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Changes in the fibrinolytic system components during extracorporeal circulation

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In 1954 Gibbon, after many years of experimental work, achieved the first successful total body perfusion in a human patient using a form of cardiopulmonary bypass. A prime aim of all workers in this field since then has been to produce safe and adequate anticoagulation of the blood during such a procedure, and to reverse it swiftly and safely at the end of the operation. Furthermore it seems advisable that there should be no (or at the most a minimal and insignificant) alteration in both the cellular and humoral elements of the blood due to this procedure. Although satisfactory results have been achieved, the methods used are still far from perfect.

Reports of haematological changes during extracorporeal circulation have varied, particularly regarding the coagulation mechanism. Where disturbances of this mechanism have been reported they have been variously ascribed to the effect of pyrogens, the type of apparatus used, the duration and rate of perfusion (Brown and Smith, 1958), inadequately cleaned and sterilized equipment, incompatible blood or inadequate haemostasis (DeWall, Long, Gemmill, and Lillehei, 1959), active trauma (Osborn, MacKenzie, Shaw, Perkins, Hurt, and Gerbode, 1955), massive blood transfusion (Matzke, Jensen, and Rygg, 1961), heparin rebound phenomenon (Holemans, Vermylen, and Verstraete, 1960), *de novo* development of circulating anticoagulants (von Kaulla and Swan, 1958), activation of the thromboplastin mechanism with consumption of essential coagulation factors (Ollendorf, Storm, Rygg, and Arnfred, 1961), secondary hypocoagulation after heparin neutralization (Matzke *et al.*, 1961), the type of cardiac lesion (Gans, Lillehei, and Krivit, 1961), and other unknown causes (Cooley, Belmonte, DeBakey, and Latson, 1957).

Thrombocytopenia constantly follows the procedure, and it is believed that it can cause a serious bleeding disorder (Perkins, Osborn, Hurt, and Gerbode, 1956). Excessive fibrinolysis, however, has been the most commonly reported disturbance and has sometimes given rise to serious bleeding (Perkins, Osborn, and Gerbode, 1958). Activation of the fibrinolytic system has since been shown to be due to an *in vivo* factor, which has sometimes apparently been dependent on the rate and duration of perfusion and on the *p*H changes occurring during this (von Kaulla and Swan, 1958), but the time of onset of maximum fibrinolytic activity has borne no relation to any specific cause. Reports on alterations of components of the fibrinolytic system (namely fibrinolysin and fibrinogen) due to bypass have varied, and little heed has been paid to the inhibitor systems.

It is the object of this study to determine and discuss changes in the fibrinolytic system observed in 18 patients with cardiac disease who were submitted to open-heart surgery and cardiopulmonary bypass.

MATERIALS

Eighteen patients who underwent cardiopulmonary bypass and open-heart surgery for various cardiac diseases in the Royal Infirmary of Edinburgh formed the subject of this study. Table I lists the relevant particulars of each patient. The patients were selected by their anticipated availability for obtaining adequate blood specimens at fixed times throughout their operative procedure.

METHODS

The method of extracorporeal circulation, using a Melrose N.E.P. rotating disc oxygenator, has previously been described (MacKenzie, Davies, Masson, and Wade, 1963) and also the heparinization and reversal of anticoagulation procedures (Cumming, Davies, Kamel, MacKenzie, Masson, and Wade, 1964). Specimens were taken as possible (1) before anaesthesia, (2) a few minutes before bypass, (3) a few minutes after commencing bypass, (4) at the end of bypass, (5) a few minutes after reversal of the anticoagulation, and (6) 30 minutes later. The 'fibrino-

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TABLE I

CLINICAL AND PERFUSION DATA OF 18 PATIENTS UNDERGOING CARDIOPULMONARY BYPASS

No.	Age/Sex	Weight (kg.)	Diagnosis	Duration of Bypass (min.)	Rate of Perfusion (ml./kg./min.)	Blood Loss (ml./kg.)
1	31 M	65	Aortic stenosis	70	49	(1) 2 (2) 3
2	4 F	17	V.S.D.	40	95	(1) 40 (2) Negligible
3	54 M	54	Double mitral	85	59	(1) 5 (2) 5
4	57 F	56	Calcified aortic cusps	84	66	(1) 3 (2) 4
5	22 F	50	Mitral incompetence	88	64	(Death from cardiac arrest)
6	9 F	26	V.S.D.	31	87	(1) 25 (2) Negligible
7	24 F	48	V.S.D.	83	76	(1) 20 (2) 23
8	8 M	23	V.S.D.	47	93	(1) 40 (2) Negligible
9	15 F	54	V.S.D.	34	69	(1) 44 (2) Negligible
10	20 F	52	V.S.D.+A.S.D.	47	67	(1) 19 (2) Negligible
11	13 M	34	V.S.D.	25	83	(1) 36 (2) 34
12	33 M	58	V.S.D.	48	58	(1) 4 (2) 2
13	9 M	29	V.S.D.	85	85	(1) 25 (2) 3
14	18 F	52	A.S.D.+cleft mitral valve	72	65	(1) 12 (2) 5
15	12 M	31	V.S.D.+pulmonary stenosis	90	79	(1) 33 (2) 6
16	32 M	71	Aortic stenosis	52	48	(1) 8 (2) 4
17	37 M	77	Aortic stenosis	70	44	(1) 6 (2) 2
18	15 M	38	V.S.D.	91	82	(1) 10 (2) 7

V.S.D. and A.S.D. = ventricular and atrial septal defect respectively
(1) and (2) = on operation day and on first post-operative day respectively

lytic activity' and/or 'activator activity' was measured by a plasma euglobulin lysis time (Macfarlane and Pilling, 1946) giving in our laboratory a normal value of more than 80 minutes. Fibrinogen was assayed by a Kjeldahl method (N = 200–500 mg./100 ml.). Plasma plasminogen was estimated by a caseinolytic assay (Remmert and Cohen, 1949) (N = 239–443 units). The 'antifibrinolysins' were measured by their ability to inhibit the action of a fibrinolysin or plasmin (Thrombolysin®) on a clot indicator system (Bozzo, Piomelli, and Schettini, 1956) (normal in our hands = 4–8 units). The techniques as applied in this study have been described elsewhere (Kamel, 1963).

RESULTS

Table II shows the results obtained in these tests.

FIBRINOLYSIS Increased fibrinolysis was found in all the patients at some time during the procedure. On nine occasions the maximum fibrinolytic activity was found during bypass, on seven occasions after reversal of anticoagulation, and on two occasions during anaesthesia but immediately before the onset of bypass. Enhanced fibrinolytic activity was transient and had abated within 30 minutes of reversal of the coagulation mechanism. In spite of the demonstration of an abnormal fibrinolytic activity in all the patients, only one transient clinically significant fibrinolytic state was encountered (case 9), which caused excessive blood loss for nearly 30 minutes after reversal of coagulation but which abated spontaneously. Apart from case 5 (who died from cardiac arrest) all other patients recovered from the operative procedure and showed no serious clinical disturbances of their haemostatic mechanism.

FIBRINOGEN In all the patients, and usually concomitant with a rise in fibrinolytic activity, a variable decrease in fibrinogen level was noted (Fig. 1).

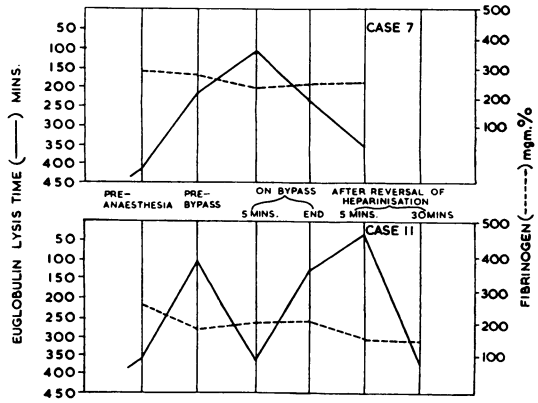

FIG. 1. *Effect of cardiopulmonary bypass on fibrinolysis (measured by euglobulin lysis time) and on fibrinogen level in plasma in two patients.*

PLASMINOGEN Of seven cases in which plasminogen levels were determined five showed a decrease which had reverted spontaneously to pre-operative levels by the time the final sampling was done 30 minutes after reversal of the anticoagulation (Fig. 2). One case showed a final rise in plasminogen (No. 14) and another a final decrease (No. 13).

TABLE II

CHANGES IN THE FIBRINOLYTIC SYSTEM IN 18 PATIENTS UNDERGOING CARDIOPULMONARY BYPASS

No.	Test	Before Anaesthesia	Before Bypass	On Bypass		After Coagulation Reversal	
				After Few Minutes (<10 minutes)	At the End	After Few Minutes	After 30 Minutes
1	ELT	220	109	214		185	203
	FN	202	220			158	264
	AF	7	< 1				7·5
2	ELT		135	60		140	
	FN		222			175	
	AF		6			8	
3	ELT	>300	100	>300	60	>300	>300
	FN	282	Clot lysed before retraction	212	Clot lysed before retraction	212	245
	AF	7·5	9	10	8·5	7	7·5
4	ELT	>330	170	163		>330	
	FN	232	195	270		217	
	AF	7·5	7	7·5		7	
5	ELT		>300	200		70	
	FN		400	375		Clot lysed before retraction	
	AF		8	6		4	
6	ELT	302	>580	295		280	
	FN	230	273	261		262	
	AF	6	5	5		4	
7	ELT	>420	223	107		334	
	FN	275	267	222		242	
	AF	9	9	9		10	
8	ELT	>506	>488	305		431	430
	FN	243	235	288		180	246
	AF	3	2	4		3	6
9	ELT	>360	>360	216		11	333
	FN	307	300	181		Clot lysed before retraction	225
	PGN	360	354	282		191	239 (After 1 hour = 300)
	AF	11	10	9		7	8 (After 1 hour = 12)
10	ELT	>300	>300			179	>300
	FN	225	238			156	269
	AF	< 1	< 1			4	5
11	ELT	>360	117	>360	138	33	360
	FN	231	173	183	199	141	137
	PGN	323		252	354	344	
	AF	10	10	9	9	10	10
12	ELT	>400	350	255	190	195	>400
	FN	281	259	235	234	258	184
	PGN	330	313	320	283	339	323
	AF	6	5	4	4	6	8
13	ELT	>360	>360	>360	81	228	>360
	FN	289	228	182	149	213	146
	PGN	325	310	266	265	254	235
	AF	9	2	2	1	1	8
14	ELT	>300	240	>300	>300	>300	>300
	FN	250	205	152	185	260	270
	PGN	183	172	300	238	249	280
	AF	10	9	8	8	8	8
15	ELT	270		210	145	95	330
	FN	195		176	236	137	199
	PGN	275		154	205	210	247
	AF	8		7	6	5	5
16	ELT	248	>360	231	25	50	>360
	FN	189	337	254	237	216	214
	PGN	269	253	262	215	272	270
	AF	5	5	2	3	4	5
17	ELT	>300	>300	>300	105	26	>300
	FN	225	220	190	170	200	231
	AF	1		1	< 1	1	3
18	ELT	322	342	492	232	>500	>500
	FN	240	230	200	150	300	
	AF	1	1	4	6	6	3

ELT=euglobulin lysis time (min.); FN=fibrinogen (mg./100 ml.); PGN=plasminogen (units); AF=antifibrinolytic activity (units)

ANTIFIBRINOLYSINS In eight patients (cases 1, 8, 9, 11, 12, 13, 16, and 17) antifibrinolysins decreased during the operation, returned to normal post-operatively, and sometimes even showed a slight increase above normal after reversal of the anti-coagulation. An overall increase was found in four patients (cases 2, 7, 10, and 18) and a decrease in another four (cases 5, 6, 14, and 15). One patient (case 3) showed an increase in antifibrinolysins before returning to normal levels, and there was virtually no change in one patient (case 4).

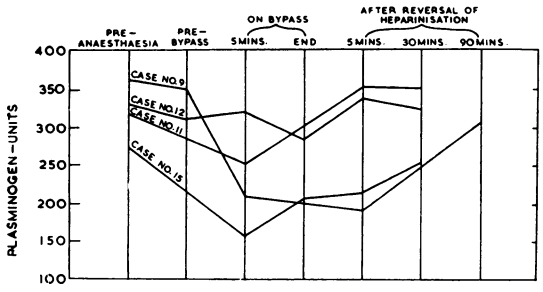

FIG. 2. *Effect on plasminogen blood levels during cardiopulmonary bypass.*

DISCUSSION

From this study of the fibrinolytic system during extracorporeal circulation in open-heart surgery it seems that activation of fibrinolysis is inevitable at some stage during the procedure, though without any serious consequences in the method used.

It is suggested that mechanical trauma might play a part in this increased fibrinolysis either *per se* or through activating thromboplastin, since in most cases the maximum rise in activity has coincided with the end of the bypass. The occurrence of the same phenomenon in seven patients following heparin neutralization might be explained (*a*) by the removal of an inhibitory effect exerted by heparin on the fibrinolytic system (though the role of heparin in fibrinolysis is not clear (von Kaulla and McDonald, 1958)) or (*b*) through a possible toxic effect of hexadimethrine bromide which had not previously been described. Hexadimethrine bromide is now withdrawn from the market because of possible toxic renal effects.

The decreases in fibrinogen and plasminogen levels during cardiopulmonary bypass found in the present study accord with reports of similar decreases associated with a fibrinolytic state (Sawyer, Fletcher, Alkjaersig, and Sherry, 1960; Nilsson and Olow, 1962).

The role of the antifibrinolysins is less certain and has been subject to much less investigation. After some operations an increase of inhibitors has been reported (Sandberg, Tsitouris, and Bellet, 1960), while in some experimentally induced fibrinolytic states there has been an increase followed by a decrease in the antifibrinolysin titre (von Kaulla, 1958). The role of fibrinolytic inhibitors is at present not really understood, largely because of the complicated technical procedures employed in cardiopulmonary bypass, because of the many drugs used during it, and also because of the lack of a simple and accurate method of assaying the antifibrinolysins.

SUMMARY

The changes in the fibrinolytic system observed in 18 patients with cardiac disease who were undergoing open-heart surgery on cardiopulmonary bypass were studied.

This investigation revealed that activation of fibrinolysis is inevitable at some time during the procedure, but it did not cause any serious consequences in the patients studied. Fibrinogen and plasminogen diminution were noted, but changes in the antifibrinolysins were less clear.

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