibrinogen values were higher in female patients than in controls, but the difference was not statistically significant.

Table 2 Coronary angiographic findings in male and female patients

	Classification according to presence and extension of coronary atheromatosis			
	Normal angiogram	Single occlusion/stenosis no atheromatosis	Single vessel atheromatosis	Multiple vessel atheromatosis
Male patients (n = 107)	7	20	12	68
Female patients (n = 26)	5	11	3	7

	Classification according to number of major coronary arteries with haemodynamically important lesions			
	Insignificant disease	Single vessel disease	Double vessel disease	Triple vessel disease
Male patients (n = 107)	8	42	36	21
Female patients (n = 26)	5	15	4	2

The concentrations of factor VIII or von Willebrand factor were similar in male patients and male controls. In contrast these factors were significantly higher in female patients than in female controls. The increase in concentration of von Willebrand factor in female patients was independent of background group differences in basic characteristics considered in covariance analysis (165.4 (11.4) vs 95.1 (16.3)%, $p < 0.01$), whereas the difference in factor VIII level was highly correlated with increased orosomucoid concentration in the patient group. There were no significant differences between male or female patients and controls for the ratio of von Willebrand factor to factor VIII. Antithrombin concentrations as measured with the two different methods and antithrombin ratios were similar in patients and controls of both sexes.

The plasminogen activator capacity (difference in plasminogen activator activity values measured before and after venous occlusion) was decreased in both male and female patients. The difference between male patients and controls persisted after control of group differences in orosomucoid concentrations alone (0.35 (0.06) vs 0.57 (0.06) PU, $p < 0.01$) or in combination with all other covariates (0.37 (0.07) vs 0.56 (0.06) PU, $p < 0.05$). The significantly lower plasminogen activator capacity in female patients compared with that in female con-

trols, however, was eliminated in the covariance analyses. The concentration of the fast inhibitor of tissue plasminogen activator was considerably increased in both patient groups and the group differences remained after correction for confounding factors.

A slight increase in antipiasmin concentration in male patients did not remain significant in the covariance analyses, whereas the moderately increased antipiasmin concentration in the female patients was not influenced by the selected covariates taken together (112.1 (4.2) vs 103.5 (3.1)%, $p < 0.05$). A small but statistically highly significant increase in prekallikrein concentration in male patients was reduced and did not reach statistical significance in analysis using all covariates. In female patients a modest increase in prekallikrein concentration was entirely dependent on increased orosomucoid levels. This was also the case for kallikrein inhibiting activity, whereas the increase in C1 inhibitor concentration in female patients was only marginally influenced by the selected covariates (126.9 (5.0) vs 100.9 (6.6)%, $p < 0.05$). Concentrations of kallikrein inhibiting activity and C1 inhibitor were almost identical in male patients and controls.

Analysis of individual data on male patients showed that 17% had values of factor VIII above the 90th percentile of matched controls, 22% had

Table 3 Haemostatic variables in patients and random controls (mean (SD))

Measurement	Male			Female		
	Patients (n = 116)	Controls (n = 116)	p value	Patients (n = 32)	Controls (n = 17)	p value
Fibrinogen (g/l)	3.52 (1.07)	3.08 (0.81)	<0.01	4.03 (1.31)	3.40 (1.01)	NS
Factor VIII (%)	105.0 (32.0)	99.7 (35.7)	NS	160.1 (78.8)	91.8 (38.0)	<0.001
vWFAg (%)	113.6 (54.5)	103.7 (40.9)	NS	162.2 (68.8)	100.1 (35.1)	<0.01
ATS (%)	104.9 (10.2)	105.1 (9.2)	NS	105.9 (13.3)	101.7 (8.8)	NS
ATAg (%)	103.0 (12.0)	103.4 (9.9)	NS	105.4 (11.7)	98.7 (11.7)	NS
PA capacity (PU)	0.31 (0.46)	0.58 (0.73)	<0.01	0.28 (0.31)	0.43 (0.32)	<0.05
t-PA inhibitor (AU/ml)	4.36 (3.18)	2.78 (1.93)	<0.001	3.80 (1.59)	2.06 (0.69)	<0.01
Antipiasmin (%)	103.1 (10.8)	99.9 (11.4)	<0.05	112.9 (15.5)	101.7 (6.7)	<0.05
Prekallikrein (%)	104.4 (14.7)	97.7 (15.7)	<0.001	105.1 (28.9)	93.3 (13.4)	NS
Kallikrein inhibiting activity (%)	111.1 (15.2)	111.3 (12.7)	NS	117.2 (22.7)	97.2 (9.5)	<0.05
C1 inhibitor (%)	114.7 (17.9)	114.0 (16.3)	NS	126.9 (14.3)	101.4 (11.0)	<0.001
Ratio vWFAg:FVIII	1.09 (0.42)	1.03 (0.39)	NS	1.10 (0.49)	1.15 (0.35)	NS
Ratio ATS:ATAg	1.02 (0.09)	1.02 (0.09)	NS	1.06 (0.08)	1.04 (0.08)	NS

vWFAg, von Willebrand factor; ATS, antithrombin activity; ATAg, antithrombin antigen; PA, plasminogen activator; t-PA inhibitor, fast inhibitor of tissue plasminogen activator; FVIII, factor VIII; PU, plough units; AU, arbitrary units.

Table 4 Haemostatic variables in male patients grouped according to the presence and extent of coronary atheromatosis

Measurement	Normal angiogram (n = 7)	Single occlusion or stenosis (n = 20)	Single vessel atheromatosis (n = 12)	Multiple vessel atheromatosis (n = 68)	F value	p value
Fibrinogen (g/l)	3.16 (1.23)	3.17 (0.55)	2.98 (0.52)	3.76 (1.18)	3.65	0.015
Factor VIII (%)	117.4 (36.2)	93.4 (31.0)	102.3 (31.6)	104.6 (28.0)	1.25	0.295
vWFAg (%)	100.0 (49.6)	96.1 (31.6)	117.4 (49.1)	116.4 (58.7)	0.84	0.478
ATS (%)	107.9 (11.0)	105.9 (9.5)	104.1 (9.2)	105.3 (10.6)	0.21	0.886
ATAg (%)	102.4 (14.0)	105.3 (12.7)	100.3 (6.8)	103.5 (12.4)	0.42	0.738
PA capacity (PU)	0.15 (0.13)	0.35 (0.47)	0.32 (0.51)	0.31 (0.45)	0.65	0.585
t-PA inhibitor (AU/ml)	6.86 (9.52)	3.82 (1.81)	2.90 (1.82)	4.78 (3.03)	0.48	0.694
Antiplasmin (%)	98.6 (10.2)	99.8 (11.1)	102.3 (8.0)	104.4 (11.1)	1.24	0.298

vWFAg, von Willebrand factor; ATS, antithrombin activity; ATAg, antithrombin antigen; PA, plasminogen activator; t-PA inhibitor, fast inhibitor of tissue plasminogen activator.

values of von Willebrand factor above the 90th percentile, and 37.5% had values of the fast inhibitor of tissue plasminogen activator about the 90th percentile (values above 135% for factor VIII, 150% for von Willebrand factor, and 3.5 AU/ml for the fast inhibitor of tissue plasminogen activator). Similar analysis of plasminogen activator capacity data showed that 20.8% of male patients had values below the 10th percentile of control subjects (values below 0.15). Limited numbers in the control group prevented this analysis in female patients.

In stepwise multiple discriminant analysis, concentrations of fibrinogen and the fast inhibitor of tissue plasminogen activator emerged as the haemostatic variables that gave the best independent discrimination between male patients and controls. The independent discriminatory power of the fast inhibitor of tissue plasminogen activator was entirely lost, however, when tobacco consumption, regular alcohol intake, and weight/height index were introduced in the discriminant function. In women concentrations of von Willebrand factor and the fast inhibitor of tissue plasminogen activator gave the best independent discrimination between patients and controls, irrespective of the introduction of possible confounding variables. When we used the two sets of haemostatic variables contained in the discriminant functions we correctly classified 65% of

male and female patients, with slightly higher values for controls.

CORRELATIONS BETWEEN HAEMOSTATIC VARIABLES AND CORONARY ANGIOGRAPHIC FINDINGS IN MALE PATIENTS

Tables 4 and 5 show the concentration of some haemostatic variables in male patients grouped according to presence and extension of coronary atheromatosis or number of significantly diseased major coronary arteries.

Analysis of variance indicated differences in fibrinogen concentration among patients grouped according to presence and extension of coronary atheromatosis (Table 4). Mean fibrinogen concentration in male patients with multiple vessel atheromatosis at angiography was significantly higher than that in male patients with single vessel atheromatosis ($p < 0.05$, as tested by the Tukey procedure). The mean fibrinogen concentration in patients with an entirely normal coronary angiogram and with single vessel occlusion/stenosis and no other angiographic evidence of atheromatosis resembled that in patients with coronary atheromatosis demonstrable in only one of the major coronary arteries.

When male patients were grouped according to the number of vessels with haemodynamically im-

Table 5 Haemostatic variables in male patients grouped according to the number of major coronary arteries with haemodynamically important lesions (mean (SD))

Measurement	Insignificant disease (n = 8)	Single vessel disease (n = 42)	Double vessel disease (n = 36)	Triple vessel disease (n = 21)	F value	p value
Fibrinogen (g/l)	3.24 (1.16)	3.41 (1.03)	3.62 (1.05)	3.68 (1.20)	0.39	0.761
Factor VIII (%)	118.1 (33.6)	96.9 (27.7)	106.2 (30.7)	104.0 (28.8)	1.38	0.254
vWFAg (%)	107.1 (50.2)	108.1 (65.0)	123.4 (44.9)	100.6 (42.5)	0.94	0.422
ATS (%)	107.9 (10.2)	106.4 (9.3)	106.9 (9.3)	100.4 (12.0)	2.22	0.091
ATAg (%)	104.8 (14.6)	104.2 (11.4)	103.2 (11.5)	101.7 (13.3)	0.22	0.632
PA capacity (PU)	0.13 (0.12)	0.36 (0.48)	0.27 (0.34)	0.34 (0.62)	0.79	0.505
t-PA inhibitor (AU/ml)	5.34 (8.19)	4.04 (2.27)	4.43 (3.29)	4.43 (1.35)	0.40	0.751
Antiplasmin (%)	99.4 (9.7)	103.2 (11.9)	103.7 (9.9)	102.4 (12.4)	0.34	0.795

vWFAg, von Willebrand factor; ATS, antithrombin activity; ATAg, antithrombin antigen; PA, plasminogen activator; t-PA inhibitor, fast inhibitor of tissue plasminogen activator.

portant lesions (Table 5), there was a tendency for patients with triple vessel disease to have lower antithrombin activity values than the remainder of the patients. This difference was not significant as analysed by the Tukey studentised range method.

No significant differences in factor VIII and the von Willebrand factor were noted between patients grouped according to two angiographic classification systems, nor were there significant group differences for any of the fibrinolytic variables.

No significant differences were found in the few female patients grouped according to angiographic findings.

Discussion

So far most of the epidemiological and aetiological research on ischaemic heart disease has mainly dealt with conventional risk factors such as smoking, hypertension, and different hyperlipoproteinaemias—studies on the haemostatic system have been scarce. Young adults with myocardial infarction probably represent a heterogeneous group.^{27–29} In most cases rapidly progressing coronary atherosclerosis is the underlying disease. In a minority, however, other predisposing factors may be operating. Since haemostatic function has been implicated in atherogenesis as well as in thromboembolic disorders, we decided to investigate the function of blood coagulation and fibrinolysis in patients with premature ischaemic heart disease. No such studies have yet been reported in representative and sufficiently large groups of young post-infarction patients.

Stepwise discriminant analysis indicated that concentrations of fibrinogen and the fast inhibitor of tissue plasminogen activator in men and von Willebrand factor and the fast inhibitor of tissue plasminogen activator in women were significant discriminants of myocardial infarction. There was a striking sex difference in the distribution of patients between the angiographic subgroups. Sixty two percent (16/26) of the female patients who had coronary angiography had no definite signs of atheromatosis nor did 25% (27/107) of male patients. Male patients with a coronary angiogram showing severe atheroma tended to have higher plasma fibrinogen concentration than patients without angiographic evidence of coronary atheromatosis. There was also a tendency for antithrombin activity values to be low in male patients with triple vessel disease.

These data suggest that disturbances of blood coagulation and fibrinolysis might have considerable independent significance for the development of myocardial infarction in young women because they predispose them to coronary thrombosis. The haemostatic alterations seen in male patients might pri-

marily be involved in the evolution of coronary atherosclerosis. These disturbances, however, might also play a part in the precipitation of infarction in individuals with severe widespread coronary atheroma.

The interpretation of the present data on fibrinogen is not clear. In previous studies^{30–32} increased fibrinogen concentrations have been found in patients with ischaemic heart disease. Furthermore fluid dynamic factors have been implicated in the siting of atherosclerotic lesions.³³ An association between blood viscosity and extension of coronary artery disease, partly due to increased fibrinogen concentrations, has been demonstrated in one angiographic study.³⁴

Our findings in male patients do not confirm earlier observations of higher plasma concentrations of von Willebrand factor in patients with angiographic evidence of atherosclerosis.³⁵ Furthermore, data from an extensive population study³⁶ have suggested that factor VIII might be a predictor of subsequent cardiovascular mortality in middle aged men, whereas the concentration of von Willebrand factor was not raised in fatal cases. An increase in both the von Willebrand factor and factor VIII might indicate a hypercoagulable state. In addition there is evidence that von Willebrand factor has an atherogenic action. Raised concentrations of von Willebrand factor might thus be a primary abnormality rather than a secondary response to the intimal injury of arterial lesions.³⁷ In von Willebrand's disease platelets adhere to subendocardial structures,³⁸ and adhering platelets are believed to release a growth factor capable of inducing extensive proliferation of smooth muscle cells.³⁹

A hereditary deficiency of antithrombin is a rare cause of venous thrombosis, whereas both increased and decreased concentrations of antithrombin antigen have been reported in ischaemic heart disease.⁴⁰ Low concentrations have been reported in the acute as well as in the recovery phase after myocardial infarction and in patients with angina pectoris associated with coronary atherosclerosis.^{36,41} In the present study normal concentrations of antithrombin were found in both male and female patients by antigen and substrate methods. Only a few patients had low concentrations of antithrombin. The lowest antithrombin concentrations (chromogenic peptide substrate method) and ratios were seen in patients with triple vessel disease.

It has been suggested that low antithrombin concentrations in individuals with angina pectoris might reflect a slow ongoing intravascular coagulation with increased consumption of antithrombin.⁴⁰ An alternative explanation would be that of increased consumption of antithrombin due

Haemostatic function in myocardial infarction

to insufficient natural protection of the atherosclerotic coronary arterial intima against blood clotting. Lower pre-existing concentrations contributing to a prethrombotic state cannot be ruled out. High concentrations of antithrombin, on the other hand, most likely represent a protective response, which may later be followed by low levels.⁵

The vessel wall content of tissue plasminogen activator, the release of tissue plasminogen activator from the endothelium, and the physiological inhibitors of fibrinolysis are regarded as the main factors regulating plasminogen activator capacity. Data from the present study suggest that the recently described rapid inhibitor of tissue plasminogen activator is an important factor in the modulation of the fibrinolytic response. The low plasminogen activator capacity found in young patients after infarction might thus primarily be due to high concentrations of this inhibitor. The additional contribution of impaired tissue plasminogen activator release to the decreased plasminogen activator capacity, however, was not clarified by the present study, since tissue plasminogen activator antigen was not determined. High plasma concentrations of the fast inhibitor to tissue plasminogen activator were also found in patients investigated before coronary artery bypass operation.⁴²

In female patients α_2 -antiplasmin and C1 inhibitor concentrations were also consistently raised. The clinical implication of these modest increases is, however, not obvious. The findings of increased concentrations of α_2 -antiplasmin and prekallikrein in male patients were only expressions of a non-specific inflammatory response, as was increased kallikrein inhibiting activity in female patients.

Apart from predisposing patients to thrombosis, decreased fibrinolytic capacity could theoretically promote the development of premature atherosclerosis. The similarity in the profile of changes in variables reflecting fibrinolysis in male patients with and those without definite coronary atheromatosis, as well as the considerably raised concentrations of the fast inhibitor of tissue plasminogen activator and the resultant low plasminogen activator activity in some patients with a normal coronary angiogram, however, are more indicative of a primary influence on the thrombotic element in myocardial infarction.

Do the haemostatic disturbances we report reflect a non-specific acute phase response to tissue damage and acute stress or do they represent pathogenetic mechanisms involved in the development of coronary occlusion? Unexpectedly increased concentrations of several well established acute phase reactants were found in patients as compared with random controls. Multivariate analysis that controlled for the influence of a non-specific

inflammatory response showed that some haemostatic abnormalities were independent discriminants between patients and controls. Furthermore in most instances the haemostatic variables showed no or only weak correlations with the acute phase reactants. Thus, the results seem to remain valid even after a persisting non-specific acute phase response has been taken into account.

The associations of some haemostatic factors with myocardial infarction and coronary atheromatosis in this cross sectional study do not necessarily imply causation. This has to be tested in prospective studies. The findings indicate, however, that risk factors other than the conventional ones might be of importance for the evolution of ischaemic heart disease.

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