MECHANISM OF DEVELOPMENT OF HYPERCOAGULATION AND HYPERFIBRINOLYSIS IN ACUTE HYPOXIA

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The secretion of tissue thromboplastic factor and of fibrinolysis activators by the intact vascular wall (especially of the veins) is increased in hypoxia. In this way the authors explain the development of hypercoagulation and hyperfibrinolysis in acute hypoxia.

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Hypoxia, like asphyxia, is accompanied by marked acceleration of blood coagulation [2, 7, 8, 12] and by increased fibrinolysis [8, 13]. At the same time the concentration of natural anticoagulants in the plasma falls [8]. The reason for these changes has not yet been discovered. There are reports in the literature that tissue thromboplastin and plasminogen activators enter the blood stream in hypoxia [13]. However, the source of these compounds is unknown.

Investigations conducted in our Department [5, 6] have shown that in certain physiological and pathological states accompanied by predominance of sympathetic influences (acute blood loss, injection of adrenalin and atropine) the intact vascular wall secretes thromboplastic factor and activators of fibrinolysis into the blood stream. Hypoxia is also accompanied by an increase in tone of the sympathetic division of the autonomic nervous system. The adrenalin concentration in the blood stream rises sharply in this condition.

We therefore carried out an investigation to determine whether the hypercoagulation and hyperfibrinolysis occurring in acute hypoxia are associated with the liberation of tissue factors of blood coagulation by the vascular wall into the general circulation.

EXPERIMENTAL METHOD

Experiments were carried out on 12 dogs weighing from 7 to 15 kg. Under hexobarbital anesthesia an incision was made in the neck, the trachea exposed, and a tracheotomy tube inserted. The left common carotid artery or jugular vein was carefully dissected. The central end of the vessel (nearer the clavicle) was ligated and a stopper was inserted into the peripheral end through a small incision. In this way the sympathetic nerves branching along the course of the vessel were preserved intact. Two cannulas, treated with silicone or paraffin wax, were inserted into the segment of the common carotid artery or jugular vein isolated as described above. The vessel was freed from blood and then perfused with physiological saline heated to 37°.

Acute hypoxia was produced by clamping the tracheotomy tube for 2 min. The effect of samples of perfusion fluid obtained before (3 samples) and after (7 samples) clamping of the tracheotomy tube was studied on the recalcification time [10], the prothrombin consumption [4, 5], thrombin time [9], and fibrinolytic activity of the blood [11] and adhesiveness of the platelets [13]. The samples of perfusion fluid were collected every minute (volume 2 ml). In control investigations 0.5 ml physiological saline was added to the plasma, while in the experimental tests the same volume of perfusion fluid was added.

EXPERIMENTAL RESULTS

Perfusion fluid passed through the humorally isolated segments of the common carotid artery or jugular vein caused a decrease in the recalcification time, an increase in prothrombin consumption, slight shortening of the thrombin time (this effect was not always observed), and an increase in fibrinolytic ac-

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TABLE 1. Effect of Perfusion Fluids Obtained from Isolated Segment of Artery before and after Onset of Hypoxia on Certain Blood Coagulation Indices in Dogs

Index	Statistical index	Control	Sample (experiment)									
			1	2	3	4	5	6	7	8	9	10
Recalcification time (in sec)	M	141,0	111	114	112	102	99	96,5	103	115	112	112
	P_1		<0,01	<0,02	<0,02	<0,01	<0,05	<0,01	<0,01	<0,05	<0,05	<0,05
	P_2		—	—	—	—	—	<0,05	—	—	—	—
Prothrombin consumption (in sec)	M	48	58	56	56	62	66	69	66	56	56	58
	P_1		<0,001	<0,01	<0,02	<0,01	<0,01	<0,001	<0,01	<0,05	<0,02	<0,01
	P_2		—	—	—	<0,05	<0,05	<0,001	<0,05	—	—	—
Thrombin time (in sec)	M	44,4	43,3	42	40,6	42	41,6	39,6	41,6	40	40	45,4
	P_1		—	<0,02	<0,05	—	—	<0,02	—	<0,02	<0,05	—
	P_2			—	—	—	—	—	—	—	—	<0,01
Fibrinolysis (in min)	M	56,6	49,8	48,4	43,3	38	47	36	40,7	40,7	39,7	38,5
	P_1		<0,01	<0,01	<0,01	<0,05	<0,05	<0,1	<0,05	<0,05	<0,05	<0,05
	P_2		—	—	—	—	—	—	—	—	—	—
Number of adhesive platelets (per cm^3)	M	135 000	—	—	171 000	—	144 000	—	177 000	—	—	—
	P_1				<0,05		—		<0,05			
	P_2						<0,1					
Adhesiveness index	M	1,39	—	—	1,64	—	1,47	—	1,43	—	—	—
	P_1				<0,05		<0,05	—	—			
	P_2						<0,05	—	<0,05			

Note. Here and in Table 2, samples 1, 2, and 3 were obtained before compression of the trachea, 4 and 5 during compression, and 6-10 after compression of the trachea. P_1 is relative to the control, P_2 relative to the data before hypoxia, i.e., to sample 3.

TABLE 2. Effect of Perfusion Fluids Obtained from Isolated Segment of Jugular Vein before and after Onset of Hypoxia on Certain Blood Coagulation Indices in Dogs

Index	Statistical index	Control	Sample (experiment)									
			1	2	3	4	5	6	7	8	9	10
Recalcification time (in sec)	M	125	95	100	94	84	88	98	84	90	95	90
	P_1		<0,05	<0,01	<0,01	<0,01	<0,01	<0,05	<0,01	<0,01	<0,05	<0,01
	P_2					<0,05	—	—	<0,05	—	—	—
Prothrombin consumption (in sec)	M	19	23	22	22	24	24	24	22	26	24	24
	P_1		<0,001	<0,05	<0,05	—	<0,05	<0,05	—	<0,05	<0,05	<0,05
	P_2					<0,05	—	—	—	—	—	—
Thrombin time (in sec)	M	40	37	36	35	35	34	35	36	35	36	36
	P_1		<0,05	<0,05	<0,05	<0,05	<0,01	—	—	—	—	—
	P_2					—	—	—	—	—	—	—
Fibrinolysis (in min)	M	61	53	53	53	43	44	50	41	56	43	44
	P_1		—	—	—	<0,05	<0,05	<0,01	<0,05	—	<0,01	<0,05
	P_2		—	—	—	<0,05	<0,01	—	<0,01	—	<0,05	<0,05

tivity of the blood and adhesiveness of the platelets (Tables 1 and 2). The effects observed could only be caused by the entry of tissue factors of blood coagulation into the perfusion fluid from the vessel wall. In fact, the increase in prothrombin consumption could only be due to liberation of thromboplastic factor into the perfusion fluid. Shortening of the thrombin time evidently was due to liberation of antiheparin substance from the tissues. The increase in fibrinolysis could be attributed to the entry either of plasminogen activators or of tissue lysokinases into the perfusion fluid. Both substances have been found in arteries and veins. Finally, the increase in adhesiveness of the platelets was probably due to liberation of adhesiveness factor from the vessel walls. Under the influence of perfusion fluid samples 1-2 min after compressing the trachea the recalcification time was still further reduced, the prothrombin consumption increased, fibronolysis activated (by perfusion fluid from the veins), and adhesiveness of the platelets diminished. This response continued for 2-3 min after removal of the clamp from the tracheotomy tube. The increased fibrinolysis persisted throughout the experiment. From 7 to 10 min after the beginning of the experiment the thrombin time returned to normal under the influence of arterial perfusion fluid, indicating cessation of the liberation of antiheparin substance into the blood stream.

The hypercoagulation occurring in acute hypoxia can therefore be explained by increased liberation of tissue thromboplastic factor from the vascular wall into the general circulation. The increase in fibrinolysis, on the other hand, is explained partly by liberation of tissue lysokinases (and also, perhaps, of plasminogen activators), mainly from the walls of the veins. An important role in this reaction undoubtedly belongs to excitation of the sympathetic nervous system. However, hypoxia alone can bring about changes in permeability of the vascular wall and the release of the tissue factors of blood coagulation into the general circulation.

Until recently doubts were expressed whether the increase in fibrinolysis is a primary response to hypoxia or whether it arises only after the formation of clots in the blood stream [1, 8]. Since this response arises within 1-2 min after clamping the trachea, it can be assumed that the increase in fibrinolysis is due to the hypoxia itself.

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