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Peculiarities of the influence of mitochondrial ATP-dependent K^+ channels activation on the function of external respiration under experimental pneumonia

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The studies were performed on male Wistar rats weighing 250-270 with experimental pneumonia (EP) induced by the method of A.M. Kulik. The animals were divided into the following groups: 1 – control; 2 - experimental pneumonia; 3 (first experimental group) - animals, which in parallel with the simulation of pneumonia were intraperitoneally administered uridine at a dose of 0.3 mg/100 g of body weight (daily within 1 week); 4 (second experimental group) - animals in which uridine was administered daily starting from day 4 (at the peak of pneumonia). Animals with EP were examined at 5th (n = 10), 9th (n = 8) and 12th (n = 6) days of the disease development, as well as 1 (n = 5) and 2 (n = 5) months after EP modeling. It was shown that in the first experimental group on the 5th day of EP development, an isoventilator restructuring of respiration was observed. In this group, from day 12 to the end of the study, there was a stenoventilator restructuring of breathing, which was characterized by an increase in tidal volume, alveolar ventilation, oxygen consumption and, accordingly, an increase in oxygen extraction from the alveoli and in the oxygen effect of the respiratory cycle. It can be assumed that in this group, an increase in the intensity of metabolism is provided by the effective activity of the respiratory system. In the second experimental group, isoventilator changes in respiration were observed with a gradual decrease in oxygen consumption and other indicators of the respiratory system efficiency. After 2 months, these changes became significant. Thus, we can talk about significant differences in the effect of uridine on the function of external respiration (i.e., apparently, on the activity of the mitochondrial ATP-dependent K^+ channel) during EP, which depended on the period of onset of uridine administration. Application of uridine immediately (1st experimental group) looks more effective and even has a stimulating effect on the respiratory function over a long period of experiment. The administration of uridine starting from the 4 partially normalizes the respiration parameters. However, after 1 month there is a depression of the functions of the respiratory system, which, probably, may further worsen. The reasons for the differences in the identified dynamics require further investigation.
Key words: experimental pneumonia; uridine; external respiration; respiratory rate; tidal volume; oxygen consumption; respiratory efficiency.

INTRODUCTION

The study of the pathogenesis of the occurrence and development of pneumonia (P) is one of the most relevant in modern pulmonology, as P encompasses 30-40% of all lung diseases and takes fourth place among the causes of mortality [1]. In recent years, according to the WHO, mortality from P has increased from 1 to 9%, which is due to resistance of pathogens to drugs and unclear pathogenetic mechanisms of P, in particular disorders of the respiratory zone cells. This leads to the altered permeability of cytoplasmic membranes, development of pulmonary edema, and subsequently to intraalveolar edema, as well as to a violation of energy metabolism in the lungs, which ultimately affects respiratory function with impaired oxygen supply.

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During P, the production of reactive oxygen species (ROS) is associated with inflammation and development of oxidative stress, which is important for cells and leads to organ damage, in our case - the lungs [2]. During severe oxidative stress, the ability of cells to eliminate ROS is depleted, which may contribute to an increase in the inflammatory response [3-5]. The protective effect of uridine may be associated with the activation of the mitochondrial ATP-dependent K^+ channels (mitoK_{ATP}), because uridine is a precursor of uridine diphosphate (UDP), which activates mitoK_{ATP} [6], and specific inhibitors of this channel, such as, for example, 5-hydroxydecanoate (5-HD), eliminate the protective effect of uridine [7, 8]. It was shown that uridine has a pronounced anti-inflammatory effect manifested, in particular, by a decreased production of pro-inflammatory cytokines [9]. Uridine can normalize even minor imbalances associated with the emerging pathological changes in animals and in isolated cells during the creation of experimental pathology, in particular, experimental pneumonia (EP). Moreover, the level of uridine in the blood is usually maintained at a relatively constant level; however, it is unclear which systems maintain this homeostasis [10, 11].

Currently available data indicate that the activation of mitoK_{ATP} is able to prevent the development of oxidative stress in the myocardium, the decomposition of ATP and creatine phosphate, reduces the generation of ROS and blocks the oxidation of glutathione [7, 8]. Moreover, it was shown, including our data, that mitoK_{ATP} is involved in the adaptation of animals to hypoxia, exerting a positive effect not only in the myocardium, but also in the lungs [12, 13], which is of particular importance in P, which is accompanied by the formation of a hypoxic state in the organism, at least of the respiratory type [14].

These observations allow us to conclude that positive effect of uridine in P may be at least partially explained by the function of mitoK_{ATP}. Moreover, it is believed that the action of uridine or its derivatives may be mediated through certain receptors, since cells contain receptors for UTP, UDP, and uridine (PY2 receptors), the activation of which directly influences metabolism [15, 16]. Therefore, receptors for uridine phosphates and uridine are proposed as targets for the development of new drugs [10]. The mechanisms mediating their action may be associated with an increase in the intracellular levels of UDF and UTF, leading to the activation of mitoK_{ATP} with an increase in the cell's energy capacity and the intensity of energy metabolism.

The aim of our study was to investigate the influence of mitoK_{ATP} activation by uridine on external respiratory function under experimental pneumonia.

METHODS

The studies were performed on 50 male Wistar rats weighing 250-270 g. Experimental pneumonia (EP) was induced according to the method of Kulik[17], by introducing into each lung 0.5 ml of non-sterile water heated to 70°C. Pneumonia was developed without the presence of viral or bacterial pathology (water was tested for infectious agents in the laboratory of the State Food and Consumer Services, Melitopol), and can be attributed to aspiration and/or partially post-traumatic pneumonia. Similar lung injuries are often observed in the neonatal period, but also occur in adulthood [18].

Animals were divided into the following groups: 1 - control, 2 - experimental pneumonia, 3 (first experimental group) - animals, which in parallel with the simulation of pneumonia intraperitoneally administered uridine at a dose of 0.3 mg/100 g of body weight (daily within 1 week), 4 (second experimental group) - animals in which uridine was applied throughout the experiment starting from the peak of pneumonia (4th day). Animals with EP were examined in the dynamics: on 5th (n = 10), 9th (n = 8) and 12th (n = 6) days of disease, as well as 1 (n = 5) and 2 (n = 5) months after EP modeling. The control group and the EP group

without the use of uridine contained 8 animals each. The rationale for uridine use was based on the fact that it activates mitoK_{ATP} channels, and through this effect influences the development of mitochondrial dysfunction, improving energy metabolism [19]. Violation of the latter is associated with pathological changes at the cellular and organelle levels, which contributes to the development of negative changes in the functioning of organs and systems in various types of pathology [20], including pneumonia.

The respiration and gas exchange pattern was recorded using an original automated setup as part of an MH6202 mass spectrometer (Ukraine) and a pneumotachograph with an MPX5050 respiration sensor. The signal from the pneumotachograph and the mass spectrometer was fed through an analog-to-digital converter to a computer, after which it was processed by the Oscillograph 2.0 program. Respiratory rate, tidal volume, amount of absorbed oxygen and emitted carbon dioxide were measured. From these indicators, other characteristics of the functional state of the external respiration system were calculated. Respiratory exchange rates were reported in the BTPS system (body temperature, vapor pressure), and gas exchange rates - STPD (standard temperature and dry air pressure).

The obtained experimental data were processed by the methods of variation statistics. Statistical processing of the results was performed using the computer program STATISICA 6. The obtained numerical data were presented as "mean ± standard error of the mean". This representation is correct because, according to the Shapiro-Wilkie test (W), the results were fitted into the normal distribution law [21]. To assess the reliability of the results, we used one-way ANOVA using a comparative Post Hoc Student-Newman-Keuls test. The results were considered statistically significant at $P < 0.05$.

RESULTS AND DISCUSSION

Parameters of the pattern of respiration and gas exchange in animals of the control group are given in Table. In further discussion of the results concerning the changes of the specified parameters in dynamics of experimental pneumonia under conditions of uridine application, control values were accepted for 100%.

Before analyzing the effect of mitoK_{ATP} activation in EP, it should be noted that in this group, the changes in the function of external respiration were expected and confirmed the available in the literature results [14]. Thus, at the peak of the EP development (4th day of the disease) there was an increase in pulmonary ventilation, which was manifested by an increase in both the minute volume of respiration (V_E) and the volume of alveolar ventilation (V_A). However, the established increase in lung ventilatory function was inefficient in providing oxygen to the body, as one of the main indicators of external respiration efficiency, namely, the ratio of alveolar ventilation to the minute tidal volume, was significantly lower than the values in control animals and fluctuated within 40-55% (at control values of 65-75%). Insufficient efficiency of lung ventilation should also include a decrease of the partial pressure of oxygen (P_AO_2) and an increase of the partial pressure of carbon dioxide (P_ACO_2) in the alveolar air to 80-85 and 38-46 mm Hg, respectively, (at control values of 95-105 and 35-40 mm Hg,

Characteristics of the pattern of respiration and gas exchange in rats of the control group

Respiration rate, min^{-1}	Respiratory volume, ml	Alveolar ventilation, $ml \cdot min^{-1} \cdot 100\ g^{-1}$	Oxygen consumption, $ml \cdot 100\ g^{-1}$	Emission of carbon dioxide, $ml \cdot 100\ g^{-1}$	Respiratory quotient	Delivery of oxygen to the alveoli, $ml \cdot min^{-1} \cdot 100\ g^{-1}$
121.2±7.8	2.04±0.16	14.41±1.01	0.40±0.26	7.73±0.51	0.78±0.14	2.99±0.21

respectively). Such changes can be considered as the presence of alveolar hypoventilation in EP [22]. In the dynamics of the study, the severity of the detected changes in external respiration decreased.

The use of uridine in the dynamics of EP development revealed significant differences in the effect of this drug on the function of external respiration and gas exchange, depending on the time of initiation of the application of mitoK$_{ATP}$ activator. In studies conducted by GM Mironova et al. [23] it was shown, that the preventive administration of uridine in the case of a nonspecific inflammatory reaction has a positive effect on energy metabolism, the oxidative-prooxidant system, etc.

We have shown that in the dynamics of EP development, the influence of the time of uridine administration on the studied parameters is often multidirectional. So the respiratory rate (f) was significantly higher than the initial level in the group with the application of uridine, carried out immediately, and when using the drug on the 5th day of the experiment, the f value did not significantly differ from the control values. Subsequently, no significant differences from the control were observed regardless of the time of drug administration and the period from the onset of EP development (Fig. 1A). This can be considered as a positive factor, since with the existing known positive dynamics of f (and most indicators of the external respiration function)

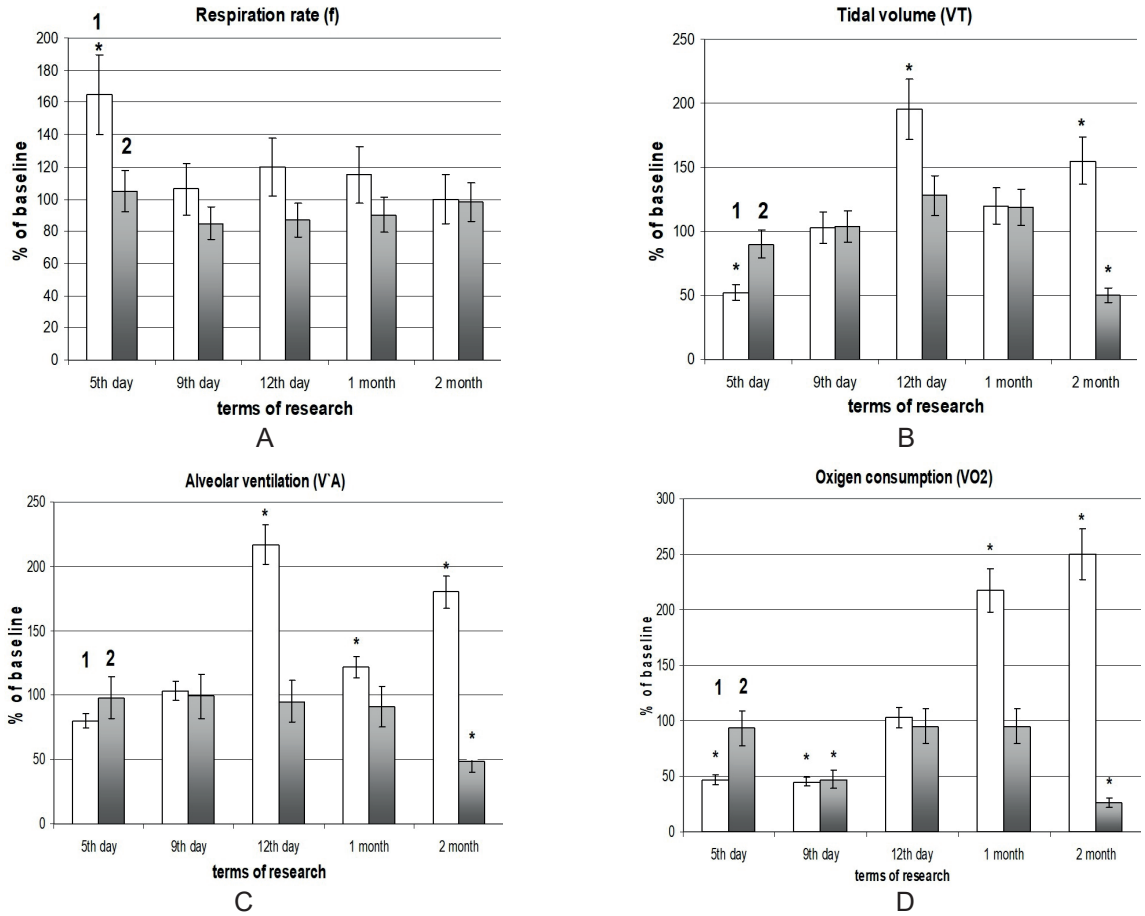

Fig. 1. Changes in some indicators of the function of external respiration and gas exchange at different times of uridine use under experimental pneumonia. 1 - the first experimental group, 2 - the second experimental group, *changes are statistically significant (P < 0,05) relative to the control, taken as 100%

with EP without its correction, they still do not reach the control values.

The respiratory volume (V_T) changed in waves throughout the experiment in the first experimental group: it decreased on the 5th day, on the 9th day it did not differ from the initial level, on the 12th day it significantly increased in relation to the control. After 1 month it did not differ from the initial level, while after 2 month it increased significantly. In the second experimental group, this indicator did not significantly differ from the initial level up to 2 months of the study, when a significant decrease of V_T was observed (Fig. 1B). The dynamics of the respiratory minute volume changes as a whole repeated the trends revealed for the tidal volume.

As for alveolar ventilation (V'_A), which determines the volume of air involved in gas exchange and which decreases with developed pneumonia, V'_A was higher than the initial level starting from the 12th day of EP development in the first experimental group. This indicates a positive dynamics of changes in the ventilatory response and oxygen supply to the organism, an increase in the gas exchange surface of the lungs (Fig. 1C). In the second experimental group, there was a tendency for this indicator to decrease throughout the entire experiment, especially after 2 months of the study.

If we analyze the oxygen consumption (VO_2) in untreated EP, it turns out that VO_2 in lung tissue significantly (approximately 30% - from 3.8 ± 0.2 to 2.7 ± 0.2 μl/h/mg dry matter) decreased on the 4th day of the disease, indicating a marked decrease in the level of oxidative metabolism in the lung tissue in this pathological process. In the future, it was possible to observe some recovery in the intensity of metabolic processes in lung tissue, but on the 12th day of the disease the level of tissue VO_2 remained reduced by an average of 15% compared to control values and was 3.2 ± 0.2 μl/h/mg dry substances. Similar changes on the 4th and 9th days of EP development were observed in relation to the total VO_2 in the organism of rats of both experimental groups, i.e. when using uridine at different periods of development of the pathological condition (Fig. 1D). However, on the 12th day of the study, the values of both groups did not differ from the initial level. After this, in the first experimental group, the consumption increased significantly reaching maximum after 2 months. This allows us to conclude that the drug has a normalizing and even mobilizing effect on the level of the energy metabolism reduced during the development of pneumonia [14]. On the contrary, in the second experimental group, VO_2 decreased to a level below the baseline also by the end of the experimental period. This may indicate differences in the effects of uridine used in different periods of EP development, despite its ability to positively influence energy metabolism. This requires further study.

The release of carbon dioxide changed in a similar way. Respiratory quotient (RQ) in both groups increased on the 9th day of the EP development (more significantly in the first experimental group), after which the tendency of its increase persisted on the 12th day. Then RQ returned to its original values.

The use of uridine had a significant and also different effects on the efficiency of external respiration, which were dependent on the period of initiation of the application of the drug. Thus, the oxygen effect of the respiratory cycle (VO_2 /f) decreased in relation to the initial level in the second experimental group to a greater or lesser extent throughout the study period. As for the first experimental group, a similar dynamics was observed at the initial period of EP development (from 5 to 12 days of the study), but after a month, and especially after 2 months, this indicator significantly increased and was (2 and 3 times, respectively) higher than the initial level (Fig. 2A). Such changes can be interpreted as an indicator of a significant increase in the efficiency of the organism's oxygen regimes [24].

This statement is also supported by the dynamics of changes in the delivery of oxygen to the alveoli (O_2 delivery): in the first experimental

group, starting from the 12th day, the indicator sharply increased, significantly differing from the initial level. Such dynamics persisted to a somewhat lesser extent until the end of the study period (Fig. 2B). In the second group, the O_2 delivery did not differ from the baseline level, decreasing after 2 months of the study.

In this connection, we can also note the peculiarities of the dynamics of oxygen extraction from the alveoli (O_2 extract). The O_2 extract decreased at 9th and 12th days in both experimental groups from the baseline. In the first group, after a month and until the end of the experiment, this indicator was significantly increased relative to the initial value (by 55 and 45%, respectively). In the second group it was also increased, however, only to the initial level.

CONCLUSIONS

The studies showed that in the first experimental group (the beginning of the use of uridine immediately after modeling the EP) on the 5th day of the development of EP, the respiratory rate increased against the background of a decrease in the tidal volume, thus, alveolar ventilation and the content of carbon dioxide in the alveoli, as well as its release, remained at baseline. That is, an isoventilator restructuring of respiration was observed. From day 12 to the end of the study in this group, there was a stenoventilator restructuring of breathing, which was characterized by an increase in tidal volume, alveolar ventilation, oxygen uptake and, accordingly, an increase in oxygen extraction from the alveoli and an increase in the oxygen effect of the respiratory cycle. It can be assumed that in this group an increase in the intensity of metabolism is provided by the effective activity of the respiratory system.

In the second experimental group (the beginning of the use of uridine on the 4th day - at the peak of the disease development), during the experiment, isoventilator changes in respiration were observed with a gradual decrease in oxygen consumption and other indicators of the efficiency of the respiratory system. After 2 months, these changes became significant.

Thus, our studies show significant differences in the effect of uridine on the function of external respiration, possibly, mediated by mitoK_{ATP} stimulation, which depended on the period of onset of uridine use. The use of uridine immediately with EP modeling looks more effective and even has a stimulating effect on the respiratory function for a long period of time. The beginning of the use of uridine on the fourth day partially normalizes the respiration parameters, however, after 1 month there is a depression of the functions of the respiratory

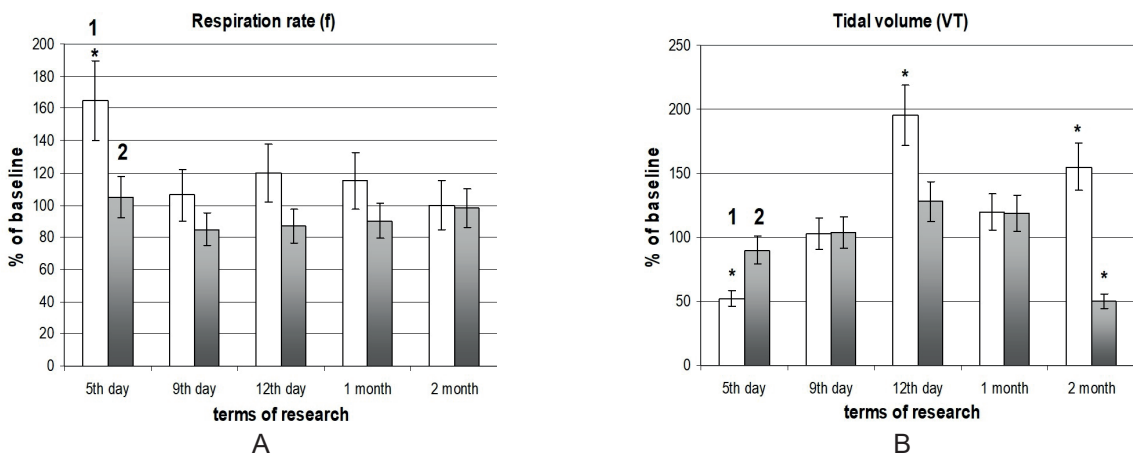

Fig. 2. Changes in some indicators of the external respiration effectiveness at different period of uridine use under experimental pneumonia. 1, 2 - experimental groups, *changes are statistically significant ($P < 0,05$) relative to the control, taken as 100%

system, which probably may further worsen. The reasons for the differences in the identified dynamics require further study.

The authors of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of co-authors of the article.

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ОСОБЛИВОСТІ ВПЛИВУ АКТИВАЦІЇ МІТОХОНДРІАЛЬНИХ АТФ-ЗАЛЕЖНИХ K^+ КАНАЛІВ НА ФУНКЦІЮ ЗОВНІШНЬОГО ДИХАННЯ ПРИ ЕКСПЕРИМЕНТАЛЬНІЙ ПНЕВМОНІЇ

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Дослідження проведено на 50 щурах-самцях лінії Вістар масою 250–270 г, котрим моделювали експериментальну пневмонію. Дослідних тварин розподілили на такі групи: 1-ша – контрольна; 2-га – експериментальна пневмонія; 3-тя (перша експериментальна група) – тварини, яким паралельно з моделюванням пневмонії внутрішньоочеревинно вводили уридин у дозі 0,3 мг/100 г (застосування уридину тривало щоденно протягом тижня); 4-та (друга експериментальна група) – тварини, яким уридин починали вводити на піку розвитку пневмонії (4-та доба) за аналогічною схемою. Тварин обстежували в динаміці: на 5 (n = 10), 9 (n = 8) та 12-ту (n = 6) добу розвитку захворювання, а також через 1 (n = 5) та 2 (n = 5) міс після моделювання пневмонії. Контрольна та дослідна (без застосування уридину) групи містили по 8 тварин. Експериментальну пневмонію моделювали за методикою Кулик, введенням у кожну легеню по 0,5 мл нестерильної води, підігрітої до 70°С . Показано, що в першій експериментальній групі на 5-й день розвитку пневмонії спостерігалася ізовентиляторна перебудова дихання, з 12-го дня і до кінця дослідження – стеновентиляторна, яка характеризувалася підвищенням дихального об'єму, альвеолярної вентиляції, поглинання кисню і, відповідно, збільшенням екстракції кисню з альвеол і підвищенням кисневого ефекту дихального циклу. Можна припустити, що в цій групі підвищення інтенсивності обміну речовин забезпечується ефективною діяльністю дихальної системи. У другій експериментальній групі протягом дослідження спостерігалися ізовентиляторні перебудови дихання при поступовому зниженні споживанні кисню і інших показників ефективності роботи дихальної системи. Через 2 міс ці зміни ставали значними. Таким чином, можна говорити про істотні відмінності впливу уридину на функцію зовнішнього дихання (тобто, мабуть, і на активність мітохондріального АТФ-залежного К-каналу) при пневмонії залежно від періоду початку його застосування. Використання уридину відразу виглядає більш ефективним і навіть чинить стимулюючу дію на дихальну функцію через тривалий проміжок часу. Початок його використання на 4-й день частково нормалізує показники дихання, однак через 1 міс спостерігається пригнічення функцій дихальної системи, яке, ймовірно, надалі може збільшуватися. Причини відмінностей виявленої динаміки вимагають подальшого вивчення.

Ключові слова: експериментальна пневмонія; уридин; зовнішнє дихання; частота дихання; дихальний об'єм; споживання кисню; ефективність дихання.

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