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RESEARCH ARTICLE

SURFACTANT ACTIVITY DISORDERS AND CORRECTION IN ACUTE LUNG INJURIES

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ABSTRACT

A In acute lung injuries there is depression of surfactant activity, exacerbating respiratory failure. Experimental and clinical studies have shown that the main mechanism to reduce the surfactant activity is toxic pulmonary edema with the lung vessels porosity increase, allowing toxic substances to pass into the alveoli followed by inactivation of the surfactant. Exogenous surfactant preparations used are also inactivated by these toxic agents. Detoxification therapy is more pathogenetically justified, which helps to eliminate toxic porosity of the pulmonary vessels and resolve respiratory distress syndrome, including in newborns, without the need for exogenous surfactant preparations.

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INTRODUCTION

Special studies have shown disorders of surfactant activity in development of acute lung injuries (ALI), such as shock lungs, respiratory distress syndrome (RDS), pneumonia, which plays a significant role in the disease progression and severity (Zasadzinski, 2010). Surfactant, reducing the surface tension in the alveoli and thus ensuring their stability on exhalation, reduces the hydrostatic pressure in the pulmonary capillaries, preventing the transudation of fluid from them (Perez-Gil, 2010). Thus, absence of surfactant leads as well to atelectasis and pulmonary edema. The main active principle of surfactant is phospholipid dipalmitoyl-phosphatidyl choline, but there are some protein components, i.e., the surfactant is a lipoprotein, synthesis which takes place in alveolocytes type II (Haller, 2018). There are several attempts to explain decrease in surfactant activity. In particular, it is considered that the fluid and protein that enters the alveoli with edema disrupt the surfactant layer, and wash it away. However, there may also be a direct inhibition of surfactant under the influence of a number of toxic substances, among which are free fatty acids and lysophosphatides. Histochemical studies have shown that within 15 minutes after intravenous administration of oleic acid, changes in the surface-active film of the alveoli and its fragmentation occur.

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And there is direct evidence that in septic complications the level of free fatty acids increases, directly correlated with mortality. The surfactant activity in developing ALI can be inhibited by endotoxin level increase in the blood (Nogueira *et al*., 2008; Speer, 2011; López-Rodriguez *et al*., 2012 and Hartmann, 2014). All this was the indication to use exogenous surfactant in ALI and RDS treatment (Duffett *et al*., 2007 and Taeusch *et al*., 2008). Nevertheless, there were doubts concerning inability of exogenous surfactant to correct respiratory failure in RDS (Bream-Rouwenhorst, 2011 and Hamilton, 2017), especially in adults on the background of pancreatitis and sepsis (Willson, 2011). However, in newborns the use of surfactant provides a more rapid decline in FiO2 down to 40% and reduction in mechanical ventilation time [14]; but, nevertheless, it was noted that the use of surfactant gave only a temporary effect and survival increase up to 7 and 28 days was not achieved. This made it possible to reduce the ventilation time and length of stay in the intensive care unit, but there was no significant reduction in mortality rate (Shalamov *et al*., 1999; Vlasenko, 2006 and Vento *et al*., 2014). The aim of this work was to find out the causes of surfactant activity disorders and possibilities of their correction in patients with ALI.

MATERIAL AND METHODS

Surfactant activity study was carried out by J.A. Clements method (Clements, 1957). To do this, 3 g of lung tissue was cut in small pieces with scissors and the surfactant was

extracted in 50 ml of isotonic sodium chloride solution. After 30 minutes of exposure with constant shaking, the extract was placed in a special cuvette with a reinforced movable barrier. In this case, the area of the cuvette could gradually or stepwise decrease from 100 to 20%, which made it possible to record the hysteresis loop of the surface tension, which was measured by the force of retraction of the quartz plate on the Wilhelmi-Longmure scales. The most informative was the surface tension with a reduction in the area of the cuvette to 20% (corresponding to the exhalation of the lungs), which reflected the maximum possible activity of the surfactant in this extract or "minimum surface tension". In describing the results of the studies below, the term "surface tension "refers to the" minimum surface tension" expressed in mN/m. Surfactant activity was determined by measuring the surface tension of the lung extracts obtained in 12 patients who died in RDS phenomena due to acute pneumonia and infectious lung destruction. Surface tension in similar pieces of the lung tissue of 20 healthy dogs was considered the normal activity of surfactant, when these dogs underwent thoracotomy under intra-tracheal anesthesia and subsequent experiments not related to the current tasks with their further withdrawal from the experiment. To clarify the causes of surfactant activity disorders and in order to exclude the whole organism influence special experiments *in vitro* were performed when the dogs lungs extracts were added to 10 ml of blood of healthy dogs (5), healthy donors (5) and 10 patients suffering from ALI (RDS, pneumonia, abscess or gangrene of the lungs).

RESULTS

The surface tension of the healthy dog lungs extracts averaged 5.2±0.7 mN/m, while in patients it was 20.29±1.6 mN/m. However, a more detailed examination revealed that the surface tension in the extracts from the most altered parts of the lungs with their "hepatisation" (most often from the posterior-lower parts) reached 27.37±3.2 mN/m. At the same time, in areas of tissue with edema phenomena, but maintaining airiness (in the upper-anterior parts of the lungs), the surface tension was only 14.41±1.29 mN/m. Even more clearly this difference is visible in Fig. 1, where the hysteresis loops of the surface activity of the pulmonary tissue extracts from the lower and upper lobes of the right lung of patient K., 33 years old are presented. In vitro experiments, it was originally established the absence of any inhibitory effects on the surfactant activity of healthy people and animals blood. At the same time, addition of blood of sick people significantly suppressed the activity of surfactant (Table 1).

Table 1. Activity of surfactant added to healthy lung extract of blood of healthy animals, healthy donors and patients (mN/M)

№	The object of study	Baseline	After addition of blood
1	Healthy dogs	5.2±0.7	5.7±1.1
2	Healthy people	5.2±0.7	5.4±0.9
3	Patients with ALI	5.2±0.7	25.08±3.76*

Note: * indicates reliability of differences from the baseline (P<0.05).

This is more clearly shown in Fig. 2, which shows the effect of adding of the same patient K blood to the dog's lung extract.

DISCUSSION

The revealed difference in surfactant activity in different parts of the lungs could depend on its additional inhibition in the places where there was the maximum entrance of toxic components from blood plasma to the alveoli in case of toxic pulmonary edema. Direct inhibition of the surfactant by some substances circulating in the blood, at first glance, may seem unlikely, because the surfactant, lining the alveolus from the inside, is protected from the effects of these substances by the alveolus-capillary membrane. However, as RDS develops the permeability of this membrane becomes increased, which allows such toxic substances together with edematous fluid to penetrate into the alveolus. In this case, their direct contact with the surfactant is possible.

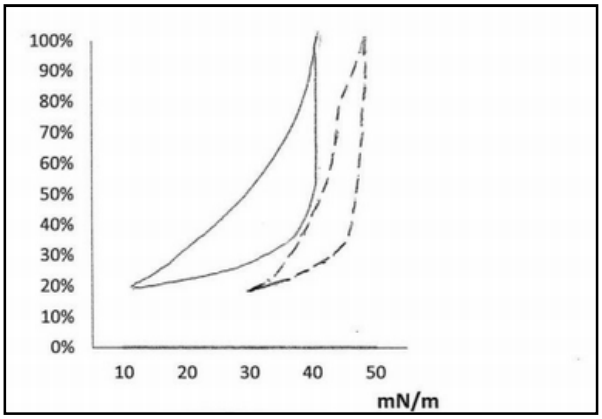

Fig. 1. Hysteresis loop extracts of the upper lobe surface tension (solid line) and lower lobe (dotteded line) of the right lung of the patient K., 33 years. The abscissa – the value of the surface tension in dyne/cm, on the ordinate axis – as a percentage of the cell area.

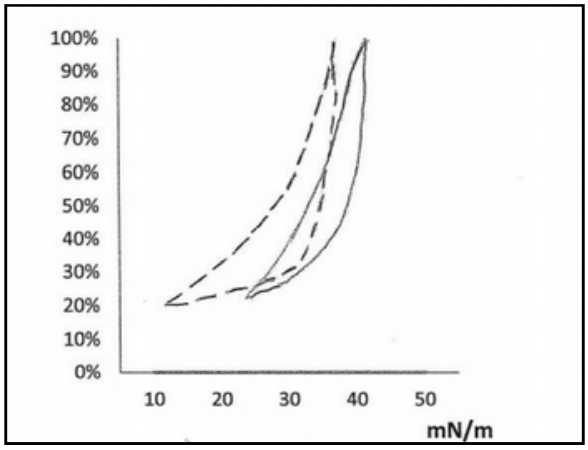

Fig. 2. The hysteresis loops of the surface tension of the extract of the lung of a healthy dog before (dotted line) and after (solid line) adding to it 10ml blood of the same patient K, 33 years old. Other symbols are the same as in fig. 1

This was confirmed by previously conducted experiments on simulation of ALI in animals (Voinov, 1991). The data obtained showed that the ALI is a result of endotoxicosis, and toxic pulmonary edema underlies RDS. The proof of RDS toxic nature promoted to develop its treatment tactics using various methods of detoxification – hemosorption and plasma exchange (Voinov, 2013; Voinov, 2013 and Voinov, 2013). Even when using the method of extracorporeal membrane oxygenation of blood (ECMO), the main effect was achieved by introducing a sorption column into the perfusion circuit. At the same time, even on the background of almost total lung damage, after 8-10 hours there was a restoration of lung airiness, and almost complete normalization was achieved in 24-36 hours. At the same time, when using ECMO only without detoxification, it takes up to two weeks to achieve the

same effect. On the other hand, with the help of detoxification, not resorting to ECMO or introduction of surfactant, it was possible to reduce mortality in severe forms of RDS from 73.7 to 31.3% (Voinov, 2016 and Voinov, 2017). Exactly the same positive effect was achieved by detoxification (membrane plasmapheresis), in the syndrome of respiratory disorders or RDS in newborns, including those deeply premature with body weight of up to 700g, in which the surfactant deficiency is considered to be the main pathogenetic mechanism of such lung lesions. At the same time without any additional surfactant in a few hours the radiographs showed recovery of the lungs airiness (Voinov, 2005 and Voinov, 2018). Thus, not quite satisfactory results of the surfactant use, on the one hand, and the achievement of much better results using detoxification methods in RDS, on the other hand, suggests that the true cause of the surfactant activity decrease is in its inhibition by toxic substances penetrating to the alveolus due to toxic vascular permeability. In this case, the introduced exogenous surfactant, as well as the natural one become exposed to these toxic substances and cease its activity. Detoxification, contributing to the elimination of vascular porosity, is pathogenetically more justified method of RDS treatment, because after toxic substances stop entering the alveolus the reproduction of natural surfactant is restored in the next few hours, which eliminates administration of its exogenous preparations (Voinov, 2011). This also refers to RDS in premature infants who do have a deficit of the surfactant, but most often RDS develops in an "adult" type as a toxic pulmonary edema when mother's endotoxins enter the fetus bloodstream if the course of pregnancy was complicated, which caused premature birth. Therefore, it is more justified to use detoxification in such newborns by a specially developed method of syringe membrane plasmapheresis (Voinov, 1996), after which there is no need for additional injections of exogenous surfactant.

Conclusion

Thus, the results of the studies performed, confirming the toxic nature of surfactant activity disorders in acute lung injuries also suggest that cessation of toxic substances entrance into the alveolus from the bloodstream, using detoxification methods is more justified than additional introduction of exogenous surfactant.

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