ROLE OF THE LUNGS IN FIBRINOLYTIC PROCESSES IN VIVO

G. M. Solov'ev, Ch. S. Guseinov,
G. Ya. Gebel', V. N. Chistyakov,
and E. V. Flerov

UDC 612.115-06:612.215

In experiments on 22 dogs receiving intravenous injections of 30% lactic acid solution, the blood flowing from the lungs was found to contain proactivators of fibrinolysis and fibrinolytic activity, and its plasminogen content was higher than that of blood flowing into the lungs.

Previous investigations have shown that many organs and tissues of the body possess a high content of tissue thromboplastin and activators and proactivators of plasminogen (profibrinolysin). In man, the lungs and brain, uterus, lymph glands, prostate, and thyroid are particularly rich in these factors. Activators and proactivators of fibrinolysis are also found in exudates of traumatic and inflammatory origin [1, 4-6, 11]. In some pathological states (extensive and traumatic operations, blood loss, premature separation of the placenta during childbirth, etc.) local liberation of tissue activator and tissue thromboplastin takes place. Sometimes the liberation of these tissue substances is generalized in character, leading to the development of subacute fibrinolysis. In all probability the tissues and organs of the living body are the sources from which tissue proactivators and, possibly, tissue thromboplastin are periodically liberated into the blood stream [2].

Detection of the presence of proactivators and determination of the degree of fibrinolytic activity of the blood flowing from the lungs and into the lungs are of great importance. The object of the present investigation was to determine these indices over a period of time and their changes under the influence of drugs activating fibrinolysis in vivo. Particular attention was paid to the blood concentration of proactivators, because an increase in fibrinolytic activity is associated with elevation of the blood level of activators, and not with any change in concentration of the other components of the fibrinolytic system [4, 11].

EXPERIMENTAL METHOD

Experiments were carried out on 22 mongrel dogs weighing from 5 to 16 kg.

Before the experiment began the dogs received a subcutaneous injection of 1% morphine solution. From 30 to 35 min later, under local anesthesia, the left external jugular vein, and both femoral veins and arteries were exposed. Under fluoroscopic control the right and left chambers of the heart were catheterized. Before general heparinization (heparin "Richter," 2-3 ml of solution per animal) began, samples were taken from the pulmonary artery and vein. Next, after injection of 1% hexobarbital solution (1 ml/kg), the animal was intubated and intravenous injection of hexobarbital (total dose 30-50 mg) and of 30% lactic acid solution began. This injection continued until the appearance of a definite vascular response (spasm) in the lungs. Usually 7-8 min after the beginning of lactic acid injection, spasm of the pulmonary vessels was observed, and lasted for 15-16 min, after which the injection of lactic acid was resumed. Altogether the injections of lactic acid were repeated 7 times. Blood samples were taken at the height of the spasm. The total dose of lactic acid given in each experiment varied from 800 to 1000 mg.

Injection of morphine and hexobarbital gave rise to a state of respiratory acidosis in the animals (pH_A 7.17±0.3, pH_V 7.02±0.04).

Research Institute of Clinical and Experimental Surgery, Ministry of Health of the USSR, Moscow.
(Presented by Academician B. V. Petrovskii.) Translated from Byulleten' Éksperimental'noi Biologi i Meditsiny, Vol. 69, No. 5, pp. 22-25, May, 1970. Original article submitted October 14, 1968.

TABLE 1. Content of Profibrinolysin and Proactivators of Fibrinolysis in Pulmonary Blood of Dogs Following Injection of Lactic Acid

Injection of lactic acid	Blood sample	Profibrinolysin (in sec)			Proactivators (in sec)			Antifibrinolysin (in sec)		
		M	$\pm\sigma$	$\pm m$	M	$\pm\sigma$	$\pm m$	M	$\pm\sigma$	$\pm m$
Before injection	V_0	454	79	20	456	71	18	236	46	12
	A_0	334	43	12	412	56	15	198	17	9
	LA_0	367	74	18	458	96	23	228	50	14
1st	A_1	355	92	29	352	76	22	238	70	31
	LA_1	299	50	17	348	59	19	213	58	33
	V_1	368	240	139	518	51	29	243	120	69
2nd	A_2	339	76	29	346	82	24	257	107	63
	LA_2	304	44	17	361	51	16	—	—	—
	V_2	410	71	51	475	163	117	250	27	19
3rd	A_3	357	132	50	336	110	35	210	42	30
	LA_3	351	43	15	325	55	18	—	—	—
	V_3	412	66	54	491	112	98	251	44	37
4th	A_4	—	—	—	288	93	12	—	—	—
	LA_4	303	68	39	330	56	28	—	—	—
5th	A_5	252	90	53	275	53	27	212	41	30
	LA_5	305	92	66	351	133	78	—	—	—
6th	A_6	—	—	—	327	60	43	—	—	—
	LA_6	—	—	—	293	39	28	—	—	

Legend to Tables 1 and 2: V) blood from femoral vein; A) arterial blood flowing from lungs; LA) venous blood entering lungs.

TABLE 2. Scatter of Data for Fractional Changes in Concentration Proactivators of Fibrinolysis in Venous and Arterial Blood in the Lungs after Injection of Lactic Acid

Injection of lactic acid	Blood sample	Profibrinolysin (in sec)	Proactivators (in sec)	Antifibrinolysin (in sec)
Before injection	V_0	300—640	320—575	190—380
	A_0	250—405	300—490	180—220
	LA_0	285—550	350—760	180—375
1st	A_1	195—540	195—505	130—325
	LA_1	205—370	290—480	180—280
	V_1	135—610	465—565	120—360
2nd	A_2	250—515	185—440	190—380
	LA_2	250—360	285—435	—
	V_2	360—460	360—590	190—310
3rd	A_3	260—640	225—610	180—240
	LA_3	280—370	260—400	
4th	A_4	280—280	255—310	—
	LA_4	230—370	280—410	—
5th	A_5	150—325	220—320	—
	LA_5	240—370	260—505	

The degree of oxygenation of the arterial blood under these conditions was 80.72±1.76%, and that of mixed venous blood 41.29± 2.72%.

Injection of lactic acid led to the appearance of metabolic acidosis (pH_A 6.93±0.06, pH_V 6.74±0.08) and to changes in the degree of oxygenation of the blood ($\%HbO_{2A}$ 76.52±1.73; $\%HbO_{2V}$ 33.16±2.54).

The following indices of function of the fibrinolytic system were studied: the blood plasminogen (profibrinolysin) concentration by Blix's method [7, 8], as modified by Larrien [9], and the blood antifibrinolysin level by Nilsson's method [10].

The numerical results were subjected to statistical analysis by the Fisher – Student method.

EXPERIMENTAL RESULTS

Under the influence of intravenous injection of lactic acid, the concentration of proactivators in blood of the pulmonary vessels was increased, and the time of lysis of the fibrin clot was correspondingly reduced. The concentration of components of the fibrinolytic system (plasminogen, antifibrinolytic activity, proactivators) in the pulmonary blood is shown in Tables 1 and 2. The concentration of proactivators in arterial blood was slightly increased over that of venous blood entering the lungs. In other words, lysis of the fibrin clot (bovine blood) in the presence of arterial blood flowing from the lungs took place in a shorter time. The concentration of plasminogen in arterial blood also was higher than in venous blood. In blood samples taken from the femoral vein at the beginning and end of the operation, the content of these components of the fibrinolytic system of the blood was appreciably lower than in the pulmonary vessels. No changes in the concentration of the antifibrinolytic fraction of the blood were observed after injection of lactic acid.

It will be noted that after injection of 30% lactic acid solution by intravenous drip, conditions favoring development of uncompensated metabolic acidosis and activation of fibrinolysis were created in the animals. As Tables 1 and 2 show, by the end of the experiment the fibrinolytic activity in all main vascular trunks was appreciably increased.

Activation of the fibrinolytic system in dogs under the influence of lactic acid injections in these experiments was accompanied by increased liberation of proactivators of fibrinolysis from the lungs into the blood stream, and this in turn accelerated lysis of a fibrin clot of donor's blood. It is impossible to be certain that the blood plasminogen concentration was increased. According to [3], the time of fibrinolytic activity of blood flowing from the lung is shorter than that of blood entering the lung. The present experiments demonstrated an active role of the lungs in maintenance of the fibrinolytic "tone" of the body by the release of proactivators of the fibrinolytic system into the blood stream.

However, it must be pointed out that the concentration of proactivators was not increased in all samples of arterial blood compared with that in mixed venous blood entering the lungs. This finding is in agreement with data obtained by observations on patients with various cardiovascular diseases in which the lungs were shown to be concerned to some degree or other in maintenance of fibrinolysis in the body.

LITERATURE CITED

1. G. V. Andreenko, Fibrinolysis. Chemistry and Physiology of the Process. Clinical Use of Fibrinolysis [in Russian], Moscow (1967).
2. D. M. Zubairov, The Clotting Power of the Blood [in Russian], Kazan' (1966).
3. M. M. Kalnyn', in: Treatment with Anticoagulants and Fibrinolytic Substances [in Russian], Kaunas (1965), p. 37.
4. M. S. Machabeli, The Blood Clotting System [in Russian], Tbilisi (1961).
5. O. K. Albrechtsen, Brit. J. Haemat., 5, 284 (1957).
6. T. Astrup, Blood, 11, 781 (1956).
7. S. Blix, Acta Med. Scand., 171, 83 (1962).
8. S. Blix, Scand. J. Clin. Lab. Invest., 14, 528 (1962).
9. M. I. Larricu, Nouv. Rev. Franc. Hémat., 5, 261 (1965).
10. I. M. Nilsson, A. Sjoerdsma, and I. Waldenstron, Lancet, 1, 1322 (1960).
11. S. Sherry, A. P. Fletcher, and N. Alkjaersig, Physiol. Rev., 39, 343 (1959).