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PULMONARY ENDOTHELIAL SYSTEM IN ABDOMINAL SEPSIS

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Abstract:

Molecular-biochemical parameters of the endothelial system of the lungs during experimental modeling of abdominal sepsis showed an ambiguous picture of the changes occurring, which were of a phase nature and depended on the timing of the development of the pathological process.

Keywords: Abdominal sepsis, lungs, endothelial system.

RELEVANCE. Throughout the last century, abdominal sepsis has been and remains a dangerous disease in which dysfunction of vital organs develops as a result of the aggression of introduced microorganisms.

The high incidence of abdominal sepsis is accompanied by high mortality, which can vary from 7.6% to 36.0% .

Intra-abdominal contamination and secondary peritonitis are a constant source of pathogen-associated molecular patterns (via spillage of intestinal contents) and through direct damage to internal and abdominal organs. This "engine of multisystem organ failure" provides continuous cytokine fuel for the raging systemic response. For example, TNF-α and IL-1 are important proinflammatory cytokines. Each has been shown to induce vascular permeability, leading to pulmonary edema and hemorrhage.IL-6 is a key molecule in initiating the febrile response, lymphocyte activation, and also plays a role in hematopoiesis. It has also been shown to cause myocardial depression.

Over the past 20 years, the recognition of the endothelium as a full-fledged system has led to a large number of experimental and clinical studies, including the study of the mechanisms of development of sepsis. During bacterial, fungal, or viral infection, exogenous molecular patterns associated with pathogens and molecular patterns associated with endogenous damage cause endothelial activation and can disrupt its structure and function, i.e., provoke the development of endothelial dysfunction.

Endothelial changes associated with sepsis should be considered useful to limit the spread of bacteria, as well as to control leukocyte recruitment and bacterial clearance. However, severe and persistent phenotypic changes in the endothelium can contribute to impaired microcirculatory blood flow, tissue hypoperfusion , and the development of life-threatening multiple organ failure .

Thus, it is very difficult to distinguish between appropriate activation and endothelial dysfunction, especially given that the endothelial cell response may vary between organs.

PURPOSE OF THE STUDY : study of the endothelial system of the lungs in abdominal sepsis.

MATERIAL AND METHODS. The studies were conducted on laboratory outbred rats in a model of abdominal sepsis that we developed. The experiments were carried out on 106 white outbred laboratory rats weighing 200-250 grams, of both sexes, fed a regular laboratory diet. The planned experimental studies, which included sampling, biopsies and necropsies, were based on the conditions specified in the 1986 Council of Europe Animal Welfare Convention.

The animals were divided into the following series of experiments: Control – 10 intact animals, not subjected to any influences or manipulations, fed a standard grain diet. The main one was 50 animals in which the experimental model of abdominal sepsis was reproduced using our improved method.

The reproduction of the experimental model of abdominal sepsis was carried out in stages, by changing the reactivity of animals and creating a purulent-necrotic focus in the abdominal cavity.

In experimental studies, blood was collected separately at the entrance and exit from the lungs. In this case, the blood at the entrance to the lungs is mixed venous blood, which came from the inferior and superior vena cava. At the exit from the lungs we received arterial blood, which was universal for the entire organism as a whole. This technique was developed and tested by a group of researchers at the Tashkent Medical Academy. Each value obtained in different blood samples was also subjected to calculation of the venous-arterial difference, that is, a value reflecting the "retention" or

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"production" of the substrate in the endothelial system of the lungs.

The entire complex of studies of patients with abdominal sepsis consisted of continuous monitoring of the state of homeostasis and functional activity of vital organs. For this purpose, functional, instrumental and laboratory research methods were carried out. Integral rating diagnostic methods, such as APACHE II, SAPS, SOFA, and the Kalf -Kalifa leukocyte intoxication index, were also actively used .

Among the indicators of the endothelial system, we examined the level of C-reactive protein (mg/l), thrombomodulin (ng /ml), von Willebrand factor (IU/ dL), intercellular and cellular adhesion molecules (ng /ml) using an enzyme immunoassay analyzer; nitrites and nitrates (%), peroxynitrite (μmol /l), nitric oxide synthase activity (μmol /min/l) according to the Griess method modified by A.P. Solodko et al . on an SF-46 spectrophotometer at a wavelength of 520 nm .

The entire set of studies met the criteria of translational medicine, which used the entire body of research, which made it possible to extrapolate the results of experimental studies into clinical practice.

RESULTS AND ITS DISCUSSION. The study of the total value of NO is considered a generally accepted indicator of the nitroxergic system for regulating vascular tone, as one of the functional criteria of the endothelial system. The average level of its content in the mixed venous blood sample at the entrance to the lungs was 26.39±3.91 μmol/l, while at the exit from the lungs in the arterial blood sample its level was higher and reached an average value of 33.41±4. 64 μmol/l. The venous-arterial difference, which averaged "+" 7.02±1.13 μmol/l, was positive and indicated the production of this element in the alveolar capillary network with release into the systemic bloodstream. It should be noted that this nature of the venous-arterial difference was typical in all series of experiments we studied. In this case, the peak values occurred in animals of the control and comparative groups ("+" 8.44±2.17 μmol/l and "+" 8.63±2.35 μmol/l, respectively). In other cases, in the dynamics of the development of the experimental model of abdominal sepsis, the production of this substrate of the nitroxergic system for regulating vascular tone decreased from "+" 8.11±2.47 μmol/l ($p < 0.05$) for the 6-hour period of reproduction of the experimental model of abdominal sepsis and up to "+" 4.69±1.62 μmol/l ($p < 0.05$) for a 24-hour period of disease development. In the subsequent 48, 72 and 96-hour periods of development of the experimental model of abdominal sepsis, the venous-arterial difference in NO increased again. However, the venous-arterial difference did not reach the initial value. Moreover, most of the indicators were of unreliable changes, reflecting the distance from the ongoing real processes associated with the development of the experimental model of abdominal sepsis.

In this regard, we carried out a dispersion analysis of the constituent elements of NO (NO^{2-} and NO^{3-}) as a percentage in the dynamics of development of an experimental model of abdominal sepsis. The predominant role in the percentage value of NO^{2-} , already for a 24-hour period of modeling abdominal sepsis is leveled, giving way to the proportional value of NO^{3-} . In other words, there is an increased production of NO^{3-} by the endothelial system in the conditions of ongoing disorders. This once again confirms the importance of assessing the component of NO decay rather than its overall value. Against the background of the changes described above, we identified changes in the concentration of the metabolic product of the transformation of NO components , in particular NO^{3-} in $OONO^-$. The average content of peroxynitrite in the mixed venous blood sample at the entrance to the lungs throughout the study exceeded its level in the arterial blood sample at the exit from the lungs (2.5 ± 0.09 μmol/L and 2.37 ± 0.03 μmol/L; $p > 0.05$).

The venous arterial difference, which was negative ("-") , indicated the active utilization of this oxidative product in the endothelial system of the lungs and a decrease in its production into the systemic arterial bloodstream. In other words, the lungs, and in this case its endothelial system, performed a barrier filtration function, creating conditions for the formation of blood that was universal in composition for all organs of the body. We identified minimal values with an unreliable level of differentiation between the content of peroxynitrite in the mixed venous blood sample at the entrance to the lungs and in the arterial blood sample at the exit from the lungs among animals in the control and comparative series of experiments. The venous-arterial difference ("-" 0.03±0.01 μmol/l), equivalent to 10%, can be safely taken as absent.

However, in the group of animals with an experimental model of abdominal sepsis, already starting from the 6-hour period of development of the pathological process, we recorded an increase in peroxynitrite in the mixed venous blood sample at

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the entrance to the lungs, which reached its maximum value at 72-96 hours of progression diseases. The level of its increase by 3.2 and 2.3 times differed in reliability in relation to the early stages of modeling abdominal sepsis (6-12 hour periods). As for the change in the level of peroxynitrite in an arterial blood sample at the exit from the lungs, we can note the relative stability in the productivity of this substrate for the 6-12-hour period of development of the experimental model of abdominal sepsis. It is during these periods that the venous-arterial difference, repeating its character as in the control series of experiments, becomes maximally significant, reaching a peak at the 12-hour period of development of abdominal sepsis ("-"1.46±0.12 μmol /l). This nature of changes in the endothelial system of the lungs in the dynamics of development of the experimental model of abdominal sepsis led to an increase in the differentiated value between venous and arterial blood samples by 3 times (p <0.001).

Meanwhile, starting from the 24-hour period of development of the experimental model of abdominal sepsis, there was a decline in the venous-arterial difference to "-" 0.74±0.12 μmol/l (p <0.05), which in subsequent periods led to an inversion of values , due to a change in the nature of the formation of peroxynitrite, which began to be actively synthesized ("+") in the endothelial system of the lungs. Its increase in the arterial blood sample at the exit from the lungs, starting from this period of development of the experimental model of abdominal sepsis, was significantly pronounced, especially at 48 hours (7.4 times relative to 6 hours and 7.1 times relative to to 12-hour periods) and to 72-hour (8.9 times relative to 6-hour and 8.5 times relative to 12-hour periods) periods.

Thus, it is possible to state an increase in peroxynitrite in various blood samples depending on the timing of the development of the experimental model of abdominal sepsis, which was characterized by a transition from a state of transient phenomena to steadily progressive ones, indicating the depletion of the compensatory capabilities of the pulmonary endothelial system itself. As evidence for the above conclusion, we consider the dynamics of changes in the activity of the iNOS enzyme in the studied blood samples at the entrance and exit from the lungs.

In particular, in intact animals the activity of this enzyme is inhibited as it passes through the endothelial system of the lungs. The same character of the ratio of endothelial cells can be seen in the ratio of the group of animals of the comparative series.

It is interesting that the venous-arterial difference continues to increase among animals with an experimental model of abdominal sepsis. However, as in the case of peroxynitrite, this pattern completely changes starting from the 24-hour period of development of the experimental model of abdominal sepsis.

The activity of this enzyme in the arterial blood sample at the exit from the lungs increases. And although such an increase was within ±10% of the level, nevertheless, we no longer received the effect of iNOS inhibition . This, in turn, may indicate a decrease in the activity of the physiological enzyme systems of endothelial and neuronal NO synthase and the progression of oxidative processes leading to the destruction of endothelial cells in the capillary network of the lungs.

In the dynamics of development of the experimental model of abdominal sepsis, identical changes occurred in the concentration of intercellular and cellular adhesion molecules. In intact animals, a decrease in the concentration of these molecules was observed as blood passed through the endothelial system of the lungs. The venous-arterial content of ICAM -1 decreased by 29.8 times (p <0.001 - significant value in the arterial blood sample at the exit from the lungs in relation to the mixed venous blood sample at the entrance to the lungs).

In terms of VCAM -1 content, the decrease was slightly less - 22.9 times, although it was also stable and significant (p <0.001 - significant value in the arterial blood sample at the exit from the lungs in relation to the mixed venous blood sample at the entrance to the lungs). Such changes correspond to physiological parameters, which are confirmed by the presence of high tone in the arterial circulatory system. Also interesting is the identical level of change in the venous-arterial difference (24.4 times, respectively) for both indicators. This occurred due to a decrease in the specific gravity of intercellular adhesion molecules and an increase in cell adhesion molecules in the mixed venous blood sample at the entrance to the lungs. When modeling abdominal sepsis, starting from the 6-hour study period, we noted a progressive decrease in the level of venous-arterial difference. At the same time, the minimum value in relation to the venous-arterial difference ICAM -1 was noted for the 24-hour period of development of the experimental model of

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abdominal sepsis, while in relation to VCAM -1 - for the 48-hour period of development of the experimental model of abdominal sepsis. This was apparently due to the stages of changes occurring in the endothelial system of the lungs, where at the first stage there was a predominance of intercellular adhesion, and subsequently - cellular adhesion, which indicates the presence of endothelial apoptosis.

We also noted a leveling of the values of the venous-arterial difference during this period of experiments in relation to vWF . The maximum level of vWF formation in the endothelial system of the lungs occurred during the 12-hour period of development of the experimental model of abdominal sepsis (1.2 times). In subsequent periods, as the pathological process progressed, an increase in the venous-arterial difference over the 24-48-hour study period indicated a cumulative characteristic between vWF in the venous blood sample at the entrance to the lungs and in the arterial blood sample at the exit from the lungs.

This nature of the changes was reflected in the subsequent development of the experimental model of abdominal sepsis, in which the productivity of vWF in the endothelial blood system at the exit from the lungs indicated active structural and functional disorders already in the pulmonary vessels.

Analysis of the venous-arterial difference showed that the endothelial system of the lungs reacted sensitively to changes occurring in the site of destruction. At the same time, the main character of the endothelial system of the lungs at the first stage was reduced to blocking the flow of pathological substrates into the systemic arterial bloodstream, and at the second stage of development of the experimental model of abdominal sepsis, the lungs cease to create a barrier to the generalization of the inflammatory process, opening the way for the development of multiple organ dysfunction.

CONCLUSIONS.

1. The increase in peroxynitrite in various blood samples depending on the timing of development of the experimental model of abdominal sepsis, which was characterized by a transition from a state of transient phenomena to steadily progressive ones, indicating the depletion of the compensatory capabilities of the pulmonary endothelial system itself.
2. The productivity of vWF in the endothelial blood system at the exit from the lungs was evidenced by active structural and functional disorders already in the pulmonary vessels.
3. The main character of the endothelial system of the lungs at the first stage was to block the flow of pathological substrates into the systemic arterial bloodstream, and at the second stage of development of the experimental model of abdominal sepsis, the lungs cease to create a barrier to the generalization of the inflammatory process, opening the way for the development of multiple organ dysfunction

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