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

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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 Cubital venous blood samples were withdrawn, with the minimum of venous occlusion, immediately before and after the exercise and the level of circulating plasminogen activator was assayed by the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 $A\text{-}B/_A \times 100$ where A and B represented the resting and post-exercise euglobulin lysis times, respectively.

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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 ($t = 3{\cdot}601$, $P < 0{\cdot}001$). 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) ($t = 2{\cdot}786$, $0{\cdot}005 < P < 0{\cdot}01$). 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)*[3]		*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
[3] 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) observed 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.

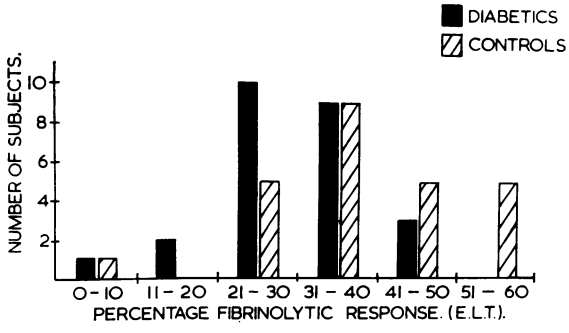

FIG. 1. *The frequency distribution of percentage fibrinolytic response to moderate exercise in young diabetic subjects and controls.*

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 antihaemophilic globulin of 70%,

TABLE II

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

Subject No.	Diabetics				Controls			
	Euglobulin Lysis Time				Euglobulin Lysis Time			
	Before	After	Increase (%)		Before	After	Increase (%)	
1	88	55	38		140	71	49	
	81	54	33	35	660	332	50	49
	69	45	35		500	257	49	
2	101	65	36		240	110	54	
	117	92	21	28	304	136	55	55
	110	80	27					
3	69	47	32		195	120	48	
	80	59	26	27	105	58	45	
	133	101	24		135	80	40	43
					77	45	42	
					83	51	39	
					148	92	38	
4	93	53	44		620	440	29	
	78	44	44	40	84	60	29	
	141	50	33		270	200	26	29
					318	213	33	
					210	156	26	
5	61	41	20		61	35	43	
	62	52	16	20	75	42	44	
	66	50	24		57	35	39	37
					65	45	31	
					81	50	38	
6	138	71	49		115	70	39	
	165	71	57	49	146	96	34	37
	83	50	40					
7	75	50	33		105	60	43	
	81	45	44	38	131	78	41	39
	65	40	39		77	47	39	
					76	50	34	
8	108	57	48		550	440	20	
	114	66	34	41	211	172	19	24
	147	84	43		745	505	32	
9	83	64	23	27	143	60	58	
	90	63	30		150	65	57	58
					150	62	59	
10	79	50	37		105	63	40	
	117	74	31	36	95	59	38	40
	91	55	40		103	60	42	
11	95	61	36		255	124	51	
	126	81	36	33	315	153	51	51
	86	62	28		262	129	51	
12	508	398	22		120	95	21	
	340	278	19	21	159	116	27	

Subject No.	Diabetics				Controls			
	Euglobulin Lysis Time				Euglobulin Lysis Time			
	Before	After	Increase (%)		Before	After	Increase (%)	
12	635	494	22		272	192	29	
					151	106	30	26
					245	185	24	
					132	98	26	
13	105	70	33		494	211	57	
	72	52	28	30	720	370	48	52
					274	137	50	
14	72	52	28		100	54	46	
	75	45	40	33	113	56	50	50
					110	52	53	
15	212	145	32		112	52	54	
	146	104	29	30	223	104	53	54
					180	80	56	
16	62	36	42		257	143	44	
	68	56	18	30	120	80	33	38
	60	55	31		140	90	36	
17	69	46	33		72	65	10	
	70	47	33	33	108	86	20	
					200	184	8	10
					320	310	3	
18	91	58	36		189	99	48	
	93	73	22	33	270	137	49	49
	95	55	42					
19	80	47	42		65	51	22	
	80	54	32	37	84	56	33	29
					94	64	32	
20	63	39	38		250	160	36	
	64	39	39	35	230	150	35	36
	70	50	29					
21	79	58	27		116	87	25	
	81	48	41	34	108	82	24	24
					110	85	23	
22	104	73	30		120	75	38	
	88	60	32	27	500	300	40	39
	73	60	18					
23	97	85	12		174	89	49	
	98	93	5	9	135	77	43	44
					100	60	40	
24	305	240	21		539	324	40	
	400	325	19	20	269	162	40	40
25	91	53	42		107	63	42	
	75	46	39	41	76	45	41	40
					95	60	37	

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.

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