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Haematological stress syndrome in atherosclerosis

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SUMMARY Forty patients with atherosclerotic peripheral vascular disease, as compared to 29 healthy controls, showed a significant increase in platelet number and activity, a neutrophil leucocytosis, and a raised level of several acute-phase reactant proteins (fibrinogen, antithrombin III, factor VIII, and serum globulin). The hyperproteinaemia was associated with increases in plasma-, serum-, and blood-viscosity and is the likely cause of the hyperviscosity of vascular disease.

These multiple haemostatic abnormalities closely resemble the non-specific, haematological stress-syndrome response to acute and chronic inflammatory disorders. In atherosclerosis also they may represent a non-specific, secondary response and neither be of aetiological significance nor reflect continuing low-grade intravascular coagulation.

The term haematological stress syndrome[1] has been used to describe the non-specific haematological abnormalities that accompany certain acute and chronic disorders. These abnormalities include an increase in platelet number and activity, a leucocytosis, and a raised plasma level of certain proteins that act as acute-phase reactants; the anaemia of chronic disorders may also co-exist. While these changes characteristically accompany inflammatory disorders and malignancy, some of the abnormalities also occur in chronic vascular disease and may contribute to platelet deposition, hyperviscosity, and thrombosis. We have therefore investigated components of the stress syndrome in patients with extensive lower limb atherosclerosis and intermittent claudication.

Patients and methods

PATIENTS

Forty men with intermittent claudication and extensive atherosclerosis, confirmed by arteriography and/or Doppler pressure measurements, were matched for age and smoking habit with 29 healthy men with no history of vascular disease. None of the claudicants had rest pain or trophic changes, and all tests were performed on fasting outpatients using a carefully standardised blood-collection technique.[2] Each of the 40 patients was re-studied four weeks later to confirm persistence of the abnormalities.

METHODS

The methods used were as previously described[2] with the following additions: haematological values (Coulter S counter), Westergren erythrocyte sedimentation rate (Accu-Tech Ltd, Littleborough), plasma antithrombin III (AT III Chromozym, Boehringer), serum globulin (Technicon SMA 1260), and fibrinogen by immunoelectrophoresis[3] (Dako Immunoglobulins, Copenhagen). Euglobulin lysis time[4] was expressed as units of fibrinolytic activity (100/lysis time in hours), and blood viscosity was measured at 37°C at shear rates of 128, 23, and 0·2 s^{-1} using a Contraves (Zurich) LS 30 viscometer. Plasma and serum viscosity were measured at 25°C using a Coulter-Harkness (Coulter Electronics, Luton) viscometer, and platelet spontaneous aggregation was measured according to Kenny *et al.*[5]

Statistical significance was determined by the Mann-Whitney U test (two-tailed).

Results

The 40 men with vascular disease were closely matched for age and smoking habit with the 29 healthy controls (Table 1), who also were tested as fasting outpatients. All 40 patients were re-studied four weeks later, but as there was no significant

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Table 1 *Mean values ± SD for clinical, biochemical, and haematological data*

	Vascular disease (40)	*Healthy controls (29)*	*p*
Age (years)	59·5 ±6·9	58·0 ±6·7	NS
Cigarettes/day	4·8 ±7·0	7·0 ±11·5	NS
Cholesterol (mmol/l)	5·83 ±0·99	5·72 ±0·95	NS
Triglyceride (mmol/l)	1·61 ±0·85	1·23 ±0·58	<0·05
Haematocrit (l/l)	0·431 ±0·04	0·437 ±0·03	NS
Erythrocytes ($\times 10^{12}$/l)	4·81 ±0·47	4·93 ±0·44	NS
Total leucocytes ($\times 10^{9}$/l)	7·38 ±1·80	5·84 ±1·75	<0·001
Neutrophils ($\times 10^{9}$/l)	4·52 ±1·53	3·55 ±1·10	<0·01
Sedimentation rate (mm/h)	20·3 ±15·1	8·2 ±7·9	<0·001

Table 2 *Mean values ± SD for platelet function tests*

	Vascular disease (40)	*Healthy controls (29)*	*p*
Platelet count ($\times 10^{9}$/l)	258·0 ±62·6	214·0 ±57·2	<0·01
In vivo microaggregates (%)	23·9 ±14·4	16·5 ±15·1	<0·05
Spontaneous aggregation (%)	10·75 ±18·18	6·10 ±4·37	NS
ADP-aggregation threshold (μM)	1·67 ±1·40	2·00 ±1·02	<0·05

Table 3 *Mean values ± SD for rheological tests and fibrinolytic activity*

	Vascular disease (40)	*Healthy controls (29)*	*p*
Plasma viscosity (mPa. s)	1·73 ±0·11	1·60 ±0·09	<0·001
Serum viscosity (mPa. s)	1·52 ±0·06	1·48 ±0·09	<0·001
Whole-blood viscosity (mPa. s)			
128 s^{-1}	4·84 ±0·34	4·53 ±0·28	<0·001
23 s^{-1}	7·17 ±0·55	6·77 ±0·51	<0·001
0·2 s^{-1}	49·67 ±6·66	45·07 ±8·37	<0·01
Euglobulin lysis time (units)	32·7 ±9·0	40·8 ±11·0	<0·01

difference ($p > 0·05$) between the paired values for any of the tests, the results for their first visit only are given in this paper. The patients with vascular disease had significantly raised total serum triglyceride, a neutrophil leucocytosis, and a raised sedimentation rate (Table 1). They also showed a raised platelet count, increased circulating platelet microaggregates,[6] spontaneous platelet aggregation

Table 4 *Mean values ± SD for plasma and serum proteins*

	Vascular disease (40)	*Healthy controls (29)*	*p*
Fibrinogen bioassay (g/l)	3·64 ±0·68	2·91 ±0·66	<0·001
immunoassay (g/l)	3·47 ±0·79	3·28 ±0·73	<0·001
Factor VIII bioassay (units/ml)	1·39 ±0·44	1·06 ±0·29	<0·01
immunoassay (units/ml)	1·32 ±0·57	0·95 ±0·38	<0·001
Antithrombin III (%)	108·7 ±17·3	97·0 ±15·0	<0·01
Globulin g/l	30·13 ±2·87	27·86 ±2·75	<0·005

Table 5 *Correlation coefficients (r) and significance (p) between plasma and blood viscosity and large molecular weight plasma proteins*

		Vascular disease (40)	*Healthy controls (29)*
Plasma viscosity v			
Fibrinogen (bioassay)	r	0·351	0·763
	P	<0·05	<0·001
Globulin	r	0·679	0·747
	P	<0·001	<0·001
Factor VIII (immunoassay)	r	0·424	0·222
	P	<0·01	NS
Whole-blood viscosity (37°C, 23 s^{-1}) v			
Plasma viscosity	r	0·607	0·084
	P	<0·001	NS
Serum viscosity	r	0·450	0·128
	P	<0·01	NS
Fibrinogen (bioassay)	r	0·483	0·101
	P	<0·005	NS
Globulin	r	0·465	0·158
	P	<0·005	NS
Factor VIII (immunoassay)	r	0·354	0·003
	P	<0·05	NS

in vitro, and a lowered platelet threshold to aggregation with adenosine diphosphate (ADP) (Table 2). There were significant increases in plasma-, serum-, and blood-viscosity (the latter measured at high-, intermediate-, and low-shear rates and adjusted to a standard haematocrit of 0·45) (Table 3), a reduction in fibrinolytic activity (Table 3), and significant elevations in several acute-phase proteins of a coagulant (fibrinogen, factor VIII, antithrombin III) and non-coagulant (serum globulin) type (Table 4).

Correlations were investigated between viscosity and the larger molecular weight plasma proteins that contribute to it (Table 5). In vascular disease, globulin correlated more closely than fibrinogen with plasma viscosity. Whole-blood viscosity correlated significantly with plasma and serum viscosity. Fibrinogen, globulin, and serum viscosity all showed

a similar level of correlation with whole-blood viscosity.

Discussion

Patients who have recently suffered surgical or accidental trauma, myocardial infarction, or acute infection show a short-term, acute-phase response consisting of increases in platelet number and adhesiveness, plasma- and blood-viscosity, erythrocyte sedimentation rate, and plasma proteins (fibrinogen, factors V and VIII, plasminogen, antithrombin III), together with a temporary lowering of fibrinolytic activity.[7-13] It is now realised that these acute changes are part of the stress response to tissue injury and are usually of a non-specific, temporary, and secondary nature.

Although a similar, but longer-term, stress response (the haematological stress syndrome) is known to occur in patients with chronic inflammatory disease and cancer,[1] it has not been generally appreciated that individual reports of platelet activation,[14-17] hyperfibrinogenaemia and hyperviscosity,[2 18] and reduced fibrinolytic activity[19-21] in patients with atherosclerosis may collectively represent a similar stress response in the steady-state of chronic vascular disease. The patients in the present study showed significant changes, on two occasions, in platelet and neutrophil counts, platelet function and fibrinolysis, and acute-phase reactant proteins; these chronic changes in atherosclerosis comprise many of the abnormalities of the stress response.

It is likely that the hyperviscosity of peripheral vascular disease[2 18 22 23] is, in part, a consequence of the chronic hyperfibrinogenaemia, although the correlation between fibrinogen and whole-blood viscosity is stated to be relatively poor, some patients showing hyperviscosity without hyperfibrinogenaemia and *vice versa*.[23] Our patients, however, also showed a significant correlation between whole-blood viscosity and total serum globulin. The raised viscosity of whole-blood, plasma, and serum in these patients is more likely to reflect this increase in level of several large molecular weight blood proteins rather than the hyperfibrinogenaemia alone.

The plasma fibrinogen level increases with age, obesity, and smoking[24] and may prove to be a major risk factor for cardiovascular disease.[25] It would not be justified to extrapolate the results of our study of patients with extensive atherosclerosis to patients with minimal or localised disease, or to the ageing or otherwise high-risk general population. The results indicate, however, the need for careful long-term studies to establish whether hyperfibrinogenaemia, hyperviscosity, platelet hyperactivity, or reduced fibrinolytic activity is of any aetiological significance in the development of vascular disease rather than a non-specific response to established atherosclerosis. It is also unknown which of these haemostatic abnormalities makes the largest contribution to the thrombotic tendency of atherosclerosis. Since multiple haemostatic abnormalities may co-exist in the severely affected patient, therapy aimed at one of them, for example, platelet hyperactivity, may fail because of the persistence of other abnormalities; this is clearly relevant to current clinical trials of anti-platelet agents in patients with cardiovascular disease.

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