ROLE OF BLOOD COAGULATION IN THE PATHOGENESIS OF ACUTE EXPERIMENTAL PNEUMONIA

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Experiments on rabbits showed that blood coagulation and thrombosis developing in blood vessels in the inflammatory foci in acute experimental pneumococcal pneumonia are not abolished by treatment with bicillin-3. The pneumonia likewise is not completely resolved. Treatment of pneumonia with heparin reduces the severity of the inflammation and abolishes thrombosis. The most effective treatment of pneumonia was by a combination of bicillin-3 and heparin. It is concluded that hypercoagulation of the blood and vascular thrombosis are components of pneumonia and respond to heparin.

The role of blood coagulation and thrombosis in the pathogenesis of acute pneumonia has received little attention in the literature. There are reports only of acceleration of blood coagulation in patients at the height of the disease [1, 2].

It was accordingly decided to study the role of blood coagulation and vascular thrombosis in the development of acute experimental pneumonia and the examine the effect of antibacterial therapy and of heparin on these processes and on the course of pneumonia.

EXPERIMENTAL METHOD

In 101 rabbits of both sexes weighing 2-3 kg acute pneumonia was produced by intratracheal injection of a 24-h culture of type III pneumococci (one billion bacterial cells/kg body weight) mixed with 10% polyvinyl alcohol solution in the ratio of 1:1 (D. S. Sarkisov's method).

Thromboelastography (TEG) was carried out the the ISK-64 thromboelastograph. The plasma recalcification time (method of Bergerhof and Rock), the plasma heparin tolerance (Poller's method), the prothrombin activity (by Tugolukov's method), activity of factors V (Wolf's method) and VII (method of Koller, Lilliger and Duckert), the thrombin time (Perlick's method), and the fibrinogen content and fibrinolytic activity on the plasma (Bidwell's method) were determined in 20 of 101 rabbits.

The animals were divided into four groups. The rabbits (27) of group 1 received no treatment after the production of pneumonia (control), the animals (27) of group 2 were treated with bicillin-3, the 26 rabbits of group 3 were treated with heparin, and the 21 rabbits of group 4 were treated with heparin combined with bicillin-3. The bicillin-3 was injected intramuscularly in a dose of 60,000 i.u./kg once every six days, and heparin in a dose of 1,200 units/kg daily.

The rabbits of the experimental groups were sacificed 11 or 19 days, and those of the control group 1-2 or 11 days (14 rabbits) after infection. Three rabbits of the control group died on the seventh to tenth days after infection. In all cases a macroscopic description and histological investigation of section through each lobe of the lung were carried out. Pieces of the lungs were embedded in celloidin-paraffin and the sections were stained with hemalum and eosin, and by the methods of Van Gieson, Gram-Weigert, and Mallory.

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TABLE 1. State of Blood Clotting System in Rabbits with Acute Experimental Pneumonia Depending on Type of Treatment During First Days after Infection (M ± m)

Index studied	Initial data	Control group	Type of treatment: bicillin-3	Type of treatment: heparin	Type of treatment: bicillin-3 and heparin
Recalcification time (in sec)	71,0±5,8	64,2±5,9	45,6±3,5	79,0±3,5	85,5±9,0
P			<0,01		
Heparin tolerance (in min)	6,0±0,3	2,4±0,2	3,8±0,3	7,8±0,4	4,6±0,2
P		<0,001	<0,001		<0,001
Prothrombin activity (%)	101,5±2,6	150,1±3,5	168,6±3,8	105,0±1,9	107,8±1,6
P		<0,001	<0,001		
Factor V (%)	99,5±1,7	120,3±1,8	139,4±3,4	104,0±1,7	107,2±2,1
P		<0,001	<0,01		<0,02
Factor VII (%)	96,1±3,3	197,6±10,1	222,7±10,2	102,3±2,4	111,5±3,4
P		<0,001	<0,001		<0,02
Fibrinogen (mg %)	198,6±6,2	365,0±34,5	324,0±36,8	287,1±26,4	624,0±46,6
P		<0,01	<0,02	<0,05	<0,001
Thrombin time (in sec)	31,3±1,0	27,4±2,2	26,1±1,1	41,8±2,8	36,6±3,0
P			<0,001	<0,001	
Fibrinolytic activity (%)	29,7±2,5	19,7±4,8	24,2±6,1	35,7±2,3	33,4±2,6
TEG: *R* (min))	5,5±0,18	2,6±0,31	2,6±0,48	5,8±0,43	5,1±1,18
P		<0,001	<0,001		
TEG: *K* (min))	2,7±0,12	2,5±0,25	3,5±0,52	3,8±0,38	3,7±0,86
P				<0,05	
TEG: *S* (min))	13,4±0,19	12,7±1,02	12,8±0,99	14,2±0,21	15,4±1,54
TEG: *Ma* (in cm)	5,2±0,07	5,4±0,14	5,6±0,26	5,6±0,16	5,6±0,22
P				<0,05	
TEG: $\frac{Ma}{R+K}$	6,9±0,25	11,0±1,41	12,8±2,20	6,0±0,54	9,7±2,12
P		<0,01	<0,02		
TEG: $<\alpha$ (in deg.)	31,7±0,85	39,0±2,42	42,5±3,90	29,4±2,20	34,0±4,40
P		<0,001	<0,01		
TEG: Index tan $\alpha \cdot 160$	101,0±3,90	130,0±11,3	156,0±22,8	94,0±9,30	116,0±19,7
P		<0,02	<0,02		

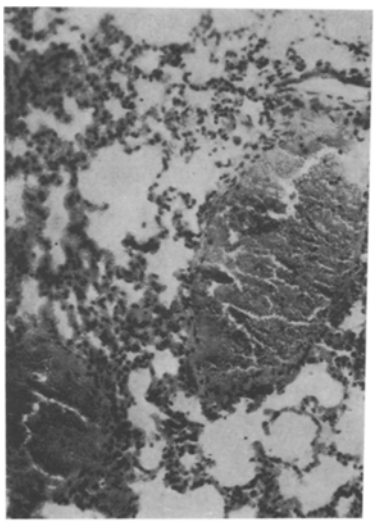

Fig. 1

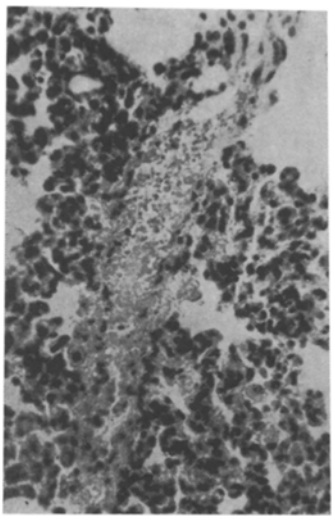

Fig. 2

Fig. 1. Thrombosis in vessels of inflammatory focus in rabbit of control group with acute experimental pneumonia. Here and in Figs. 2 and 3, section stained with hemalum eosin, Objective 10, homal 2.

Fig. 2. Focus of resolution of inflammation with thrombosis in lumen of arteriole in rabbit with acute experimental pneumonia after treatment with bicillin-3.

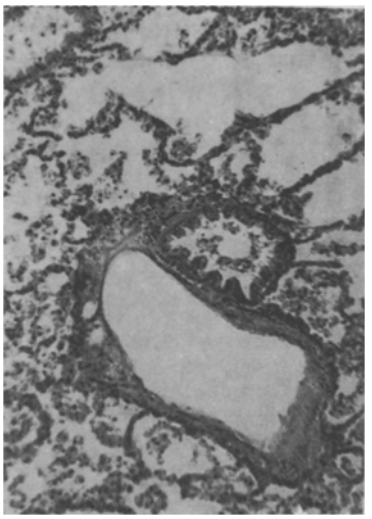

Fig. 3. Pattern of resolving acute pneumonia with macrophagal reaction in rabbit after treatment with bicillin-3 combined with heparin.

EXPERIMENTAL RESULTS

The investigation showed that acute pneumonia in the rabbits of groups 1 and 2 is accompanied on the first days after infection by hypercoagulation of the blood. This was shown by acceleration of the general clotting power of the blood (TEG, plasma recalcification time, plasma heparin tolerance), by an increase in procoagulant activity of the anticlotting system (thrombin time, fibrinolytic activity). In the rabbits of groups 3 and 4 at these times, while procoagulant activity was increased and no changes were found in the anticlotting system, the total clotting power of the blood was not significantly different from originally (Table 1).

At the time of sacrifice, i.e., on the eleventh and nineteenth days after infection, the blood of the rabbits of group 1 still retained a tendency toward hypercoagulation. In the animals of group 2 by this time the procoagulant activity remained increased, but no changes were found in the anticlotting system and the total clotting power of the blood. Under the influence of heparin treatment (group 3), activity of the procoagulants except fibrinogen was down to normal, fibrinolytic activity was slightly increased, and blood clotting was slowed.

Morphological investigation showed that one or two days after infection the rabbits of group 1 had signs of progressive pneumonia with inflammatory edema, with accumulation of fibrin in the exudate, and with widespread thrombosis in the capillaries and arterioles in the foci of inflammation. Three animals which died showed a typical picture of lobar pneumonia with marked thrombosis in the small vessels. In the other 14 animals, killed 11 days after the beginning of the experiment, progressive focal pneumonia was observed, with the accumulation of a serous exudate with or without leukocytes and mixed with fibrin and often with erythrocytes in large groups of alveoli, by thickening of the alveolar septa and by thrombosis in the capillaries and arterioles (Fig. 1). In some sections areas of abscess formation were seen. The macrophagal response was well marked.

Microscopic investigation of sections through the lungs of the rabbits of group 2 showed zones with signs of well marked inflammation. Thrombosis was seen much less frequently in the small blood vessels and capillaries than in group 1. Areas with signs of inflammation were found chiefly in the zone of thrombosed vessels (Fig. 2). The macrophagal reaction was slight. In the animals of this group no significant difference was found in the microscopic picture of the pneumonia in the lungs of rabbits sacrificed 11 and 19 days after the beginning of infection.

In the rabbits of group 3 the inflammation in the lungs showed a tendency to resolve with a marked macrophagal reaction. In most cases thrombosis was not present in the vessels, and thrombi found in occasional sections were in the stage of absorption.

In the study of sections of the lungs of the animals of group 4 no pneumonic foci were found. Only in some sections was a serous exudate containing leukocytes present in the alveoli. No changes in the blood vessels, including thrombosis, were present in rabbits sacrificed 11 or 19 days after infection (Fig. 3).

In acute experimental pneumococcal pneumonia marked hypercoagulation of the blood combined with thrombosis in the blood vessels of the inflammatory focus are thus observed and are not abolished by antibiotic therapy (bicillin-3). Administration of heparin alone in most cases prevented thrombosis and considerably reduced the severity of the inflammation. Combined treatment of the experimental pneumonia with antibiotics (bicillin-3) and heparin was the most effective method.

It can thus be concluded that hypercoagulation of the blood and vascular thrombosis are interconnected processes with an important role in the pathogenesis of acute experimental pneumonia.

LITERATURE CITED

1. N. M. Evdokimov, The State of the Clotting and Anticlotting Systems of the Blood in Influenza and Certain Diseases of the Lungs. Author's Abstract of Candidate's Dissertation, Leningrad (1968).
2. V. I. Patrushev, Lab. Deol, No. 8, 506 (1970).