Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i17.2747

"EXPLORING THE MECHANISMS OF HYPOTENSIVE REFLEXES ELICITED BY OZONE THERAPY: AN EXPERIMENTAL STUDY"

Kupriyanov Sergey Vladilenovich[1], Mohammad Alhasan[2]*, Uchterova Nadezhda Dimitrievna[3]

[1]I. N. Ulianov Chuvash State University, head of normal and pathological physiology department, Dr. Habil. Med., Professor, 428032, Cheboksary, Leningradskaya str., 14, flat 35, E-mail: Kuper-SV@yandex.ru, Tel. 8(8352)58-67-93, mobile phone: 8(917)672-36-09, ORCID https://orcid.org/0000-0002-5272-7397
[2]*I. N. Ulianov Chuvash State University, 5, Rue de la Forêt 6196 Eisenborn Junglinster, luxembouerg, E-mail: mohammedalhasan395@gmail.com, mobile phone : +352 661 034 827, ORCID: https://orcid.org/0009-0005-9776-9979
[3]I. N. Ulianov Chuvash State University, PhD in Medicine, associate professor, 428023, Cheboksary, Grazhdanskaya, 109, flat 312, E-mail: 55dd@mail.ru, mobile phone: 8(906)136-73-41, ORCID: https://orcid.org/0000-0003-1808-6845

***Corresponding Author: -** Mohammad Alhasan
*I. N. Ulianov Chuvash State University, 5, Rue de la Forêt 6196 Eisenborn Junglinster, luxembouerg, E-mail: mohammedalhasan395@gmail.com, mobile phone : +352 661 034 827, ORCID: https://orcid.org/0009-0005-9776-9979

Abstract:
We examined the effects of ozonated saline infusion into the hemodynamically isolated segment of vertebral arteries on cardiorespiratory reflexes in anesthetized cats. This intervention elicited concomitant reflex responses, such as systemic hypotension and respiratory depression. These cardiorespiratory inhibitory effects were specific to the initial perfusion with ozonated solutions.

Subsequent infusions of ozonated saline into the same isolated segment of vertebral arteries induced variable reflex responses of the respiratory and cardiovascular systems. These responses were either bidirectional or biphasic, with a predominance of a hypertensive response. These modifications were related to the nonspecific adaptive effects of ozone exposure.

Under the conditions of Novocain blockade of vertebral artery chemoreceptors, all the reflex responses were abolished. This confirmed their reflexogenic origin. Therefore, the effects of ozone exposure, similar to any other pharmacological agent used for therapeutic purposes, depend on its concentration in the organism. Ozone exposure exhibits both a local humoral effect, extensively documented in the literature, and general reflex effects that are demonstrated in this study. These reflex effects are mediated by vascular reflexogenic zones and their respective CNS centers.

Keywords: vascular reflexogenic zone, vertebral artery, cardiorespiratory system, ozone, ozonetherapy.

Introduction:

Gases are widely used in practical medicine. At the same time, some of them, relatively described not long ago, are difficult to recognize as well-studied [23]. The widespread utilization of ozone-oxygen mixtures in practical medicine highlights the necessity for a comprehensive investigation into the mechanisms through which ozone affects the human body. In clinical practice, ozone is recognized for its various properties, including detoxification, analgesic effects, stimulation of oxygen-dependent processes, bactericidal (fungicidal and viricidal) actions, optimization of pro- and antioxidant systems, hemostatic and anticoagulant effects, as well as immunomodulation. However, the underlying mechanisms responsible for these effects have not been sufficiently explored and are currently attributed solely to its direct interaction with tissues or foreign agents [10, 12, 15, 17 – 19, 34]. Notably, there is a lack of information in the available literature regarding the impact of ozone on the central mechanisms regulating homeostasis, particularly within vital systems such as the cardiovascular and respiratory systems.

Previous research conducted in our laboratory has demonstrated that perfusion of the hemodynamically isolated zone of the vertebral arteries (maintaining solely nerve connections with the body) with physiological concentrations of lactic acid solutions, alkaline and buffer solutions, as well as therapeutic doses of angio protectors, elicits reflex changes in arterial vessel tone, cardiac activity, and systemic arterial pressure (SAP) [5, 6, 8, 9, 30]. These studies have elucidated the central mechanisms underlying the emergence of pressor and depressor reactions originating from reflexogenic zones of the vertebral and carotid arteries.

Building upon the aforementioned findings, the present study aimed to address the following inquiries: Does the activation of chemoreceptors in the zone of the vertebral artery by a physiologically concentrated solution containing therapeutically effective doses of ozone impact systemic blood pressure levels and external respiration? Furthermore, do the administration of ozonated solutions, as employed in clinical settings, have the potential to induce not only a direct effect on tissues (as established in the literature), but also elicit concurrent reflex reactions within the respiratory and cardiovascular systems? If so, what is the nature of these central responses?

Method:

The experiments were conducted on adult cats of both genders, weighing between 1.9 and 3.7 kg, under urethane anesthesia (administered at a dosage of 1.0 gram per kilogram of animal body weight). The cats had an initial arterial pressure ranging from 105 to 135 mm Hg, and the experiments were carried out under natural respiration conditions.

To achieve hemodynamic isolation of the reflexogenic zone of the vertebral arteries, we employed the technique described in previous publications [4, 7]. A leading cannula was inserted into the isolated vascular zone, usually on the right side of the cat's body. An ozonated Ringer-Locke solution, maintained at a temperature range of 37-38°C and a constant pressure of 100±15 mm Hg, was delivered through this cannula from the Marriott vessel. The perfusate was allowed to flow out through the incised extracranial segment of the vertebral artery (at the second cervical vertebra), with the distal end of the artery ligated. This method ensured perfusion of the reflexogenic zone without accompanying pressure changes or activation of baroreceptors. As a control, we introduced a pure physiological solution into the vertebral artery zone. Additionally, to block adjacent tissues, novocaine blockade was performed in the perfusate outflow area. Another crucial method of control involved the introduction of an ozone solution into the vertebral artery following a 15-20 minute novocaine blockade of its chemoreceptors.

The bubbling of the saline (physiological) solution was carried out using standard procedures [11, 15, 19], utilizing equipment from renowned manufacturers such as AO "Lepse Plant" (Russia) and "Medozons-BM" (Russia). The ozone concentration in 200-400 ml of saline solution was determined based on the duration of bubbling. Under these conditions, a 10-minute exposure resulted in an ozone concentration ranging from 400 to 1600 micrograms/L in the solution. Such a solution is commonly used for intravenous injections in clinical settings [1, 11]. For solutions with lower concentrations, the ozonation time was reduced to 5 minutes.

To stimulate the chemoreceptors in the vertebral artery zone, the aforementioned ozone-oxygen mixture solution was administered until reaching the maximum severity of systolic arterial pressure (SAP) [25-29] and external respiration reactions, at which point the intervention was discontinued. The duration of these interventions varied from 50 to 90 seconds, with some cases lasting longer. Arterial pressure was measured in the femoral artery using the universally accepted occlusive method, while external respiration was recorded through tracheostomy pneumography. Cardiorespiratory reactions were assessed by evaluating changes in SAP levels (mmHg) and the amplitude of external respiration as a percentage of its initial, pre-intervention level.

The statistical processing involved utilizing the recorded hemodynamic and respiratory system indicators measured during the peak intensity of their respective reactions in each experiment. The data were quantitatively assessed in absolute units or percentages relative to their initial (pre-intervention) levels. In cases where control interventions were used and their values were considered as 0, the data were evaluated accordingly. The collected data were processed and analyzed using the MS Excel 2016 spreadsheet environment and the Statistica 7.0 package (StatSoft Inc., USA). The significance of the results was evaluated using Student's t-test, with p-values below 0.01 considered statistically significant. The analysis was conducted on an IBM PC Pentium III computer, and the sign test method was also employed [3].

- **RESULTS AND THEIR DISCUSSION**
- 59 observations were carried out on 18 animals (Table 1).

Table 1
Reflex effects on external respiration and systemic arterial pressure (SAP)
- **from chemoreceptors of the vertebral artery zone**
- **when ozonated saline solution is injected into them**

Nature of the intervention	Direction of the reaction	Severity of reactions (M±m); relative standard deviation	*p*	Number of observations, n	Sign test rate (reliability with probability)
First perfusate introductions (at the beginning of the experiment)	*	The amplitude of external respiration (in % of its initial level) – 50.46±6.98; v=0.062	≤0.01	31	99 – 99.5 %
		SAP level – 10.1±1.12 mmHg; v=0.054	<0.01		
	**	-	-	8	-
Subsequent injections	*	-	-	2	-
	**	-	-	18	-
Novocaine blockade of chemoreceptors					
Perfusion with an ozone-oxygen mixture	No changes in cardiorespiratory activity		-	9	100 %

- Notes:
- Total number of observations (including control ones) – 68.
- * – Combined respiratory depression and a decrease in the level of SAP.
- ** – Simultaneous responses of external respiration and arterial pressure of other directions.

*1-1

Intervention	Percentage of interventions with a decrease in SAP level	Average reduction of SAP in mmHg	Average suppression of external respiration in percentage of initial value
Ozone injection	80.43%	10.1 ± 1.12	50.46 ± 6.98

| Novocaine block | 0% | 0 | 0 |
| Saline perfusion | 0% | 0 | 0 |

*1-2

Intervention	SAP level before intervention in mmHg	SAP level after intervention in mmHg	Change in SAP level in mmHg
Ozone injection (first time)	120.8 ± 2.3	110.7 ± 2.1	-10.1 ± 1.2
Ozone injection (second time)	121.3 ± 2.4	123.5 ± 2.6	+2.2 ± 1.4
Novocaine block	121.7 ± 2.5	121.8 ± 2.5	+0.1 ± 0.9
Saline perfusion	122.1 ± 2.6	122.2 ± 2.6	+0.1 ± 0.8

According to the data presented in the table, a decrease in the level of systolic arterial pressure (SAP) was observed in 80.43% of the interventions, with an average reduction of 10.1±1.12 mmHg. Simultaneously, there was a suppression of external respiration, amounting to 50.46±6.98% of its initial value. Throughout the experiment, a depressive reaction of the general blood pressure was consistently observed at the initial stage.

Subsequent to repeated ozone injections into the same vascular reflexogenic zone (in 20 cases), the reactions exhibited instability, with a notable prevalence of blood pressor response. However, the decrease in SAP level could not be replicated after a 15–20 minute interval following the introduction of 0.5 ml of a 2% novocaine solution into the vertebral artery zone (in 9 additional control observations) (refer to Figure 1).

In the field of physiology, the disappearance of reactions subsequent to pharmacological blockade of the receptive field using novocaine is considered one of the primary methods to establish their reflexive nature. Furthermore, the described reflexes were not reproduced when the vertebral artery was perfused with a "pure" saline solution devoid of ozone, indicating that these reactions were not a result of baroreceptor activation in the studied zones.

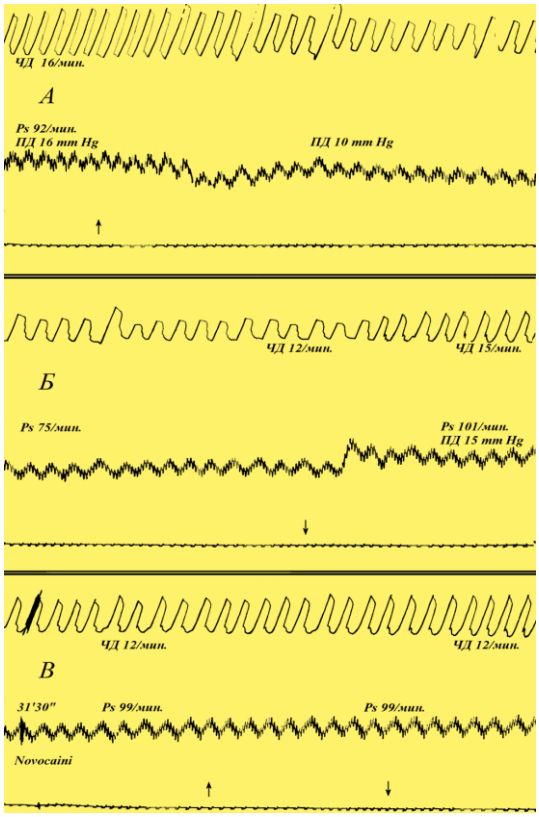

Fig. 1. The activity of the respiratory and cardiovascular systems during the introduction of ozonated saline solution into the vertebral artery zone (before and after its novocaine blockade).

А, Б and В are consecutive parts of one kimogram (obtained on one animal).
А – the initial state of the animal and the beginning of the reaction to the ozonated solution introduction (beginning moment of perfusion is marked with an up arrow);
Б – continuation of the same reaction and exit from it (termination of perfusion – down arrow);
В – the same intervention after novocainization of the vertebral artery zone.
Top down (in А, Б and В): pneumogram; systemic arterial pressure level (indicating heart rate and pulse pressure, in part В the stop of the recording is indicated – 31 min. 30 sec.); the beginning and end of interventions are indicated by arrows; time mark (scale division – 2 sec.).
Abbreviations: ЧД – respiratory rate, Ps – pulse, PP – pulse pressure, /мин. – per minute.

The acquired data clearly needs to be divided into two distinct groups. The primary group pertains to the reflex changes in the cardiorespiratory functional system, which were observed in response to the initial administrations of ozonated saline solution into the vascular reflexogenic zone at the beginning of the experiment. The secondary group focuses on the subsequent ozone activation of chemoreceptors in the studied zone, specifically examining the changes in external respiration and SAP.

During the initial perfusion phase, characterized by one to four injections of ozonated solution, a statistically significant ($p < 0.01$) suppression of respiratory function was observed, accompanied by a simultaneous decrease in SAP levels. This finding suggests a consistent impact on the reflexes of both the respiratory and cardiovascular systems, pointing towards a unidirectional effect.

However, as multiple injections were administered in the same zone, the reactions of external respiration and arterial pressure displayed a distinct two-phase pattern, as illustrated in Figure 2. Interestingly, repeated perfusions often triggered reactions of SAP increase and stimulation of external breathing, indicating varying and directional responses.

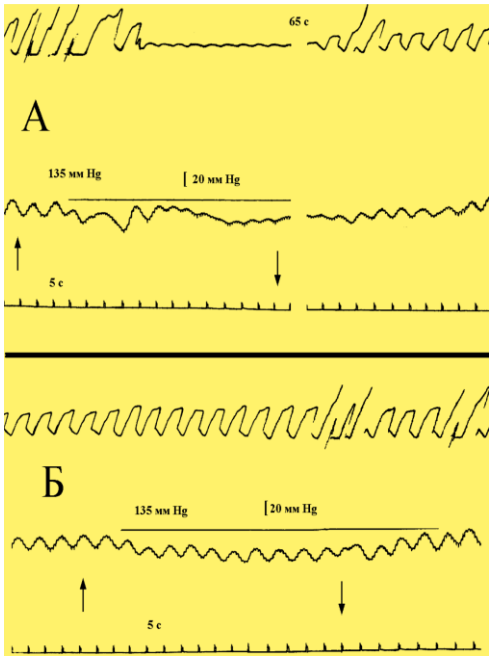

Fig. 2. The occurrence of multidirectional reactions of the respiratory and cardiovascular systems with repeated perfusion of the vascular reflexogenic zone by ozonated Ringer-Lockes solution (of one animal).

А – the first introduction (65 с – the segment of registration of observations lasting 65 seconds was removed), Б – repeated perfusion (the same animal).

Top down (on А and Б): pneumogram, level of systemic arterial pressure (with an isoline, pressure level and calibration of the severity of the change), the intervention beginning and its end (arrows), time mark (5 с – 5 sec.).

How can we explain such a change in reactions? What is the potential physiological significance of the reflexes observed on general blood pressure and external respiration when the chemoreceptors in the vertebral artery zone are activated by ozone?

It is well-known that ozone, when in solution, dissociates into free (molecular) and atomic oxygen. This free oxygen has an impact on the chemoreceptors found in reflexogenic zones of the blood vessels, leading to a reflexive decrease in SAP, which is opposite to the effect of CO_2 on these chemoreceptors. The depressant effect of oxygen on SAP levels in the reflexogenic zones is already established. This depression is necessary due to the initial increase of oxygen intake by the tissues [2**,33,35,**37]. Excessive oxygen tension in cells can have negative effects on metabolism [16**,32**] and result in oxidative stress, potentially causing structural damage to the cells of blood vessels [20, 21]. Therefore, by introducing ozone in our experiments, we simulate the development of hyperoxia in the entire organism. The depressive reflex we observed leads to a decrease in the excess oxygen intake by the tissues, achieved by reducing the blood flow to them. Additionally, compensation for hyperoxia occurs through the suppression of external respiration. Thus, the respiratory and cardiovascular systems work together as a cardiorespiratory functional system, ultimately resulting in decreased oxygen supply to the tissues. This reflexive effect of ozone is in line with its known direct α-adreno blocking effect on smooth muscle vascular cells, as described in the literature [15]. Clearly, these two actions synergize, leading to the dilation of major arteries and a hypotonic effect. The reflexive reactions we described, such as the decrease in arterial pressure and respiratory depression, are compensatory and adaptive in nature, and are being reported by us for the first time in this paper. We have been unable to find similar data in other sources.

Furthermore, we observed that the prolonged administration of ozone leads to an increase in the concentration of atomic oxygen, which can have an alternative effect on chemoreceptors. Furthermore, undissociated ozone is not a natural stimulus for the body's chemoreceptors and may not have a specific target. The higher concentration of atomic oxygen and undissociated ozone manifests their aggressive toxic properties, compromising the integrity of cell membranes, particularly in the chemoreceptors we studied. This could be due to increased oxidation of phospholipids, lipoproteins, and damage to polypeptide chains and proteins [1]. It is worth noting that ozone, when present in high concentrations and with prolonged exposure, has a toxic effect on the entire organism [13,25,36], as well as on various rheological and biochemical parameters of the blood in vitro, such as lipid peroxidation of the erythrocyte membrane [14,22]. The body's response to an actual painful stimulus is consistent, typically resulting in an increase in systemic blood pressure and an increase in respiration [22-24**,31**].

CONCLUSION:

The effects of ozone, much like any medicinal substance used for therapeutic purposes, are dependent on its concentration within the body. The duration of exposure plays a significant role as well. An ozonated saline solution with an ozone-oxygen mixture concentration ranging from 400 to 1600 micrograms/L can exhibit both therapeutic and toxic effects. The actions of ozone encompass both local humoral effects (which have been extensively described in the literature) and general reflexive effects. The latter influences the functioning of the cardiorespiratory system indirectly through the vascular reflexogenic zone of the vertebral arteries.

It is reasonable to hypothesize that, in clinical practice, the reflexive component of the hypotensive effects observed in ozone infusion therapy is more pronounced. This is due to the fact that within the entire body, the reflexes we discovered for the first time are not limited to the chemoreceptors solely in the vertebral arteries but also involve all vascular reflexogenic zones.

Recommendations and future projects that can be worked on:

- Exploring the rostral ventrolateral medulla and the sympathetic ganglia.
- Comparing the effects of ozone therapy with other forms of oxygen therapy, such as hyperbaric oxygen therapy or normobaric oxygen therapy.
- Investigating the optimal dose, duration, frequency, and route of administration of ozone therapy for different conditions.
- Evaluating the long-term effects and side effects of ozone therapy.

REFERANCES:

1- Alekhina S.P. et al. Ozone therapy. - N.Novgorod: Vector-TiS, 1996. - 16 p.
2- Guyton A. Physiology of circulation: Cardiac output and its regulation. - M.: Medicine, 1969. - 472 p.
3- Kaminsky L.S. Medical and demographic statistics. - M.: Statistics, 1974. - 351 p.
4- Kupriyanov S.V. The state of systemic arterial pressure in cats during stimulation of chemoreceptors of the reflexogenic zone of vertebral arteries // Aviakosm. and ecol. medicine. - 1996. - V. 30, No. 1. - P. 60-62.
5- Kupriyanov S.V. Chemoreflexes of the zone of vertebral arteries and carotid sinus in acidosis and alkalosis in acute experiment and clinic // Kazan medical journal. - 2007. - V. 88, No. 1. - P. 20-23.
6- Kupriyanov S.V. Functional characteristics of the interoceptive zone of vertebral arteries // Morphological reports. - 2007. - No. 3-4. - P. 39-43.
7- Kupriyanov S.V., Agadzhanyan N.A. Reflexogenic zone of vertebral arteries. - Cheboksary: Publishing house of ChSU, 2005. - 136 p.
8- Kupriyanov S.V., Gavrishkina N.V. Chemoreceptor activity of the zone of vertebral arteries // Ross physiol journal named after I.M.Sechenov. - 2004. - V. 90, - No. 8. - P. 485-488.
9- Kupriyanov S.V., Kupriyanov V.S., Drandrov G.L., Vodyanov N.G. The role of reflexogenic zones of vertebral and carotid arteries in the formation of cardiovascular respiratory functional system // Bulletin of restorative medicine. - 2008. - No. 1 (23). - P. 78-85.
10- Lisitsyn D.M. et al . Kinetic parameters of oxidation of individual fatty acids by ozone // Bull exp biol and med. - 2004. - V. 138, No. 11. - P. 517-519.
11- Maslennikov O.V., Kontorschikova K.N. Practical ozone therapy. - N.Novgorod: Vector TiS , 2003. - 52 p.
12- Muratov I.D. Use of ozone for local treatment of purulent-inflammatory processes // Children's surgery. - 2005. - No. 1. - P. 50-53.
13- Mukhina I.V., Zhemarina N.V., Evdokimova O.S., Mironov A.A. Functional state of the rat brain during parenteral administration of ozonated saline solution // Materials XX Congress physiol. society named after I.P.Pavlov. - M., 2007. - P. 345.
14- Pavlova O.E. Influence of ozone on rheological properties of blood : Author's abstract dis cand biol sciences. - M., 1998. - 17 p.
15- Sizova E.N. et al . Influence of ozone on contractile activity and chemoreactivity of longitudinal musculature of the horn of the uterus of non-pregnant rats // Ross physiol journal named after I.M.Sechenov. - 2003. - V. 89, - No. 4. - P. 427-435.
16- Chandan K. Sen, Osmo Hänninen Glutathione homeostasis: cardiac physiological protection against oxygen toxicity caused by physical exercise // Physiol journal named after I.M.Sechenov. - 1995. - V. - 81, - No. 11. - P. 143-150.
17- Bocci V. Ozone as a bioregulator Pharmacology and toxicology of ozonetherapy today // J Biol Regulators and Homeostatic Agents. - 1997. - V. 10, - No 2/3. - P. 31-53.
18- Dotan Y et al Ibid - 2004. - No 43. - P 1-28.
19- Dvorak V. Ozone Use of ozone in industry and medicine // New in dentistry. - 2005. -V. 128, - No 4. - P. 84-88.

20- Minuz Pietro, Fava Cristiano, Cominacini Luciano. Oxidative stress, antioxidants and vascular damage // Brit J Clin Pharmacol. - 2006. - V. 61, - No 6. - P. 774-777.
21- Procaccini E.M., De Martino G., Picone G., D'Alicandro G., Monfrecola G.G. Effects of hyperbaric oxygen on cutaneous microflow // Ital Dermatol e Venereol. - 2005. - V. 140, - No 6. - P. 663-667.
22- Koller E.A. et al. Studies on the role of the lung deflation reflex // Respir Physiol. - 1970.
23- Nakao A., Sugimoto R., Billiar T.R., McCurry K.R. Therapeutic antioxidant medical gas // J Clin Biochem Nutr. - 2009. - No 44. - P. 1-13.
24- Anand I.S., Chandrashekhar Y., Rao S.K., Malhotra R.M., Ferrari R., Chandana J., Ramesh B., Shetty K.J., Boparai M.S. Body fluid compartments, renal blood flow, and hormones at 6, 000 m in normal subjects // J Appl Physiol. - 1993. - No 74. - P. 1234-1239. **CAS PubMed Web of Science® Google Scholar.**
25- Heindl S., Lehnert M., Criée C.-P., Hasenfuss G., Andreas S. Marked sympathetic activation in patients with chronic respiratory failure // Am J Crit Care Med. - 2001. – No 164, - P. 597-601. **CAS PubMed Web of Science® Google Scholar.**
26- Marshall J.M. Peripheral chemoreceptors and cardiovascular regulation // Physiol Rev. - 1994. - No 74. - P. 543-594. **CAS PubMed Web of Science® Google Scholar.**
27- Daly M., De B., Jones J.F. Respiratory modulation of carotid and aortic body reflex left ventricular inotropic responses in the cat // J Physiol. - 1998. - No 509. - P. 895-907. **PubMed Web of Science® Google Scholar.**
28- Greenwood P.V., Hainsworth R., Karim F., Morrison G.W., Sofola O.A. The effect of stimulation of carotid chemoreceptors on the inotropic state of the left ventricle // J Physiol. - 1976. - No 266. - P. 47P-48. **PubMed Google Scholar.**
29- Hainsworth R. Reflexes from the heart // Physiol Rev. - 1991. - No 71. - P. 617-658. **CAS PubMed Web of Science® Google Scholar.**
30- Narkiewicz K., Kato M., Pesek C.A., Somers V.K. Human obesity is characterized by a selective potentiation of central chemoreflex sensitivity // Hypertension. - 1999. - No 33. - P. 1153-1158. **CAS PubMed Web of Science® Google Scholar.**
31- Sevre K., Bendz B., Rostrup M. Reduced baroreceptor reflex sensitivity and increased blood pressure variability at 2400 m simulated cabin altitude // Aviat Space Environ Med. - 2002. - No 73. - P. 632-634. **PubMed Web of Science® Google Scholar.**
32- Dutta S., Zimmer M., Sies H., Carlson R.W., Cullen W.J., Thayer J.W. Comparative toxicology of ozone and t-butyl hydroperoxide on isolated rat lung // Free Radical Res Commun. - 1989. - V. 8, - No 1. - P. 27-35.
33- Fletcher G.F., Balady G.F., Froelicher V.F., Hartley L.H., Haskell W.L., Pollock M.L. Exercise standards. A statement for healthcare professionals from the American Heart Association. Writing Group Special Report // Circulation. - 1995. - V. 91, - No 2. - P. 580-615.
34- Cross C.E., De Lucia A.J., Reddy A.K., Hussain M.Z., Chow C.K. Ozone interactions with lung tissue. Biochemical approaches // Am J Med. - 1976. - V. 60, - No 7. - P. 929-935.
35- Halliwill J.R., Morgan B.J., Charkoudian N. Peripheral chemoreflex and baroreflex interactions in cardiovascular regulation in humans. J Physiol // - 2003. - No. 552. - P. 295-302. **CAS PubMed Web of Science® Google Scholar.**
36- Agadjanyin N.A., Kupriyanov S.V. Role of chemoreceptors in the zone of vertebral arteries in the formation of the cardiorespiratory functional system // Bulletin of Experimental Biology and Medicine. - 2009. - V. 148, - No 1. - P. 1-4.
37- Zanardi I., Borrelli E., Valacchi G., Travagli V., Bocci V. Ozone: a multifaceted molecule with unexpected therapeutic activity // Curr Med Chem. - 2016. - No 23. - P. 304-314.