

The role and place of nitroxidergic regulation of the endothelial system in the pathogenesis of acute lung abscess

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Abstract

Background: Purulent-destructive lung diseases remain a priority among the causes of generalized infection and death. The key to the progression of infection in acute lung abscesses may be associated with impaired barrier-filtration function of this organ, which is based on endothelial dysfunction.

Method: The experiments were carried out on 32 Chinchilla rabbits, in which the model of acute lung abscess was reproduced. Investigated in blood samples at the entrance and exit from the lungs, such indicators as nitrates, nitrites, peroxynitrite, NO-synthase and von Willebrand factor.

Conclusion: Nitric oxide produced because of iNOS activation is intended for non-specific protection of the body against a wide range of pathogenic agents, inhibits platelet aggregation and improves local blood circulation. However, these changes do not occur. The main role in this direction is assigned to peroxynitrite, which, due to its pathogenicity, worsens the already process associated with endothelial dysfunction. The nature of the changes in the parameters of the nitroxidergic regulation of the endothelial system in the lungs has a staging: compensated and decompensated. All this is of a natural nature, based on certain relationships between the indicators of the nitroxidergic regulation system.

Keywords: Endothelial Dysfunction, Experimental Simulation, Generalization of Inflammation, Inflammation, Lung Abscess, Lung Barrier Function, Nitroxidergic Regulation System

Introduction

Progress in the diagnosis and treatment of patients with purulent-destructive lung diseases contributed to the frequent detection in them of combined disorders of the activity of various organs and systems, identified by clinicians as “multiple organ failure syndrome”. A significant role in the development of this syndrome is played by the generalization of the pathological process after the breakthrough of the barrier of the endothelial system of the lungs, leading to the occurrence of a body reaction in the form of septic shock [2].

It is known that nitric oxide (NO) was discovered by R. Furschgott [8,9]. Interest in NO is determined by the fact that it is the most stable of free radicals, continuously formed in the vascular endothelium in many organs, provides adequate tissue perfusion, blood pressure levels, protects the myocardium from arrhythmia; lungs from hypoxia and toxic effects of thromboxane A₂ [4]. In addition, NO provides an anti-inflammatory effect on the walls of blood vessels and regulates the release of histamine by mast cells

[6]. Reacting with oxidants, NO forms a highly toxic compound, peroxynitrite [7].

The ability of the lungs to participate in the metabolism of several biologically active substances was suggested by I.P. Pavlov, who noted in 1887 the unique fibrinolytic properties of the lung tissue. In 1953, Julius Comro suggested that the lungs control the concentration of many substances in the blood. The first works of Nagaishi C. in relation to vasoactive substances confirmed this assumption, and a huge number of similar works published in recent years have increased the attention of the whole problem. Subsequently, other terms appeared: “endogenous lung filter”, “lung barrier”, etc., the primary of which is the idea of the metabolic activity of the lungs, aimed at controlling the level of a number of substances circulating in the systemic circulation. Among such mechanisms, the role of nitroxidergic regulation of the endothelial system in the lungs in their purulent-destructive diseases, which, according to many researchers, is one of the key links in the pathogenesis of the generalization of the process, is not entirely clear [13,14].

The aim of our study was to determine the role and place of nitroxidergic regulation of the endothelial system in the pathogenesis of acute lung abscess.

Materials and Methods

Experimental studies were carried out on 32 laboratory rabbits of the Chinchilla breed, weighing 2.0-2.5 kg, of both sexes, without external signs of the disease, which underwent a 10-day quarantine in a vivarium. The animals were kept under standard conditions. Animal nutrition consisted of a standard diet. All experimental studies were reviewed, discussed and approved by the bioethical committee of the Ministry of Health of the Republic of Uzbekistan and fully complied with the terms of the 1986 Council of Europe Convention for the Protection of Animals.

Acute lung abscess in animals was modeled according to our method by injecting into lung tissue 1 ml per 1 kg of animal of 5% suspension of rabbit autocal [3]. Over the next 7 days, the animals developed a clinical picture of an acute lung abscess, which was confirmed by x-ray studies.

The endothelial system in the lungs was studied in terms of nitrates (NO₂), nitrites (NO₃), peroxyxynitrite (ONOO⁻), as well as the enzyme activity of NO synthases (eNOS and iNOS) in various blood samples, which were determined by the Griess method modified [11]. The concentration of nitrites was calculated according to the equation of the calibration curve, considering the dilution during deproteinization. Optical density was measured on an SF-46 spectrophotometer at a wavelength of 520 nm.

Table 1: The content of NO (μmol/l) in various blood samples in the norm and in the dynamics of the development of an experimental model of acute lung abscess.

| Process dynamics | Blood samples | |
|--|---------------|-------------|
| | Venous | Arterial |
| Control group | 16,41±0,45 | 25,51±0,72 |
| 1 day | 18,25±0,61 | 22,4±0,88 |
| 3 day | 22,94±0,92* | 24,14±0,5 |
| 7 day | 29,53±0,93* | 17,61±0,67* |
| 14 day | 37,71±0,63* | 14,52±0,33* |
| * p<0,05: Reliable value in relation to the control series of experiments. | | |

Reproduction of the experimental model of acute lung abscess led to a progressive increase in the level of NO in the mixed venous blood at the entrance to the lung with a progressive decrease in it in the arterial blood sample. The venous-arterial difference, starting from the 1st day of the development of the pathological process, decreased by more than 2 times, and on the 3rd day by 9 times, remaining in a positive value, similar to the control series of experiments. However, starting from the 7th day of the experiments, the venous-arterial difference turned into the opposite value, reducing the level of this metabolite in the arterial blood flow system. Low levels of NO in the arterial blood sample

The von Willebrand factor (VWF) was studied on a Humaclo DUO closed-type automatic analyzer (Germany) using a set of reagents from Human (Germany).

At the same time, along with the traditional methods of analyzing the results, including the determination of the average content of the metabolic product and the average error (M±m), in each of these blood samples in all examined animals, for each experiment, the difference between the content of substrates in the inflowing (mixed venous blood) was calculated for each experiment, through a catheter installed at the mouth of the right atrium) to the organ (lungs) and flowing (arterial blood, through a catheter installed in the left carotid artery) from it blood, designated by us as a venous-arterial difference. Possible values of the venous-arterial difference were: a plus value, indicating the synthesis of the substrate in the lungs; minus value, indicating the consumption or inactivation of the studied substrates in the lungs; zero value, which indicated a neutral ratio of the lungs to the test substrate. A similar research technique was performed in animals on days 1,3,7, and 14 of the development of the pathological process.

All studies were carried out in the central scientific research laboratory of the Tashkent Medical Academy from 2020 to 2021.

Results and Discussion

The level of NO content in different blood samples differed significantly (p<0.05), which confirms the well-known data on the predominance of the role of this indicator in the arterial circulatory system. A positive value of the venous-arterial difference indicated a high activity of the endothelial system of the lungs (Table 1).

apparently contributed to the development of arterial pressure instability, which is one of the reasons for the generalization of infection with the development of septic shock.

The formation of NO in the endothelial system of the lungs was accompanied by an increase in the activity of the eNOS enzyme from 2.82±0.14 μmol/min/l in mixed venous blood to 5.63±0.17 μmol/min/l (p<0.05). A similar trend was noted by us in the arterial blood sample, respectively (Table 2).

Table 2: eNOS activity ($\mu\text{mol}/\text{min}/\text{l}$) in various blood samples in normal conditions and in the dynamics of development of an experimental model of acute lung abscess.

| Process dynamics | Blood samples | |
|--|------------------|------------------|
| | Venous | Arterial |
| Control group | 2,82 \pm 0,14 | 5,63 \pm 0,17 |
| 1 day | 3,15 \pm 0,14 | 6,11 \pm 0,32 |
| 3 day | 2,23 \pm 0,19 | 4,21 \pm 0,24 |
| 7 day | 2,02 \pm 0,10 | 3,91 \pm 0,09* |
| 14 day | 1,72 \pm 0,12* | 3,42 \pm 0,17* |
| * p<0,05: Reliable value in relation to the control series of experiments. | | |

On the 1st day of acute lung abscess modeling, the activity of this enzyme increased both in mixed venous and arterial blood samples. At the same time, an increase in the activity of this enzyme in the endothelial system of the lungs was not significant in relation to the control series of experiments. In subsequent periods, the activity of this enzyme progressively decreased, reaching its minimum value on the 14th day of the pathological process, both in mixed venous and arterial blood samples. It should be noted that the decrease in NOS activity in mixed venous and arterial blood samples was accompanied by a decrease in its formation in the endothelial system of the lungs. That is, the reproduction of the experimental model of acute lung abscess was accompanied by the development of endothelial dysfunction in this organ, manifested by the low activity of this enzyme under study. At the same time,

a significant violation of the nitroxidergic regulation system was noted in the early stages of the development of an experimental model of acute lung abscess.

The activity of iNOS isoenzyme (Table 3) in the control series of experiments was significantly higher in mixed venous blood than in arterial blood sample (p<0.05). The venous-arterial difference was of a “minus” nature and indicated the deactivation of this enzyme in the endothelial system of the lungs under normal conditions. The development of an experimental model of acute lung abscess led to an increase in the activity of the iNOS isoenzyme, reaching a maximum significant value on the 14th day of the experiment (p<0.05).

Table 3: iNOS activity ($\mu\text{mol}/\text{min}/\text{l}$) in various blood samples in normal conditions and in the dynamics of development of an experimental model of acute lung abscess.

| Process dynamics | Blood samples | |
|--|------------------|------------------|
| | Venous | Arterial |
| Control group | 0,23 \pm 0,04 | 0,1 \pm 0,03 |
| 1 day | 0,26 \pm 0,02 | 0,09 \pm 0,01 |
| 3 day | 0,27 \pm 0,02 | 0,09 \pm 0,02 |
| 7 day | 0,39 \pm 0,03* | 0,16 \pm 0,01* |
| 14 day | 0,48 \pm 0,03* | 0,2 \pm 0,02* |
| * p<0,05: Reliable value in relation to the control series of experiments. | | |

The arterial blood sample was characterized by relative stability of the activity of the iNOS isoenzyme on the 1st-3rd day of the development of the pathological process, which was associated with an increase in its venous-arterial difference in this period compared to the control series of experiments (p<0.05).

the nitroxidergic system of endothelial function regulation in the lungs, had an identical pattern in metabolic processes (Table 4).

Despite the fact that on the 7th and 14th days of the development of the pathological process there was a twofold increase in the level of venous-arterial difference in the activity of the iNOS isoenzyme (p<0.05), nevertheless, significantly increased in relation to the control series of experiments and its activity in the arterial blood sample at the exit from the lungs (p<0.05). That is, in the late stages of the development of an experimental model of acute lung abscess, arterial blood was significantly enriched with the active iNOS isoenzyme. We deliberately focus on this fact, since the level of change in ONOO-, which is a toxic intermediate product of

The level of ONOO- in the control series of experiments decreased from 1.51 \pm 0.04 $\mu\text{mol}/\text{l}$ in mixed venous blood at the entrance to the lungs to 0.60 \pm 0.04 $\mu\text{mol}/\text{l}$ in the arterial blood sample at the exit from the lungs (p<0.05). The venous-arterial difference was of a “minus” nature, utilizing this product in the endothelial system of the lungs.

In the early stages of reproduction of the experimental model of acute lung abscess, there was an increase in the content of ONOO- in mixed venous blood, which, apparently, came from a purulent-septic focus.

An increase in the utilization of this substrate in the endothelial

system of the lungs at this time contributed, due to the activity of the barrier-filtration function of the lungs, to keep its concentration in the arterial blood within normal limits.

The progression of the development of the experimental model of acute lung abscess led to an increase in the concentration of ONOO- in mixed venous blood, reaching its maximum value on the 14th day of the experiments.

Table 4: The content of ONOO- ($\mu\text{mol/l}$) in various blood samples in the norm and in the dynamics of the development of an experimental model of acute lung abscess.

| Process dynamics | Blood samples | |
|--|---------------|------------|
| | Venous | Arterial |
| Control group | 1,51±0,04 | 0,60±0,04 |
| 1 day | 1,82±0,07 | 0,72±0,05 |
| 3 day | 1,95±0,08 | 0,55±0,1 |
| 7 day | 2,71±0,08* | 2,99±0,13* |
| 14 day | 3,43±0,18* | 5,26±0,19* |
| * p<0,05: reliable value in relation to the control series of experiments. | | |

It should be noted that it was during these periods of research in the arterial blood sample that there was a significant increase in the concentration of this product, which is a toxic substrate for the membrane structures of endothelial cells, contributing to damage to the latter. The lungs in this period are transformed from a “consumer organ” into a “producer organ”, contributing to the release of ONOO- into the arterial bed. Damage to the endothelial system of the lungs, which occurs on the 7th and 14th days of the development of the pathological process, acts as the first link in the trigger mechanism for the generalization of the septic process.

in the functional capacity of the lungs, leading to an increase in the venous-arterial difference compared to the control series of experiments by 1.8 times on the 1st and 3rd days of the development of the pathological process (p<0.05). However, an increase in VWF utilization in the endothelial system of lung capillaries did not contribute to its normalization in arterial blood.

One of the criteria for damage to endothelial cells is the blood level of VWF (Table 5). Utilization of this product by the lungs in the control series of experiments stated the fact of its participation in the activity of the barrier-filtration function of the lungs. Early modeling of acute lung abscess led to a significant increase in the content of this substrate in mixed venous blood at the entrance to the lung. At the same time, there was a significant increase

The level of VWF in the arterial blood sample exceeded the control values on the 1st day of the pathological process by 21 times, and on the 3rd day by 48 times. Apparently, this was due to the inclusion of processes of endothelial dysfunction in the nitroxidergic system and the onset of disseminated intravascular coagulation. In the subsequent periods of development of the experimental model of acute lung abscess, progressive endothelial dysfunction led to a significant increase in the level of this substrate both in the mixed venous blood and in the arterial blood sample, reaching its peak on the 14th day of the pathological process.

Table 5: The content of VWF ($\mu\text{mol/l}$) in various blood samples in the norm and in the dynamics of development of an experimental model of acute lung abscess.

| Process dynamics | Blood samples | |
|--|---------------|------------|
| | Venous | Arterial |
| Control group | 0,65±0,06 | 0,10±0,01 |
| 1 day | 3,1±0,14* | 2,1±0,16* |
| 3 day | 5,70±0,19* | 4,8±0,08* |
| 7 day | 18,4±0,56* | 25,6±0,37* |
| 14 day | 27,1±0,74* | 36,2±0,64* |
| * p<0,05: Reliable value in relation to the control series of experiments. | | |

The venous-arterial difference in these terms of the experiments was characterized by a “plus” value, which was due to the accession of the endothelial system to the formation of this product in the lungs. This fact is direct evidence of the progression of endothelial dysfunction in the lungs. The level of venous-arterial difference increased on the 7th day of the pathological process to “+” 7.20±1.15 $\mu\text{mol/l}$ and on the 14th day of the disease - to “+” 9.10±1.66 $\mu\text{mol/l}$, respectively 13 and 16.5 times.

NO and partially reduced oxygen undergo a rapid interaction with the formation of peroxynitrite, which damages the cells of the endothelial system, primarily the lungs themselves. This reaction contributes to the removal of NO from the vascular wall, as well as from the surface of alveolocytes [5].

In turn, peroxynitrite is a potent oxidant that can damage the alveolar epithelium and the surfactant system of the lungs [1]. It causes

the destruction of proteins and lipids of membranes, damages the endothelium, increases platelet aggregation, and participates in the processes of endotoxemia. Its increased formation was noted in the syndrome of acute lung injury [15].

Studies of the content of the isoenzyme of the nitroxidergic regulatory system (iNOS) showed a greater specificity of changes compared to eNOS. As you know, this enzyme, which is the product of activation of non-pathological cells; it is produced by cytokines, lipopolysaccharides, and other pathologically dependent cellular formations [12].

Nitric oxide produced because of iNOS activation is intended for non-specific protection of the body against a wide range of pathogenic agents, inhibits platelet aggregation and improves local blood circulation. However, these changes do not occur. The main role in this direction is assigned to peroxynitrite, which, due to its pathogenicity, worsens the already process associated with endothelial dysfunction. The key role in these changes is played by the high activity of iNOS, which is stimulated by pro-inflammatory cytokines [16]. In other words, the severity of cytokine production in the systemic circulation depends entirely on the degree of damage to the lungs by the inflammatory process.

It is known that the basis of acute lung injury is the effect of NO and peroxynitrite on elastase. Kobayashi et al. also registered an increase in the content of both iNOS and several cytokines in bronchoalveolar fluid in patients with acute lung injury syndrome [10].

Conclusion

Thus, the nature of changes in the indicators of nitroxidergic regulation of the endothelial system in the lungs has a staging. In the early stages of the pathological process, the lungs adjusted changes in the concentrations of certain studied substrates by increasing or decreasing their barrier-filtration functional activity. The progression of the inflammatory process, turning into sepsis, contributed to the inhibition of this functional activity, which was reflected in changes in the composition of arterial blood at the exit from the lungs.

The deviation in the physiological parameters of the barrier-filtration function of the lungs, which we stated in the dynamics of the development of the experimental model of acute lung abscess compared with the control series of experiments, in our opinion, is natural, based on certain relationships between the indicators of the nitroxidergic system of regulation.

Ethical clearance

All experimental studies were reviewed, discussed, and approved by the bioethical committee of the Ministry of Health of the Republic of Uzbekistan and fully complied with the terms of the 1986 Council of Europe Convention for the Protection of Animals.

Source of Funding

Self.

Conflict of Interest

No.

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