Fibrinolytic response to moderate exercise in young male diabetics and non-diabetics

J. D. CASH AND R. C. MCGILL

From the South-east Scotland Regional Blood Transfusion Research Laboratories and the Diabetic Department, Royal Infirmary, Edinburgh

SYNOPSIS The euglobulin lysis time was measured in 25 young male insulin-dependent diabetics and 25 age- and sex-matched healthy controls before and after a standardized moderate treadmill exercise procedure. There was a statistically significant mean shorter resting euglobulin lysis time in the diabetic group but their ability to respond to the exercise procedure was significantly impaired. It is suggested that this impaired fibrinolytic reactivity may be related to the diminished vaso-active reactivity previously reported in young diabetics.

Earlier studies, reported from this laboratory, on the fibrinolytic response to such stimulants as exercise and intravenous adrenaline demonstrated that in normal subjects it was possible to isolate a subgroup whose ability to generate plasminogen activator to these short stimuli appeared to be impaired (Cash, 1966; Cash and Allan, 1967). It was proposed that these individuals might be at risk to conditions such as atherosclerosis, thrombosis, and shock in which defective fibrinolysis has been considered to be an aetiological factor (Astrup, 1956; McKay, 1965; Hardaway, 1966). Atheroma is particularly common in diabetes, in which condition its consequences are responsible for much of the morbidity and mortality. Thus the following communication is a logical extension of our earlier studies in which the fibrinolytic response to exercise is compared between a group of young male insulin-dependent diabetics and age- and sex-matched controls.

SUBJECTS AND METHODS

Table I gives the clinical data of 25 insulin-dependent diabetics aged 19 to 30 years (mean: 25.0 ± 3.8), who were willing to participate in the study. The 25 healthy male control subjects were undergraduates and colleagues aged 18 to 30 years (mean: 26.2 ± 2.9).

Experiments were performed in a procedure room at a temperature of 19 to 20°C between 9.00 am and 12 noon. The diabetic patients were requested to take their usual breakfast and morning dose of insulin. All subjects

abstained from smoking and excessive exercise on the morning of the procedure and a pre-exercise rest for 30 minutes was obligatory. The exercise consisted of walking on a treadmill moving at 3.4 mph at 5° elevation for eight minutes. Cubital venous blood samples were withdrawn, with the minimum of venous occlusion, immediately before and after the exercise and the level of circulating plasminogen activator was assayed by the euglobulin lysis time (Cash, 1966). All subjects were studied on more than one occasion and the interval between each visit was at least one week. The percentage fibrinolytic response was calculated as $A-B/A \times 100$, where A and B represented the resting and post-exercise euglobulin lysis times, respectively.

RESULTS

Details of the results of all subjects are shown in Table II and the frequency distribution of the fibrinolytic responses in Figure 1. The mean resting euglobulin lysis time in the diabetic and non-diabetic population was 119 ± 104 minutes and 203 ± 158 minutes, respectively. The difference between these values was highly significant ($t = 3.601$, $P < 0.001$). Although there was a higher resting level of circulating plasminogen activator in the diabetic patients, it was possible to isolate a subgroup of poor responders ($< 20\%$) and their mean percentage response (31.7 ± 8.3) was significantly less than the normal controls (39.7 ± 11.5) ($t = 2.786$, $0.005 < P < 0.01$). In both populations there was no correlation between the fibrinolytic responses to the exercise procedure and the resting levels of plasminogen activator as measured by the euglobulin lysis time.

TABLE I
CLINICAL DETAILS OF DIABETIC SUBJECTS

Subject No.	Age (yr)	Duration of Diabetes (yr)	Insulin Requirement (Units) ^a		Diabetic Complications
			Morning	Afternoon	
1	26	14	16 sol, 28 PZI	—	None
2	24	4	28 sol, 48 PZI	—	None
3	22	12	8 sol, 40 PZI	6 sol	Albuminuria
4	29	3	44 sol, 56 PZI	—	None
5	30	4	32 sol, 56 PZI	—	None
6	30	8	40 sol, 40 PZI	—	Diabetic retinopathy
7	22	3	16 sol, 24 PZI	20 sol	None
8	26	3	30 sol, 40 PZI	—	None
9	30	7	16 sol, 32 PZI	18 sol	None
10	30	16	12 sol, 36 PZI	—	Diabetic retinopathy
11	20	4	24 sol, 40 PZI	16 sol	None
12 ¹	29	15	32 sol, 32 SL	32 sol, 32 SL	Diabetic retinopathy
13	20	3	8 sol, 36 PZI	—	Diabetic retinopathy
14	28	5	12 sol, 16 PZI	—	None
15	21	3	24 sol, 40 PZI	—	None
16	20	6	10 sol, 24 PZI	—	None
17 ²	24	1	24 sol, 32 PZI	—	None
18	28	17	24 sol, 40 PZI	—	Albuminuria
19	27	11	20 sol, 40 PZI	24 sol	Diabetic retinopathy
20	22	3	20 sol, 36 PZI	—	Diabetic retinopathy
21	23	1	16 sol, 16 PZI	—	None
22	19	13	56 sol, 44 PZI	—	Albuminuria
23	28	10	20 sol, 80 PZI	—	Diabetic retinopathy and albuminuria
24	22	1	12 sol, 12 PZI	—	None
25	24	9	8 sol, 40 PZI	—	None

¹ Insulin resistance treated with prednisolone 5 mg bd

² Epileptic: well controlled by phenobarbitone 30 mg tds

^a The numbers represent the units of either soluble (sol), zinc protamine (PZI) or semi lente (SL) insulin.

DISCUSSION

There is little agreement between the results of previous studies on the resting level of spontaneous fibrinolysis in diabetic patients. This may be due to the heterogeneity of the fibrinolytic assays employed and the populations of diabetics studied. Hathorn, Gillman, and Campbell (1961) and Fearnley, Chakrabarti, and Avis (1963) demonstrated lower spontaneous fibrinolysis compared with age-matched controls, whereas Denborough and Patterson (1962), MacKay and Hume (1964), and Tanser (1967) obser-

ved no difference between their diabetic patients and normal controls. Our finding of a significantly higher level of circulating plasminogen activator in these young male diabetic patients compared with the age- and sex-matched controls is difficult to explain. It may be of some significance that the group of diabetics we studied was more homogeneous in terms of age, sex, and insulin-dependence than in earlier studies, although MacKay and Hume (1964) found no significant difference between diabetics aged more or less than 45 years of age. The euglobulin lysis time is perhaps the best method readily available for the assay of circulating plasminogen activator (Fearnley, 1965), and the assays employed in other studies were less specific. However, as we are uncertain whether all antifibrinolytic substances are absent from precipitated euglobulin, the finding of Sandberg, Muller, Bellet, Feinberg, Gagnon, and Gelber (1963) of a markedly diminished plasma antifibrinolytic activity in diabetics receiving insulin may have contributed to our findings.

The biological significance of an increased resting level of plasminogen activator is not clear but Egeberg (1963), in a study of 30 diabetics, 24 of whom were on insulin therapy, demonstrated a relative hypercoagulability *in vitro* in terms of a shorter average plasma cephalin time and an average increase of antithrombin globulin of 70%,

FIG. 1. The frequency distribution of percentage fibrinolytic response to moderate exercise in young diabetic subjects and controls.

TABLE II

EUGLOBULIN LYSIS TIME BEFORE AND AFTER MODERATE EXERCISE IN 25 YOUNG MALE DIABETICS AND 25 YOUNG MALE CONTROLS

Subject No.	Diabetics			Controls			Subject No.	Diabetics			Controls		
	Euglobulin Lysis Time			Euglobulin Lysis Time				Euglobulin Lysis Time			Euglobulin Lysis Time		
	Before	After	Increase (%)	Before	After	Increase (%)		Before	After	Increase (%)	Before	After	Increase (%)
1	88	55	38	140	71	49	12	635	494	22	272	192	29
	81	54	33	660	332	50		151	106	30			
	69	45	35	500	257	49		245	185	24			
2	101	65	36	240	110	54	13	105	70	33	494	211	57
	117	92	21	304	136	55		72	52	28	720	370	48
	110	80	27								274	137	50
3	69	47	32	195	120	48	14	72	52	28	100	54	46
	80	59	26	105	58	45		75	45	40	113	56	50
	133	101	24	135	80	40					110	52	53
4				77	45	42	15	212	145	32	112	52	54
				83	51	39		146	104	29	223	104	53
				148	92	38					180	80	56
5	93	53	44	620	440	29	16	62	36	42	257	143	44
	78	44	44	84	60	29		68	56	18	120	80	33
	141	50	33	270	200	26		60	55	31	140	90	36
6				318	213	33	17	69	46	33	72	65	10
				210	156	26		70	47	33	108	86	20
				61	35	43					200	184	8
7	62	52	16	75	42	44	18				320	310	3
	66	50	24	57	35	39		91	58	36	189	99	48
				65	45	31		93	73	22	270	137	49
8				81	50	38	19	95	55	42			
				115	70	39		80	47	42	65	51	22
				146	96	34		80	54	32	84	56	33
9	138	71	49	105	60	43	20	63	39	38	250	160	36
	165	71	57	131	78	41		64	39	39	230	150	35
	83	50	40	77	47	39		70	50	29			
10	75	50	33	105	60	43	21	79	58	27	116	87	25
	81	45	44	131	78	41		81	48	41	108	82	24
	65	40	39	77	47	39					110	85	23
11				76	50	34	22	104	73	30	120	75	38
				550	440	20		88	60	32	500	300	40
				211	172	19		73	60	18			
12	147	84	43	745	505	32	23	97	85	12	174	89	49
	83	64	23	143	60	58		98	93	5	135	77	43
	90	63	30	150	65	57					100	60	40
13				150	62	59	24	305	240	21	539	324	40
				105	63	40		400	325	19	269	162	40
				95	59	38		91	53	42	107	63	42
14	91	55	40	103	60	42	25	75	46	39	76	45	41
	95	61	36	255	124	51					95	60	37
	126	81	36	315	153	51							
15	86	62	28	262	129	51							
	508	398	22	120	95	21							
	340	278	19	159	116	27							

proaccelerin of 23%, and fibrinogen of 44% above the average controls. It is possible that the high level of plasminogen activator is a physiological response to this relative hypercoagulability.

Although the mean resting levels of plasminogen activator in the diabetic population appeared to be higher than those of the controls, their ability to generate plasminogen activator to the exercise was diminished. This finding is contrary to that of Tanser (1967), who studied a group of 30 diabetics and observed no significant difference in their fibrinolytic response with an age-matched control group following a subcutaneous injection of adrenaline. However, only 10% of Tanser's patients were

below 30 years of age and it is possible that many of the others were not insulin-dependent. Furthermore, the many variable factors known to govern adsorption of subcutaneously administered drugs (Goodman and Gilman, 1965) may have contributed to this finding. It is also possible that the relatively short duration of the fibrinolytic stimuli in our experiments may be relevant, for we have demonstrated in healthy subjects that some poor fibrinolytic responders to a short period of exercise will respond normally to a more prolonged procedure (Cash and Woodfield, 1967). Although adrenaline is probably responsible, in part, for the fibrinolytic response to exercise, there is no evidence that

diabetics are less able to release catecholamines following exercise (Larsson, Persson, Sterky, and Thoren, 1964). It is generally assumed that the mechanism by which adrenaline causes the release of plasminogen activator is a passive one (Holemans, 1965), that is to say, the result of anoxia (subsequent to vasoconstriction) or minute trauma (following vasodilatation) of the vascular endothelial units which are believed to be the source of plasminogen activator in the circulation (Todd, 1959). If this is so then the work of West, Sawrey, Bird, Wilson, and Hatcher (1965) may be of interest, for these authors demonstrated a significantly diminished vasoactive response, in terms of calf and foot blood flow, in a group of young diabetics with no clinical evidence of atherosclerosis, following intravenous adrenaline.

In view of the small number of diabetic subjects in this study no attempt has been made to correlate the results with their dosage of insulin, duration of diabetes, and complications. However, our findings emphasize that the study of this aspect of fibrinolysis in diabetic patients may prove to be useful.

We wish to thank all the volunteers; Dr R. A. Cumming, Director of the South-east Scotland Regional Blood Transfusion Centre, for his invaluable help; Dr L. J. P. Duncan, physician in charge of the Diabetic Department,

for permission to study his patients; Professor K. W. Donald, Department of Medicine, for the use of the treadmill; Dr D. G. Woodfield for his many helpful suggestions; and Mr A. G. E. Allan for his technical assistance. This research programme has been supported by a grant from the Scottish Hospital Endowments Research Trust.

REFERENCES

- Astrup, T. (1956). *Lancet*, **2**, 565.
 Cash, J. D. (1966). *Brit. med. J.*, **2**, 502.
 —, and Allan, A. G. E. (1967). *Brit. J. Haemat.*, **13**, 376.
 —, and Woodfield, D. G. (1967). *Nature (Lond.)*, **215**, 628.
 Denborough, M. A., and Patterson, B. (1962). *Clin. Sci.*, **33**, 485.
 Egeberg, D. (1963). *Scand. J. clin. Lab. Invest.*, **15**, 533.
 Fearnley, G. R. (1965). *Fibrinolysis*. Arnold, London.
 —, Chakrabarti, R., and Avis, P. R. D. (1963). *Brit. med. J.*, **1**, 921.
 Goodman, L. S., and Gilman, A. (1965). *The Pharmacological Basis of Therapeutics*, 3rd ed. p. 7. Macmillan, New York.
 Hardaway, R. M. (1966). *Syndromes of Disseminated Intravascular Coagulation*. Thomas, Springfield, Ill.
 Hathorn, M., Gillman, T., and Campbell, G. D. (1961). *Lancet*, **1**, 1314.
 Holemans, R. (1965). *Amer. J. Physiol.*, **20**, 511.
 Larsson, Y., Persson, B., Sterky, G., and Thoren, C. (1964). *Lancet*, **1**, 350.
 MacKay, N., and Hume, R. (1964). *Scot. med. J.*, **9**, 359.
 McKay, D. G. (1965). *Disseminated Intravascular Coagulation*. Hoeber, Harper and Row, New York.
 Sandberg, H., Muller, O., Bellet, S., Feinberg, L. J., Gagnon, F., and Gelber, L. (1963). *Amer. J. med. Sci.*, **245**, 153.
 Tanser, A. R. (1967). *J. clin. Path.*, **20**, 231.
 Todd, A. S. (1959). *J. Path. Bact.*, **78**, 281.
 West, R. O., Sawrey, K. R., Bird, G. S., Wilson, D. L., and Hatcher, J. D. (1965). *Clin. Sci.*, **29**, 41.