ANTIENZYME FUNCTION OF THE LUNGS IN ACUTE PANCREATITIS

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Development of the syndrome of acute pulmonary disturbances is one of the most serious complications of acute pancreatitis and is accompanied by changes in the mechanics of respiration, ventilation, oxygenation, and the pulmonary blood flow, leading to arterial hypoxemia [3, 5]. The causes of these disturbances are enzyme poisoning and gross disorders of the systemic and pulmonary circulation [3, 5].

It was accordingly interesting to study the antienzyme function of the lungs in the course of experimental pancreatitis, and the investigation described below was undertaken for this purpose.

EXPERIMENTAL METHOD

Experiments were carried out on 22 mongrel dogs weighing 18-22 kg. Pancreonecrosis was induced by the method in [1] by injecting autologous bile under pressure into the pancreatic duct. Under intravenous thiopental anesthesia (20 mg/kg), after premedication with trimeperidine (5 mg/kg), the cranial vena cava, pulmonary artery, and thoracic aorta were catheterized. The antienzyme function of the lungs was assessed by their ability to inactivate elastase — an enzyme with an extensive injurious action [6]. Activity of elastase and its inhibitor in arterial and mixed venous blood was determined by the method in [2]. The venous-arterial elastase gradient also was calculated, to give some idea of the regulatory effect of the lungs on pancreatic enzymes [7]. The pressure at the mouth of the venae cavae — the central venous pressure (CVP), in the pulmonary artery (PAP), and at the mouth of the aorta (AP) and also the ECG in three standard leads were recorded on the Mingograph-82 (Siemens-Elema, Sweden). The cardiac output (CO) and circulating blood volume (CBV) were determined by a radiocardiographic method with ^{131}I-albumin. The acid-base state and gaseous composition of the blood were investigated by the micro-Astrup method. The pulmonary shunt was determined after 20 min of hyperoxygenation by Berrgren's equation with the aid of a nomogram [8]. The investigation was carried out immediately after premedication and induction of anesthesia (background), and also after 1, 3, 7, and 12 h of the experiment. There were two series of experiments: series I) a model of acute pancreatitis was reproduced in 16 dogs, and led to severe hemodynamic and respiratory disturbances, with ultimate death of the animal; series II) (control) — laparotomy only was performed on six dogs.

The experimental results were subjected to statistical analysis using nonparametric criteria.

EXPERIMENTAL RESULTS

All animals with acute pancreatitis died between 6 and 14 h after its induction. The diagnosis of pancreonecrosis was confirmed histologically in all cases. The lungs of the experimental animals were edematous, with subpleural hemorrhages. Microscopic examination revealed signs of injury to the lungs in 12 animals — collapse of the alveoli, interstitial edema and microthrombi in the capillaries. No such changes or gross disturbances of the circulation and gas exchange were observed in the control dogs (Table 2). The elastase level in the arterial and mixed venous blood of the control animals remained virtually unchanged, and not until after 12 h was a very small increase observed ($P < 0.05$). The venous-arterial elastase gradient also was low in the dogs of this series (Fig. 1, II). As results of the experiments of series I show, the development of acute pancreatitis is accompanied by a marked increase in blood elas-

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TABLE 1. Antienzyme Function of Lungs, Hemodynamics, and Gas Exchange in Experimental Pancreatitis (series I)

Parameter studied	Background (n=16)	Background after induction of acute pancreatitis, h			
		1 (n=16)	3 (n=12)	7 (n=10)	12 (n=6)
Elastase, μg/ml/min					
artery	9,9	14,5	12,2	18,3*	19,5*
vein	13,7	21,3*	21,7*	17,7*	20,7*
CBV, ml/kg	94,6±2,7	66,0±5,5*	56,1±4,3*	48,2±3,9*	41,6±3*
CO, ml/min·kg	127,2±8,5	82,9±8,2*	65,6±2,6*	52,1±3,7*	43,5±4,1
AP_{mean}, mm Hg	110,8±4,6	139,8±6,9	120,3±8,6	62,3±3,2*	49,8±4,0*
PAP_{mean}, mm Hg	12,6±0,2	15,7±0,3	19,6±1,0*	19,2±1,2*	18,0±1,5
CVP, mm water	65,5±2,2	20,0±6,3*	8,3±2,8*	0	0
p_aO_2, mm Hg	86,3±4,6	94,0±2,2	79,2±1,3	65,3±4,1*	52,8±3,8*
Pulmonary shunt, %	8,4±0,7	10,2±0,5	9,1±0,4	21,9±0,6*	25,9±1.0*

Legend. *P < 0.05 compared with control.

TABLE 2. Antienzyme Function of Lungs, Hemodynamics, and Gas Exchange in Control Animals (series II)

Parameter studied	Background (n=6)	Time of investigation, h			
		1 (n=6)	3 (n=6)	7 (n=6)	12 (n=6)
Elastase, μg/ml/min					
artery	7,1	7,2	9,0	6,6	10,0
vein	10,9	10,9	12,1	10,9	15,2*
CBV, ml/kg	99,7±2,1	98,0±2,6	97,1±1,8	94,5±1,9	92,7±1,7
CO, ml/min·kg	128,3±3,6	133,7±6,0	121,3±4,9	116,2±6,8	115,6±8,1
AP_{mean}, mm Hg	110,8±4,6	114,2±4,6	117,7±4,4	108,3±5,2	101,7±5,2
PAP_{mean}, mm Hg	13,1±0,6	13,8±0,6	13,7±0,6	14,6±1,1	13,0±0,7
CVP, mm water	60,0±10,6	56,7±6,7	50,0±4,9	43,3±6,7	40,3±6,7
p_aO_2, mm Hg	86,7±5,0	90,7±4,7	95,0±2.9	89,0±4,1	83,3±6,8
Pulmonary shunt, %	7,3±0,7	7,0±0,8	6,7±0,9	6,0±1,0	8,3±1,1

Legend. *P < 0.05 compared with background.

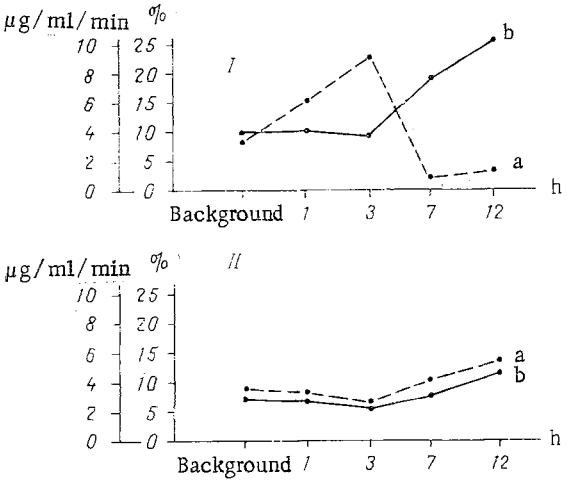

Fig. 1. Time course of venous-arterial elastase gradient and pulmonary shunt in experimental pancreatitis (I) and control (II). Abscissa, time of investigation (in h). a) Venous-arterial elastase gradient (in μg/ml/min); b) pulmonary shunt (in % of cardiac output).

tase activity (Table 1). The content of the enzyme in mixed venous blood in this case was increased 1 h after induction of acute pancreatitis and it remained at twice the initial level until death of the animals. Despite this fact, the concentration of elastase in arterial blood remained low during the first 3 h of the disease; the venous-arterial elastase gradient, moreover, rose sharply, and was almost 3 times as high as in the control ($P < 0.05$). It can thus be concluded that in the early stages of acute pancreatitis the lungs function as an active metabolic organ and play an important role in detoxication of the blood.

The cellular level of pulmonary metabolism has not yet been adequately studied. It is suggested that alveolar macrophages, neuroendocrine cells, and mast cells of the lungs possess definite activity [7]. However, according to Young and Tierney [10], the principal functioning unit of pulmonary metabolism is the endothelial cell. Endothelial cells of the pulmonary capillaries possess kininase and kinin-producing activity. In addition, they contain a universal antienzyme system which determines the degree of "protection" of the lung against circulating enzymes [9, 10]. This explains the phenomenon of the decrease in elastase activity of the blood as it passes through the lungs, which the writers observed experimentally. Similarly, the lungs metabolize serotonin, histamine, certain prostaglandins, and proteases [4, 7]. Deficiency of the antienzyme system of the lungs creates the possibility of their injury in various critical states [10]. Metabolic activity of the liver, which breaks down toxic agents arriving from the pancreas in the portal blood flow and, ultimately, in the pulmonary circulation [4], has a considerable influence on the prognosis of the disease. Meanwhile, a fall in the blood elastase level "after the lungs" is evidence that the lungs also play an important compensatory role, reducing the toxic action of enzymes on vitally important organs and on the peripheral circulation. In fact, in the early stages of the disease, stabilization of the arterial pressure, pulmonary shunt, and p_aO_2 was observed, reflecting compensation of initial circulatory disturbances. However, after 7-12 h of experimental pancreatitis, the venous-arterial elastase gradient was sharply reduced, indicating disturbance of the antienzyme function of the lungs (Fig. 1, I). As a result, the concentration of the enzyme increased in the arterial blood. During this period, a critical fall in cardiac output and arterial pressure were observed, with an increase of pressure in the pulmonary artery and pulmonary shunt, and the development of marked arterial hypoxemia. Parallel with disturbance of the antienzyme function of the lungs, decompensation of the hemodynamics and gas exchange was thus observed. To a certain extent, the decrease in the inactivating power of the lungs was connected with an increase in the pulmonary shunt, for in the late stages of the disease more than 25% of the cardiac output does not come into contact with functioning regions of lung tissue. It is also probable that during progression of the pathological process, exhaustion of tissue inhibitors of lung tissue develops. A vicious circle is set up: injury to the lungs under the influence of pancreatic enzymes leads to an increase in the shunt, and this is accompanied by a further increase in the blood enzyme level. This aggravates the disorders of oxygenation, the circulation, and metabolism. As an organ rich in elastin, the lungs are evidently quickly vulnerable to the destructive action of elastase. Other substances entering the bloodstream in pancreatogenic shock also have a harmful action on the lungs: Phospholipase, trypsin, collagenase, fatty acids, etc. [3]. Interstitial edema, collapse of the alveoli, and microembolism and thrombosis of the pulmonary capillaries develop, and these changes correspond to the early stages of the shock lung syndrome [4, 5].

In the early stages of acute pancreatitis, the lungs thus function as an active metabolic organ and take part in enzyme inactivation in the blood. During progression of the disease, the antienzyme function of the lungs becomes exhausted and this is accompanied by profound hemodynamic and respiratory disturbances and it plays an important role in the pathogenesis of acute pancreatitis.

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