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Research Article



Features of the course of traumatic shock when using respiratory mixtures with a high content of inert gases

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Abstract

This study evaluated the efficiency of using gas mixtures with increased concentrations of inert gases on a hemorrhagic shock model in experimental animals. Massive blood loss is considered a trigger mechanism of severe pathophysiological reactions (impaired peripheral perfusion, acidosis, hemostasis system dysfunction, and multiple organ failure). Inert gases (helium, argon, and xenon) attract attention as potentially useful in various pathological conditions. The study was conducted on 15 same-sex pigs of the same breed, weighing 40–50 kg, randomized into three groups with five each: control group, inhalation of 100% oxygen; “agohhep” group, inhalation of the “Aroxxen” gas mixture: 35% argon, 58% oxygen, 0.2% xenon, and nitrogen as the rest of the volume; and “agohhep-krypto” group, inhalation of the gas mixture “Aroxxen-krypto”: 35% argon, 40% oxygen, 10% krypton, and nitrogen as the rest of the volume. Dynamic monitoring of vital signs and sampling of materials were conducted before blood loss, with blood loss of 20% and 45% of the volume of the circulating blood 60, 120, and 180 min after blood loss. The survival rate of animals and respiratory and circulatory states were evaluated by clinical and laboratory indicators. With blood loss of 45% of the circulating blood volume, no statistically significant differences in mortality were found between the groups. All animals survived for 180 min in the post-hemorrhagic period. In the agohhep-krypto group, average blood pressure values after blood loss and throughout the follow-up period were significantly higher than those in the control and agohhep groups ($p < 0.05$). During shock simulation as a result of blood loss, base deficiency gradually worsened in all groups. However, starting from the second hour of observation, base deficiency began to be compensated in the control and agohhep-krypto groups and the agohhep group, it continued to increase significantly ($p < 0.01$). During the follow-up after blood loss, the level of lactatemia significantly increased in the agohhep group (by 10 times at the end of the follow-up), which is significant different from those in the control and agohhep-krypto groups ($p < 0.01$). Thus, compared with the use of Aroxxen gas, the use of Aroxxen-krypto gas of the proposed composition in acute massive blood loss makes it possible to achieve a less pronounced attrition of the acid–base balance in experimental animals.

Keywords: nitrogen; argon; respiratory mixtures; inert gases; oxygen; krypton; xenon; acute blood loss; traumatic shock.

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Научная статья

Особенности течения травматического шока при использовании дыхательных смесей с повышенным содержанием инертных газов

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Резюме

Оценивается эффективность использования газовых смесей с повышенной концентрацией инертных газов на модели геморрагического шока у экспериментальных животных. Известно, что массивная кровопотеря рассматривается как пусковой механизм тяжелых патофизиологических реакций (нарушение периферической перфузии, ацидоз, дисфункция системы гемостаза, полиорганная недостаточность). Инертные газы (гелий, аргон и ксенон) привлекают внимание как потенциально полезные при различных патологических состояниях. Исследование проведено на 15 однополой свиньях одной породы, массой 40–50 кг, рандомизированных на 3 группы по 5 в каждой: контрольная группа — ингаляция 100 % кислорода; группа «агоххеп» — ингаляция газовой смеси «Агоххеп»: аргон — 35 %, кислород — 58 %, ксенон — 0,2 %, азот — остальной объем и группа «агоххеп-крипто» — ингаляция газовой смеси «Агоххеп-крипто»: аргон — 35 %, кислород — 40 %, криптон — 10 %, азот — остальной объем. Динамический контроль жизненных показателей и забор материалов для исследования проводили перед кровопотерей, при кровопотере 20 и 45 % объема циркулирующей крови, через 60, 120 и 180 мин после кровопотери. Выживаемость животных, состояние систем дыхания и кровообращения оценивали по клиническим и лабораторным показателям. Установлено, что при кровопотере 45 % объема циркулирующей крови статистически значимые различия по летальности между группами отсутствовали. Все животные выжили в течение 180 мин в постгеморрагический период. В группе «агоххеп-крипто» значения среднего артериального давления после кровопотери и на протяжении всего периода наблюдения были значимо выше, чем в контрольной группе и группе «агоххеп» ($p < 0,05$). В ходе моделирования шока в результате развивающейся кровопотери во всех группах постепенно нарастал дефицит оснований. Однако начиная со 2-го часа наблюдения, в контрольной группе и группе «агоххеп-крипто» дефицит оснований стал компенсироваться, а в группе «агоххеп» продолжал достоверно ($p < 0,01$) нарастать. Также в течение всего периода наблюдения после кровопотери в группе «агоххеп» существенно повышался уровень лактатемии (к концу наблюдения — в 10 раз), значимо различаясь с контрольной группой и группой «агоххеп-крипто» ($p < 0,01$). Таким образом, использование газа «Агоххеп-крипто» предложенного состава при острой массивной кровопотере позволяет добиться менее выраженного нарушения кислотно-щелочного баланса у экспериментальных животных в сравнении с использованием газа «Агоххеп».

Ключевые слова: азот; аргон; дыхательные смеси; инертные газы; кислород; криптон; ксенон; острая кровопотеря; травматический шок.

Как цитировать

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BACKGROUND

Blood loss is the most common cause of death in trauma and wounds [1–3]. Massive blood loss is considered a trigger for severe pathophysiological reactions, such as impaired peripheral perfusion, acidosis, dysfunction of the hemostatic system, and multiple organ failure. A decrease in oxygen delivery causes cellular hypoxia, triggering cell death [1, 2, 4]; thus, cytoprotection methods to improve treatment results are urgently needed.

In recent years, inert gases such as helium, argon, and xenon have gained attention because of their potential benefits in various pathological conditions. Several studies have shown that the inhalation of xenon and argon protects against ischemia–reperfusion injury [5] and has neuroprotective properties in craniocerebral injury [6–8]. A recent systematic review by Liang, Ahmad, and Dickinson [9] of 32 studies (14 for argon and 18 for xenon) in 1384 experimental models, including cerebral ischemia, craniocerebral injury, circulatory arrest, and cardiopulmonary bypass, demonstrated that both gases had positive neuroprotective effects ($p < 0.001$). The overall effect size was 18.1% for argon (95% confidence interval (CI), 8.1%–28.1%) and 34.1% for xenon (95% CI, 24.7%–43.6%). This indicated that xenon was generally more efficient than argon. Although xenon has demonstrated beneficial effects on various neurological injury models [10], its high cost complicates its routine use. Conversely, argon is easy to manufacture, is harmless, and has no environmental effects. To date, argon has demonstrated neuroprotective effects on models of stroke [11], subarachnoid hemorrhage [12], cardiac arrest [13–15], and hypoxic encephalopathy [16–18], reduced infarct volume [19], and prevented renal graft dysfunction in animal studies [20].

Currently, the concept of providing assistance to patients with wounds and injuries is formulated and linked to the “golden hour” rule, which promotes the provision of medical care in a hospital setting within an hour from the moment of injury or wounding. Considering that the peak mortality rate occurs in the first 30 min after injury, the early provision of qualified medical care is of paramount importance. However, adhering to this rule is not always possible. This period can often exceed 2–3 h, which is caused by the remoteness of the injury site, terrain, and inability to evacuate. Moreover, the delay in transporting patients to a hospital is a problem not only for civilian healthcare but also for providing assistance in armed conflicts.

In this regard, the medical services of the armies of different countries (Russia, USA, and Israel) and civil healthcare ambulance services are taking several measures to extend the “golden hour” and improve treatment outcomes for the wounded and injured. Thus, at the prehospital stage, transfusion of blood products, and in some cases, whole blood, is actively initiated. In the early 21st century, military conflicts contributed to the revision of the strategy of infusion–transfusion therapy in wars. Military doctors

in Israel, France, Germany, and since 2016, the USA have widely used lyophilized plasma in the first minutes after injury. In addition to “dried” plasma and to save individuals with the most severe wounds (with unstable hemodynamics), early whole blood transfusion has received renewed interest. Over the years of conflicts in Iraq and Afghanistan, American and British military doctors have gained extensive practical experience in the use of O (I) Rh-negative whole blood. In addition, to provide qualified assistance as early as possible, the deployment of advanced resuscitation and surgical teams closer to the combat zone has been organized, which has already been implemented in Russia, the USA, France, Germany, and Belgium.

Currently, respiratory support at the prehospital stage during the provision of care is limited to the use of an oxygen–air mixture. According to Gardner and Menon [6], in recent decades, active development has occurred in the study of the protective effectiveness of a normobaric breathing mixture of gases with a high content of inert gases to assist in patients with craniocerebral injury, lethal blood loss, and ischemic stroke of the brain.

Owing to the high effectiveness of inert gases at the preclinical and clinical levels, the question arises about the advisability of their use in managing patients with polytrauma. Thus, the use of gas–air mixtures can potentially extend the “golden hour” during the evacuation of a wounded or injured person, acting as an additional cardio- and neuroprotector and reducing the negative consequences of acidosis, hypothermia, and hypocoagulation.

This study aimed to evaluate the efficiency of using gas mixtures with increased concentrations of inert gases in a model of hemorrhagic shock in experimental animals.

MATERIALS AND METHODS

The study was conducted on 15 pigs of the same sex and breed that weighed 40–50 kg and were randomized into three groups of five animals each. In control group (CG) 1, 100% oxygen was inhaled. In “aroxxen” group 2 (AG), a gas mixture “aroxxen” was used consisting of argon (35%), oxygen (58%), xenon (0.2%), and nitrogen (rest). In the “aroxxen–krypto” group (AKG), the “aroxxen–krypto” gas mixture was used, consisting of argon (35%), oxygen (40%), krypton (10%), and nitrogen (rest).

Randomization was performed using the envelope method. Individuals with illness or in a weakened state were not included in the study. The experiments were conducted in compliance with the rules for the use and maintenance of laboratory animals in accordance with the Law of the Russian Federation “On Veterinary Science” No. 4979-1 of May 14, 1993,¹ and the recommendations

¹ Law of the Russian Federation “On Veterinary Medicine” No. 4979-1 of May 14, 1993 [electronic resource] Unofficial. source: Legal reference system ConsultantPlus[®] URL: https://www.consultant.ru/document/cons_doc_LAW_4438/?ysclid=lmjlexjdd6613553034 (date of access July 2, 2023).



Fig. 1. Oxygen and gas "Arroxen" supply system from the bag Ambu
Рис. 1. Система подачи кислорода и газа «Аррохен» из баллона через мешок Амбу



Fig. 2. Gas "Arroxen-krypto" supply through an automatic gas mixer
Рис. 2. Подача газа «Аррохен-кrypto» через автоматический смеситель газов

of the Declaration of Helsinki². The study was conducted in a specialized operating room for performing surgical interventions on large laboratory animals and consisted of four stages, namely, preparatory, modeling of severe acute blood loss, inhalation of oxygen or gas mixtures, and assessment of the effectiveness of the test object. The tests were performed under vivarium conditions, that is, the animals were kept at an ambient temperature of 19–23 °C in draft-free ventilated rooms. Before the tests, the personnel were instructed on the procedure of

conducting the tests, recording of the results, and safety measures.

At the preparatory stage, 1 day before the experiment, the animals were given limited food but had free access to water. Then, they were preweighed. Changes in vital signs were monitored, and research materials were collected before the blood loss simulation, with blood loss volumes of 20% and 45% of the circulating blood volume (CBV), and at 60, 120, and 180 min after blood loss.

When modeling acute severe blood loss in a dressing room, anesthesia was induced by intramuscular injection of a solution of Zoletil 100 (20 mg/kg animal weight) into the neck area. After anesthesia induction, the animals were placed on the operating table in the supine position, and tracheal intubation was performed to prevent the aspiration of saliva

² European Convention for the Protection of Vertebrate Animals Used for Experimental or Other Scientific Purposes (Strasbourg, 03/18/1986) [electronic resource]. Access from the Information System on Human Rights Documents and Thematic Publications // URL: <http://www.echr-base.ru/CED123.jsp> (access date July 2, 2023).

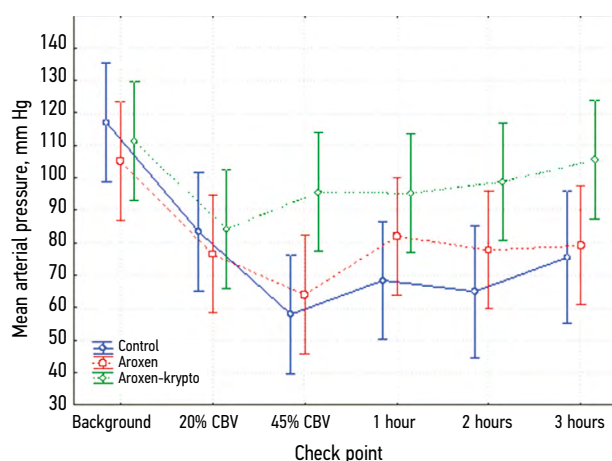


Fig. 3. Dynamics of mean blood pressure in groups with blood loss

Рис. 3. Динамика значений среднего артериального давления в группах на фоне кровопотери

and gastric contents into the respiratory tract. Throughout the experiment, the animals were breathing independently, and a solution of Zoletil 100 was administered intravenously to maintain anesthesia. A temperature measurement sensor was placed rectally.

Under ultrasound navigation, Seldinger catheterization of both femoral arteries was performed with the installation of 6-Fr sheaths for invasive monitoring of arterial blood pressure, modeling of blood loss, and blood sampling for tests.

Blood loss was simulated by collecting blood for 40 min through the left femoral artery using the Gemma apparatus manufactured by Plasmofilter (Russia). In all animals, the blood loss volume was 45% of the CBV. The total blood loss volume (in mL) and the percentage of the total CBV were calculated using the following equation:

$$V_{CBV} = M \times 0.07,$$

where V_{CBV} is the volume of circulating blood (in mL) and M is the mass of the animal (in g).

When using the test objects, after 20% blood loss of the CBV, the test gases or oxygen were supplied through the endotracheal tube, which, after reaching the final blood volume loss (45% of the CBV), continued for another 180 min.

Oxygen and aroxen were supplied from a cylinder through an ambu bag from Medplant (Russia) (Fig. 1), and aroxen-krypto gas was supplied through a gas mixer (Fig. 2).

The blood pressure (BP), heart rate (HR), and respiratory rate (RR) were recorded using a system of sensors connected to a device for monitoring vital functions. Blood gas composition and lactate content were determined using the VetScan i-STAT 1 analyzer from Abbott (USA).

The primary endpoint was the assessment of animal survival. The secondary endpoints were the results of the clinical assessment based on indicators of the respiratory and circulatory systems (BP, HR, and RR), laboratory assessment of differences in the partial pressure of carbon

dioxide (pCO_2) and oxygen (pO_2), oxygen saturation (SpO_2), acid–base balance (pH), base excess (BE), bicarbonate (HCO_3^-), and lactate levels in arterial blood.

Statistical analysis of the results was performed using MS Excel (Microsoft Corp., USA) and Statistica 10 (StatSoft. Inc., USA). Estimates of the average values of the studied indicators are presented in the text in the form of mathematical expectation (M), 95% confidence interval of mathematical expectation (95% CI), mean-square deviation (σ), median (Me), mode (Mo), and boundaries of the upper and lower quartiles (H_{25} and H_{75}). The sample size was not previously calculated. The significance of the differences was assessed using the Mann — Whitney U -test and Wilcoxon T -test.

The experimental study was approved by the Bioethics Commission at the St. Petersburg State Veterinary University (Protocol No. 4 of 05/06/2022).

RESULTS AND DISCUSSION

All animals met the study endpoints. No technical failures in gas inhalation occurred, and no animals were withdrawn from the study.

Primary endpoint. Despite achieving a blood loss of 45% of the CBV, no statistically significant differences in mortality were found between the studied groups of animals. During the study, one animal in the CG died 75 min after the end of blood loss. In the experimental groups, all animals survived for 180 min after the hemorrhagic period.

Secondary endpoints. In both CG and experimental groups, BP decreased because of blood loss. The mean BP is an indicator of tissue perfusion. No statistically significant differences were found between groups 1 and 2. In group 3, the mean BP values were significantly ($p < 0.05$) higher after the blood loss and throughout the follow-up period in comparison with the CG and AG, which were 95.8 ± 21.2 , 58 ± 12.9 , and 64 ± 16.9 mm Hg, respectively (Fig. 3).

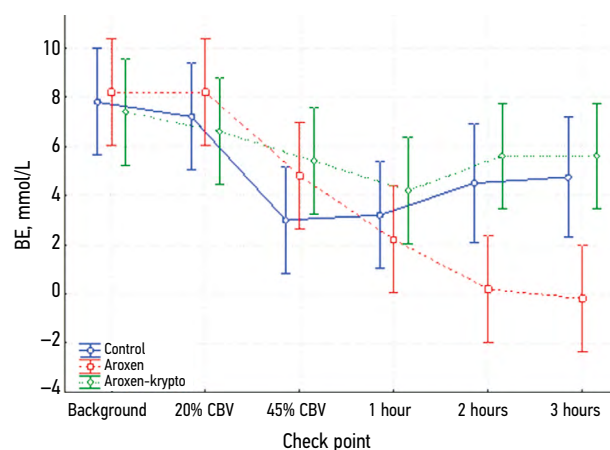


Fig. 4. Dynamics of bases and BE in groups with blood loss

Рис. 4. Динамика избытка оснований (BE) в группах на фоне кровопотери

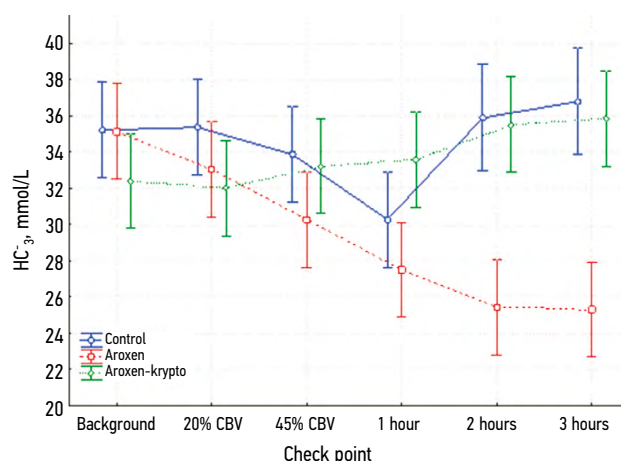


Fig. 5. Dynamics of HCO_3^- levels in groups with blood loss

Рис. 5. Динамика уровня HCO_3^- в группах на фоне кровопотери

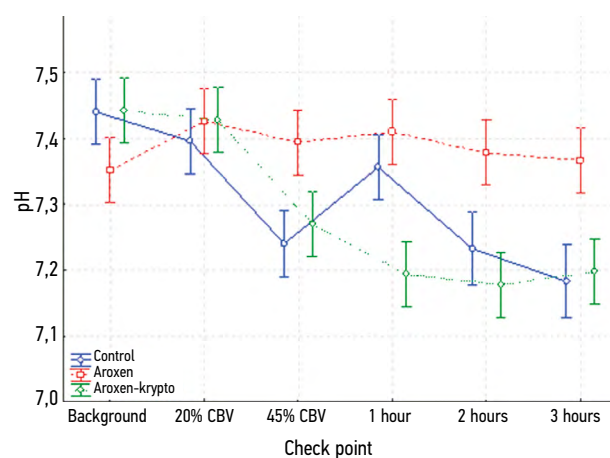


Fig. 6. Dynamics of pH levels in groups with blood loss

Рис. 6. Динамика уровня pH в группах на фоне кровопотери

As a compensatory reaction to acute massive blood loss, tachycardia developed in all groups. Throughout the follow-up period from the end of blood loss in the CG, the HR increased from 88 ± 6.3 to 133.2 ± 6.4 beats/min.

Whereas in the AG and AKG, it increased from 87.6 ± 13.8 to 109.8 ± 23.5 beats/min and from 81.6 ± 6.5 to 104.2 ± 17.9 beats/min, respectively. AG and AKG, which received different gas mixtures, also exhibited differences

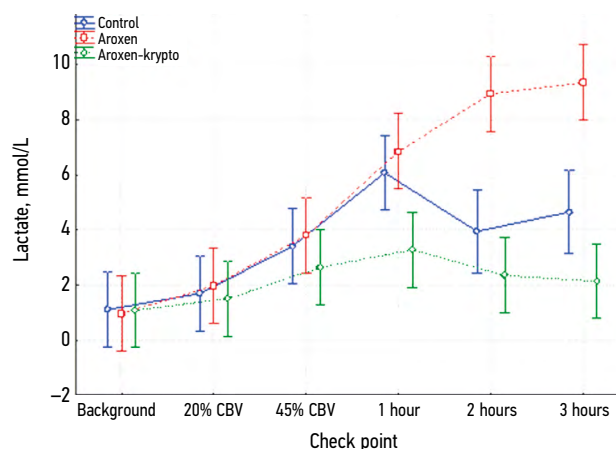


Fig. 7. Dynamics of lactate levels in groups with blood loss

Рис. 7. Динамика уровня лактата в группах на фоне кровопотери

in the dynamics of gas composition indicators and the acid–base balance of arterial blood. The most pronounced differences were found in the changes in the values of BE, lactate, pH, and HCO_3^- .

During the simulation of shock as a result of blood loss, alkalipenia gradually increased in all groups, whereas no statistically significant differences were found during blood loss. However, starting from the second hour of follow-up, the alkalipenia began to be compensated in the CG and AKG, whereas in the AG, the increase in alkalipenia persisted, and the differences became statistically significant, $p < 0.01$; Fig. 4).

Thus, in the AG that received the aroxen mixture, severe respiratory acidosis occurred, which was manifested as a decrease in the level of HCO_3^- (from the initial 35 ± 2 to 25 ± 4 mmol/L by the end of the experiment) and an increase in the blood pH level (from initial 7.35 ± 0.10 to 7.37 ± 0.04 by the end of the experiment). Meanwhile, in the CG and AKG, changes were less pronounced (Figs. 5 and 6). After 2–3 h, the differences between the groups became statistically significant. In addition, statistically significant ($p < 0.01$) differences were noted in the “baseline indicators” and “blood loss” points in each group.

The initial lactate level in the arterial blood of animals was comparable and amounted to 1.1 ± 0.5 (CG), 0.96 ± 0.46 (AG), and 1.09 ± 0.46 mmol/L (AKG). One hour after reaching the planned blood loss volume (45% of CBV) in the CG and AKG, the lactate level, having reached maximum values of 6.07 ± 4.18 and 3.28 ± 1.29 mmol/L, respectively, began to stabilize, and in the AG, it was still increasing. Throughout the follow-up period after blood loss, lactatemia in the AG worsened significantly in comparison with those in the CG and AKG ($p < 0.01$), and the lactate level by the end of the follow-up period exceeded the initial one by 10 times (Fig. 7). Moreover, the lactate level in the AKG throughout the follow-up period was lower, and its fluctuations were less pronounced than in the CG.

Thus, the study of traumatic shock accompanied by acute massive blood loss, using breathing mixtures with high contents of inert gases in an experiment on large laboratory animals, established that they positively affect the course of shock. However, this effect was achieved only in the group with a higher concentration of noble gases (AKG), which was manifested by less pronounced changes in the gas composition of arterial blood. In addition, changes in blood gas parameters in the CG were similar to those in the AG. The differences in lactate levels during the follow-up period and the changes in HRs were statistically significant. When using high concentrations of inert gases, hyperlactatemia was less pronounced, and the mean BP did not decrease below 90 mm Hg during blood loss, whereas when using 100% oxygen, the average BP was at 60 mm Hg.

CONCLUSION

1. The use of aroxen–krypto gas of the proposed composition for acute massive blood loss achieves a less pronounced change in the acid–base balance (hyperlactatemia and alkalipenia) in experimental animals in comparison with the use of aroxen gas.

2. When using aroxen–krypto gas, the level of blood lactate in the post-hemorrhagic period is statistically significantly lower than that in animals that received pure oxygen.

3. The use of gas–air mixtures with a high content of inert gases can potentially improve the treatment outcomes of wounded and patients with acute massive blood loss because of the less severe impairment in the acid–base balance and maintained BP levels during their evacuation.

4. Considering that the addition of inert gases (argon, krypton, and xenon) to the oxygen breathing mixture increases the efficiency of anti-shock and anti-hypoxic oxygen therapy for massive blood loss, further experimental

and clinical studies with the possible subsequent introduction of this technology into medical practice appear promising.

5. The prospects of such studies are associated with the possibility of combining the composition of the artificial breathing mixture with the concentrations of gases included in it and the safety of increasing the duration of exposure caused by the reduced risk of side effects that occur when breathing pure oxygen. The therapeutic efficiency of gas mixtures will probably increase if the concentrations of xenon, krypton, and argon increase.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

The contribution of each author: A.M. Nosov — research planning, performing surgical interventions, writing an article; V.A. Petrov — research planning, development of gas-air mixtures; K.N. Demchenko — performing surgical interventions, data analysis; N.A. Morgunov — research planning, article writing; R.E. Lakhin — general concept development, statistical data processing; N.A. Zhirnova — laboratory blood analysis, writing an article;

S.P. Kolvzan — search and analytical work, writing an article.

Competing interests. The authors declare that they have no competing interests.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Вклад каждого автора: А.М. Носов — планирование исследования, выполнение оперативных вмешательств, написание статьи, анализ данных; Н.А. Моргунов — планирование исследования, написание статьи; Р.Е. Лахин — разработка общей концепции, статистическая обработка данных, разработка общей концепции; Н.А. Жирнова — лабораторный анализ крови, написание статьи; С.П. Колвзан — поисково-аналитическая работа, написание статьи.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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