PULMONARY BARRIER FUNCTION IN SURGICAL SEPSIS

In this article we show the role of procalcitonin (PCT) as a marker of prognosis of acute respiratory distress syndrome of extrapulmonary origin. At the first and second days after modeling surgical sepsis in male rabbits, PCT concentration was low due to consumption by lungs, whereas for the third and fourth days it increased, probably, due to the inclusion of lungs in the pathological process. These changes are primarily indicative of the transition of local inflammatory process in generalized form, in which lungs, in particular their barrier-filtration functions played the key role.

Keywords: Acute respiratory distress syndrome, surgical sepsis, systemic inflammatory response syndrome, inflammatory markers, procalcitonin, pulmonary barrier function.

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Introduction

Acute respiratory distress syndrome (ARDS) of extrapulmonary origin is a severe, life-threatening form of acute parenchymatous respiratory failure, which develops as a nonspecific reaction in the beginning phase of unaffected lungs in prolonged peripheral microcirculation disorders associated with tissue hypoperfusion and the occurrence of severe and prolonged circulatory hypoxia (Afanasyeva et al., 2007; Gelfand et al., 2007; Kassil et al., 2006). Major share (71%) of the total number of etiologic causes of ARDS of extrapulmonary origin occupies pathology of septic nature (sepsis, septic shock, acute destructive pancreatitis, II-III degree burns that more than 28% of body surface) (Baker et al., 2000; Gazin, 2008; Kassil et al., 2003; Reghunathan et al., 2005).

According to the literature (Afanasyeva et al., 2007; Barkhatova, 2008; Kameneva et al., 2008) adhering to the cytokine theory of the origin and development of sepsis, the most adequate marker of this pathological process is considered to be procalcitonin (PCT). Afanasyeva et al. (2007), Reghunathan et al. (2005) attributed this index to markers of severe sepsis. Since the early 90’s, PCT had the attention of researchers who are trying to figure out whether it is a specific marker of infection. For the first time the data on the increased concentration of PCT in blood during inflammation were obtained by a group of French military doctors (Dr. Carsin et al.) who studied markers of acute lung injury in patients with extensive burns. As a potentially useful marker in the study also PCT was examined, and it was found that its concentration was significantly increased in many cases, often being many times higher than its concentrations in tumors. Retrospective analysis revealed that patients with the highest levels of PCT in blood developed infectious complications, including sepsis and septic shock (Afanasyeva et al., 2007; Reghunathan et al., 2005).

At the same time, until the mid 60’s there was a view that the role of lungs is limited only by function of gas exchange (Baker et al., 2000; Barkhatova, 2008; Gazin, 2008; Kassil et al., 2003). Only in last decades the role of lungs has been evaluated in non-gas exchange functions, this gave impetus to a deeper study of lungs. Besides the basic functions of gas exchange, lungs is proved to play the major role in endogenous and exogenous protection, provide detoxification, inhibition, deposition of many biologically active substances (Afanasyeva et al., 2007; Barkhatova, 2008; Gelfand et al., 2007; Kameneva et al., 2008; Kassil et al., 2003; Reghunathan et al., 2005).
We suppose that the importance of specific activities of PCT has a definite value in evaluating the state of pulmonary barrier function, violation of which is the basis for the development of ARDS and generalization of purulent-septic process.

In this context, the aim of our study was to evaluate pulmonary barrier function by the nature of changes in PCT content in different blood samples from lungs as a marker of prognosis of ARDS of extrapulmonary origin.

**Materials and methods**

Experiments were done in 48 outbred male rabbits weighing 1500-2300g, being fed standard rations in a vivarium. Animals were divided into two series. The first series were control intact (uninfluenced) animals (12 rabbits). The second series were animals in which ARDS of extrapulmonary origin was modeled according to our original technique by reproduction necrotizing fasciitis of soft tissues on the background of the changed reactivity of microorganism (a positive decision for the patent No.IAP 2010 0499 from 13.10.2010).

Assessment of pulmonary barrier function in control and influenced animals at the 1, 2, 3 and 4 days after reproduction of pathological process carried out according to PCT levels in blood serum of samples taken from endovascular catheter installed at entrance (the mouth of the right atrium - deoxygenated venous blood) and output (carotid artery - arterial blood) of lung. In this case, along with the definition of average levels of PCT in venous (VB) and arterial blood (AB) samples, we calculated the differences in PCT concentrations, designated by us as a venous-arterial difference (VAD).

Slaughter of animals was performed taking into account the recommendations of the European Committee for the humane treatment of laboratory animals in dynamics at the 1, 2, 3 and 4 days of pathological process.

Pieces of organs were fixed in formalin and glutaraldehyde according to traditional methods. Coloration of tissue sections was carried out by hematoxylin eosin and fuxin - methylene blue.

**Results and discussion**

PCT level, a product of the endocrine system, in control experiments was low, ranging from 0.1 to 0.7 ng/ml in VB and AB, respectively. This indicator in VB was a mean of 0.41±0.04 ng/ml and in AB - 0.39±0.05 ng/ml (Table 1). VAD was low, averaging “-“ 0.02±0.01 ng/ml.

<table>
<thead>
<tr>
<th>Series of experiments</th>
<th>Blood samples</th>
<th>VAD</th>
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<tbody>
<tr>
<td></td>
<td>VB</td>
<td>AB</td>
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<tr>
<td>Control</td>
<td>0.41±0.04</td>
<td>0.39±0.05</td>
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<tr>
<td>1 day</td>
<td>0.55±0.05</td>
<td>0.27±0.03</td>
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<tr>
<td>2 day</td>
<td>1.20±0.15</td>
<td>0.50±0.06</td>
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<tr>
<td>3 day</td>
<td>32.7±0.93</td>
<td>44.5±0.95</td>
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<tr>
<td>4 day</td>
<td>48.5±1.30</td>
<td>65.8±2.30</td>
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Note: * P<0.05 – significant value to control series of experiments.

A variance ratio analysis of pulmonary barrier-filtration function in 12 animals showed that in 5 cases this function was absent, in 4 animals was negative, in 3 animals was positive. In general, we can consider that in norm lungs do not influence on changes in the content of this compound in the circulating blood, and the dispersion positions identified on VAD are not reliable.
For the first day after the experiment, there were no apparent changes in pulmonary barrier-filtration function in relation to PCT, except insignificant increase in utilization of the substrate by lungs, which increases as compared with the control group with a series from “−” 0.02±0.01 ng/ml to “−” 0.28±0.05 ng/ml (p<0.1). This, in its turn, led to a decrease in the content of this substrate from 0.55±0.05 ng/ml in VB to 0.27±0.03 ng/ml in AB.

In these series of experiments, development of ARDS of extrapulmonary origin was morphologically characterized by thrombi appearance and leukocytes congestion in pulmonary microvessels with further formation of edema in interstitial tissue and appearance of microatelectasis.

A similar pattern of change in pulmonary barrier-filtration function was observed by us for the 2\textsuperscript{nd} day after modeling pathological process. A moderate increase in PCT in VB up to 1.2±0.15 ng/ml decreased to 0.5±0.06 ng/ml in AB. In this case, VAD was “−” 0.7±0.13 ng/ml. It should be noted that the variance analysis of VAD revealed a uniformity of nature of pulmonary barrier-filtration function in all 12 animals.

Morphological studies of lungs showed that at the 2\textsuperscript{nd} day of development of pathological process in this organ, the number of non-obturation microatelectasis increased and disseminated. Edema of interstitium increased, hemorrhages and inflammation focuses appeared. Interendothelial capillary spaces were expanded. In the lumen of many alveoli appeared fluid, which was rich for the protein, filaments of fibrin, and desquamated alveocytes.

At the next 3\textsuperscript{rd} and 4\textsuperscript{th} days of modeling the pathological process, we observed a significant elevation of PCT in both VB and AB samples, more significantly in last case (p<0.05). The maximum value of this indicator was registered in AB for the 4\textsuperscript{th} day of the experiment, which reached up to 65.8±2.3 ng/ml. It should be noted that in those periods of observation, VAD value ranged from “minus” values to “plus” ones, i.e. the consumption of this substrate by lungs changed at the 1-2 days of pathological process and instead of its reducing in lung output PCT production increased. In these terms, apparently, PCT was produced by lungs, which increased its levels in AB.

Variance analysis of changes in pulmonary barrier-filtration function showed that, if at the 3\textsuperscript{rd} day VAD in 59% cases was moderately low (less than 12.9 ng/ml), then for the 4\textsuperscript{th} day of disease it was pronounced in 91.6% of cases (above 13.7 ng/ml).

**Conclusion**

Thus, the first and second days of pathological process were characterized by the consumption of PCT by lungs, whereas the third and fourth days by its production, which was probably due to the inclusion of lungs in the pathological process. These changes are primarily indicative of the transition of local inflammatory process in generalized form, in which lungs, in particular their barrier-filtration function played the key role.

**References**


Gazin, K., 2008. “Informative markers in assessing the severity of endotoxemia in purulent-necrotic lesions of lower extremities in diabetic patients” [Klinicheskaya laboratornaya diagnostika], in Russian, No.12, pp.17-20