Hypoxia resistance among the aged patients with chronic obstructive lung disease: possibilities of using hypoxic trains

E.O. Asanov¹, I.A. Diba¹, Y.I. Golubova¹, S.O. Asanova², M.V. Belikova³

¹ State Institution "D. F. Chebotarev Institute of Gerontology NAMS of Ukraine", Kyiv, Ukraine,

²Pharmarketing company «Zdravo», Kiev, Ukraine,

³National University of Physical Education and Sports of Ukraine, Kiev, Ukraine

Correspondence: eoasanov@ukr.net

Received: 14.01.2020; Accepted: 22.01.2020; Published: 07.07.2020

Abstract. Age-related morphological and functional changes in the body lead to the development of arterial hypoxemia, tissue hypoxia and hypoxic changes, which reduces the body's resistance to hypoxia and contributes to the development of lung diseases, in particular chronic obstructive pulmonary disease (COPD) in the elderly. The aim of the study was to clarify the effect of interval normobaric hypoxic training (INHT) on hypoxia resistance in elderly patients with COPD. The survey showed that with an increase in bronchial obstruction, the shifts of blood saturation during hypoxia increase. The course of INHT leads to increased resistance to hypoxia, and also increases the ventilation response to hypoxia in elderly patients with COPD.

Key words: COPD, resistance to hypoxia, intermittent hypoxic training, aging.

As is known, hypoxia is the cause or characteristic of aging [1, 2]. Age-related morphofunctional changes in the body lead to the development of arterial hypoxemia, tissue hypoxia and hypoxic shifts [1, 2]. All this causes a decrease in the body's resistance to hypoxia and promotes the development of lung diseases, in particular, chronic obstructive pulmonary disease (COPD) in the elderly [1, 2]. Thus, in the elderly and aging, the preconditions for the development of pulmonary pathology and increase its course.

COPD is one of the leading causes of death worldwide [3, 4]. By 2020, COPD is expected to be third in the cause of death and fifth in disability causes [3]. COPD mortality is increasing faster than mortality from cardiovascular disease. COPD is one of the major pathological processes that contribute to accelerated aging, development of pulmonary insufficiency, disability and premature death of elderly people [3, 4]. With the development of COPD in elderly patients due to bronchial obstruction and disorders of pulmonary gas exchange, age-related hypoxic shifts, arterial hypoxemia, tissue hypoxia and resistance to hypoxia decrease even more [1, 2]. This leads to increased symptoms of the disease, decreased physical activity, quality of life and can cause complications in elderly with COPD [5].

Opportunities for medical therapy in the elderly are limited. In this regard, drug-free treatment - interval normobaric hypoxic training (INHT) - periodic breathing with hypoxic mixture at normal barometric pressure [6-8] is of interest. INHTs lead to activation of respiration, pulmonary gas exchange, systemic blood flow, improvement of microcirculation, increase of activity of respiratory enzymes and antioxidant systems. Our experience with the use of INHT has also shown their effectiveness when used

in elderly patients with COPD [5]. However, the effect of INHT on hypoxia resistance in elderly COPD patients has not been studied.

Purpose of the study

To find out the effect of INGT on hypoxia resistance in elderly patients with COPD.

Subjects and Methods

The study included 30 patients with COPD of the elderly (60-74 years), I-II centuries. spirometry and flow-volume curve of forced exhalation on a Spirobank apparatus (Mir, Italy). The diagnosis of COPD was established in accordance with the recommendations of the GOLD and the order of the Ministry of Health of Ukraine No. 555 of 27.06.2013. All patients received appropriate bronchodilator therapy for at least two months prior to enrollment. Before inclusion in the study, patients were abolished broncholytic drugs: prolonged β_2 - agonists for 12 hours, and prolonged M-cholinolytics for 48 hours. During the study, elderly patients with COPD were allowed to use inhalation a short-acting β_2 -agonist salbutamol on demand, as an emergency medication to relieve the symptoms of COPD. The study was conducted in accordance with ethical guidelines. Participation in the study was voluntary, all surveyed received detailed information about the study and signed informed consent.

To solve these problems, elderly patients with COPD were divided into two groups: patients of the first group (15 people) received real INHT, patients of the second group (15 people) received simulated INHT.

An important role in INGT is the level of hypoxia at which training is conducted. This is due to the fact that the interval hypoxic effect during training should be sufficiently pronounced to have a therapeutic effect. At the same time, hypoxic effects should not be undue, as this can lead to undesirable side effects. In the existing approach, the level of hypoxia is calculated on the basis of the group-average data and is the same for all. This approach is more convenient and easy to apply. However, individual tolerance and resistance to hypoxic effects are not taken into account. When routinely using the hypoxic training method, the likelihood of insufficient therapeutic effect or the development of side effects is high, which is especially true for elderly patients.

Therefore, in this study, an individual approach was used to select the level of hypoxia at which the training was conducted. For this purpose, before the course of INHT, each of the subjects conducted a hypoxic test with a gradual decrease in the concentration of oxygen in the gas mixture being inhaled. In this case, the response of the body to the hypoxic effect was determined by the individual hypoxic threshold - the level of concentration of oxygen in the gas mixture, which is inhaled, which do not yet occur negative phenomena in the body. To this end, during hypoxic testing, oxygen content of the gas mixture, ventilation, ventilation, hemodynamics (heart rate (heart rate), blood pressure (BP)), electrocardiogram (ECG) were recorded [7]. They also monitored blood oxygen saturation (SpO₂), a parameter that reflects the degree of arterial hypoxemia. The harmful effect of hypoxia begins to manifest itself when the oxygen tension in the blood (PaO₂) drops to 46-50 mm Hg. which corresponds to the SpO₂ index of 80% [7]. Therefore, we can assume that this level of SpO₂ is limiting.

The hypoxic test could be stopped under the following conditions:

1. Achievements of critical heart rate [$\text{Heart Rate}_{\text{crit.}} = \text{Heart rate.} + (220 - \text{age} - \text{HR}) / 2$].
2. Increased blood pressure > 200 mm Hg.
3. Reduction of SpO₂ < 80%.
4. Increased respiratory rate by 50% or more from baseline.
5. Achievement of 10% O₂ content in the inhalable gas mixture.
6. Depression of the ST segment greater than 1 mm and / or the occurrence of rhythm disturbances on the ECG.
7. Appearance of heart pain, dizziness, fainting, etc.
8. Refusal of the patient.

For the trainings, a hypoxic mixture was used in which the O₂ content was 1-2% higher than the hypoxic mixture at which the hypoxic sample was discontinued.

Resistance to hypoxia is the ability of the organism to resist to the changes in homeostasis in the condition of hypoxia. To determine the resistance of the organism to hypoxia before and after the course of real and simulated INHT among the aged patients with COPD, it has been done a hypoxic test with 12% oxygen content for twenty minutes. The measurements were made on the 17-th - 18-th minutes of hypoxic breathing with 12% O₂ content. Ventilation rates (minute breathing rate(VE)), SpO₂ was registered for 5 minutes with air breathing, 20 minutes with hypoxic breathing, and 5 minutes after passing to air breathing. The degree of reduction of SpO₂ during the hypoxic test reflects the ability of the organism to resist the hypoxic effects, that is resistance to hypoxia.

The course of hypoxic training consisted of 10 daily sessions. Each session included hypoxia cycles (5 minutes), alternating cycles of normoxia (5 minutes) (only 3 five-minute cycles of breathing with hypoxic mixture).

For carrying out hypoxic tests and INHT they used the automated software-hardware complex "Hypotron" (Ukraine), created by the Kiev scientists of NTUU "KPI" [9]. The operation of the apparatus is based on the method of reverse breathing, when the inhalation and exhalation of air is carried out in a closed circuit of a given volume. As a result of oxygen consumption by the body, its concentration in the inhaled air decreases to a predetermined concentration and is then maintained at a constant level. Carbon dioxide in the gas mixture is absorbed by the lime. "Hypotron-M" automated software-hardware complex allows dosing the level of hypoxic load, controlling the parameters of saturation, ventilation (breathing volume, respiratory rate, minute breathing volume), cardiovascular system (heart rate, blood pressure). It is important to note that the original software of the automated complex "Hypotron" allows to monitor the parameters of the cardiorespiratory system directly during hypoxic exposure. This helps to achieve high therapeutic efficacy and safety during hypoxic training. It should also be noted that the software of the complex "Hypotron" allows not only to conduct hypoxic training, but also to evaluate the response to hypoxic effects and to determine resistance to hypoxia. The reaction to hypoxia by means of the complex "Hypotron" is determined by conducting hypoxic tests (with a gradual decrease in the concentration of oxygen in the gas mixture inhalation or with a constant concentration of oxygen in the gas mixture inhalation) with monitoring of indicators of the cardiorespiratory system (respiratory system), respiratory rate, heart rate, blood pressure, ECG, SpO₂). This allows you to choose the most optimal level of hypoxic stimulus during hypoxic training.

The obtained data were processed by the methods of variational statistics using the computer program "Statistica 7.0 for Windows". The average values of the indicators (M), their errors (m), and the correlation coefficient (r) were calculated. All indicators studied had a normal distribution and therefore parametric statistical procedures were used. Differences in mean values in the studied groups were evaluated by Student's test. Differences at $p < 0.05$ were considered significant.

Results and Discussion

Studies have shown that when breathing hypoxic gas mixture, blood saturation in all elderly patients with COPD was significantly reduced, on average, by $(18.23 \pm 0.26)\%$. Such a decrease in blood saturation can be regarded as a pronounced arterial hypoxemia. Figure 1 shows that elderly patients with COPD with an increase in disorders of the bronchial patency shift saturation in hypoxia, on average, also increase. There is a significant correlation ($r = 0.50$, $p = 0.006$) of the displacement of blood saturation in hypoxia with bronchial obstruction. It is possible to assume that in patients of elderly with COPD resistance to hypoxia is determined by bronchial obstruction/

Such a decrease in blood saturation can be regarded as a pronounced arterial hypoxemia. Figure 1 shows that elderly patients with COPD with an increase in disorders of the bronchial patency shift saturation in hypoxia, on average, also increase. There is a significant correlation ($r = 0.50$, $p = 0.006$) of the displacement of blood saturation in hypoxia with bronchial obstruction. It is possible to assume that in patients of elderly with COPD resistance to hypoxia is determined by bronchial obstruction. Results of the study and their discussion. Studies have shown that when breathing hypoxic gas mixture, blood saturation in all elderly patients with COPD was significantly reduced, on average, by (18.23) (Fig. 1).

Figure 1. Dependence of bronchial patency on the changes of SpO₂ in respiration of 12% O₂ in elderly patients with COPD. Notes: FEV₁ - forced expiratory volume in the first second, l; SpO₂ - blood saturation, %.

The study of the ventilatory response to hypoxic stimulus showed that the examined elderly patients with COPD in response to hypoxia have increased ventilation (Fig. 2).

Figure 2. Dynamics of ventilation with respiration of 12% O₂ in elderly patients with COPD before (solid line) and after (dashed line) the course of real INHT. Notes: 0-5 minutes - breathing with air, 5-25 minutes - breathing 12% O₂, 25-30 minutes - breathing with air; Stroke - minute breathing volume, l / min.

The increase in ventilation in elderly patients with COPD occurs only for 4-5 minutes. The ventilation is then reduced slightly and maintained at approximately this level until the end of the hypoxic test. After cessation of hypoxic effects in elderly patients with COPD during the transition to

breathing with air, a short-term preservation of ventilation was observed at the level that was at the end of the hypoxic test and only then its decrease to the baseline level was observed. Keeping the index at or below the load level has been described mainly for physical activity as a "Linnhardt phenomenon" [10]. However, there is a study where this phenomenon was detected even after short-term hypoxic exposure [10]. The cause of this phenomenon is the elimination of oxygen debt and the transition to a new level of regulation after the cessation of loading. Therefore, the manifestation of the Linnard phenomenon indicates the accumulation of non-oxidized products of metabolism and oxygen debt during hypoxic effects in the examined elderly patients with COPD.

Analysis of the results of the study revealed that course use of INHT in elderly patients with COPD leads to an increase in blood saturation (Table).

**Influence of real and simulated INHT on ventilatory response to hypoxia
In elderly patients with COPD**

Indicators	Simulated INHT		Real INHT	
	Initial state	After the course	Initial state	After the course
SpO₂, %				
air	94.61 ± 0.25	95.15 ± 0.27	94.56 ± 0.24	95.63 ± 0.26*
hypoxia	76.36 ± 0.29	77.23 ± 0.31	76.38 ± 0.26	78.53 ± 0.41*
Δ	-18.24 ± 0.22	-17.94 ± 0.28	-18.19 ± 0.21	-17.11 ± 0.18*
VE, l/min				
air	9.27 ± 0.22	9.35 ± 0.20	9.21 ± 0.21	10.23 ± 0.16*
hypoxia	11.31 ± 0.27	11.42 ± 0.20	11.38 ± 0.25	12.42 ± 0.21*
Δ	2.05 ± 0.19	2.08 ± 0.18	2.18 ± 0.15	2.19 ± 0.18
ΔVE/ΔSpO₂	- 0.11 ± 0.012	- 0.11 ± 0.010	- 0.11 ± 0.011	- 0.13 ± 0.012*

Notes: * - $p < 0.05$ compared to baseline; ΔVE/ΔSpO₂ – ventilator response to hypoxia; VE – respiratory minute volume; Δ – shift of the corresponding index at hypoxia; SpO₂ – blood saturation, %; with hypoxia the measurements were performed for 17-18 minutes breathing hypoxic mixture with 12% O₂.

However, as shown by the study, after the course of administration of INHT in patients with COPD elderly, the reduction of blood saturation in breathing with hypoxic gas mixture was less significant (see table.). Such changes in the displacement of SpO₂ during breathing by hypoxic gas mixture under the influence of INHT can be regarded as an increase in resistance to hypoxia in elderly patients with COPD. One of the leading mechanisms for compensating for hypoxic shifts is the ventilation response.

Thus, the increase in ventilation in response to shifts in blood saturation (ΔVE/ΔSpO₂) characterizes the ventilatory response to hypoxia. This indicator reflects the response of the VE to the displacement unit of saturation. The analysis of the obtained data showed that the ventilatory response to hypoxia after the course of administration of INHT in the elderly with COPD increased (see table).

At the same time, the use of simulated INHTs did not increase the ventilatory response to hypoxia and did not increase hypoxia resistance in elderly patients with COPD (see table).

The use of INHT has also led to a decrease in bronchial obstruction in elderly patients with COPD. This was evidenced by the increase in their speed indicators reflecting the patency of the bronchi.

Thus, after training in elderly patients with COPD, an increase in forced expiratory volume during the first second of FEV1 was observed (1.66 ± 0.05 and 1.84 ± 0.05 l / s, respectively, before and after training, respectively, $p < 0.05$), exhalation rates of 25%, 50% and 75% of exhalation volume - MEF25 (1.78 ± 0.10 and 2.20 ± 0.12 l / s, before and after training, respectively, $p < 0.05$), MEF50 (1.37 ± 0.09 and 1.69 ± 0.10 l / s, before and after training, respectively, $p < 0.05$), MEF75 (1.16 ± 0.10 and 1.44 ± 0.09 l / s, before and after training, respectively, $p < 0.05$).

In contrast, simulated training did not contribute to increased bronchial patency in elderly patients with COPD: FEV1 (1.66 ± 0.07 and 1.68 ± 0.07 l / s, before and after training, respectively, $p > 0.05$), MEF25 (1.76 ± 0.06 and 1.79 ± 0.06 l / s, before and after training, respectively, $p > 0.05$), MEF50 (1.29 ± 0.05 and 1.30 ± 0.05 l / s, before and after training, respectively, $p > 0.05$), MEF75 (1.05 ± 0.10 and 1.11 ± 0.05 l / s, before and after training, respectively, $p > 0.05$).

Studies have shown that conducting hypoxic tests and INGTs using the "Hypotron" hardware system is convenient and safe. INGTs do not cause adverse reactions and are well tolerated in patients.

Conclusions

1. In elderly patients with COPD, resistance to hypoxia is determined by bronchial obstruction.
2. The course application of INHT leads to increased resistance to hypoxia. One mechanism for this is to increase the ventilatory response to hypoxia in elderly patients with COPD.
3. The use of the "Hypotron" hardware complex makes it possible to safely and efficiently determine the response to hypoxia and to perform INHT.

Author Contributions: All authors participated equally in writing this commentary.

Conflicts of Interest: The authors declare no conflict of interest.

Information about Authors:

Ervin Asanov - DSc (Medicine), Principal Scientific Researcher of the Department of Clinical Physiology and Pathology of Internal Organs of the State Institution "D. F. Chebotarev Institute of Gerontology NAMS of Ukraine"; <https://orcid.org/0000-0003-4021-1710>

Iryna Dyba - PhD (Medicine), Junior Researcher of the Department of Clinical Physiology and Pathology of Internal Organs State Institution "D. F. Chebotarev Institute of Gerontology NAMS of Ukraine"; <https://orcid.org/0000-0002-4212-8868>

Seviliya Asanova - Medical Representative of the Farmarketing Company "Zdravo"; <https://orcid.org/0000-0003-0311-2254>

Juliya Holubova - Junior Researcher of the Department of Clinical Physiology and Pathology of Internal Organs State Institution "D. F. Chebotarev Institute of Gerontology NAMS of Ukraine"; <https://orcid.org/0000-0001-9988-9628>

References

1. Korkushko, O.V., Chebotarev, D.F., Chebotarev N.D. Vozrastnyye izmeneniya dykhatel'noy sistemy pri starenii i ikh rol' v razvitii bronkholegochnoy patologii. [Age-related changes in the respiratory system during aging and their role in the development of bronchopulmonary pathology]. UkrainianPulmonology Journal 2005, 3, 35-41.
2. Dyer, C. The interaction of ageing and lung disease. Chron. Respir. Dis. 2012, 9 (1), 63-7.
3. Global Strategy for the Diagnosis, Management, and prevention of COPD 2015, available at: www.goldcopd.org.
4. Chronic Obstructive Pulmonary Disease (COPD). Centers for Disease Control and Prevention 2012, available at: www.cdc.gov/Features/COPD/.
5. Asanov, E.O.; Polyagushko, L.G.; Os'mak, E.D. at al. Terapiya bronkhial'noy obstruktsii u pozhilykh bol'nykh s KHOZL: primeneniye interval'nykh normobaricheskikh gipoksicheskikh trenirovok s ispol'zovaniyem avtomatizirovannogo programmno-apparatnogo kompleksa "Gipotron-M" [Therapy of bronchial obstruction in elderly patients with COPD: the use of interval normobaric hypoxic training using the automated software and hardware complex "Hypotron-M"]. Problemy stareniya i dolgoletiya 2015, 3-4, 340-47.
6. Kolchynskaya, A.Z.; Tsyganova, T.N.; Ostapenko, L.A. Normobaricheskaya interval'naya gipoksicheskaya trenirovka v meditsine i sporte [Normobaric interval hypoxic training in medicine and sport]. Medicina: Moscow, 2003; p 408.
7. Korkushko, O.V.; Asanov, E.O Shatilo V.B. at al. Effektivnost' interval'nykh normobaricheskikh gipoksicheskikh trenirovok u pozhilykh lyudey. [The effectiveness of interval normobaric hypoxic training in the elderly person]. Problemy stareniya i dolgoletiya. 2004, 2, 155-61.
8. Bernardi, L. Interval hypoxic training. Adv Exp Med Biol 2001, 502, 377-99.
9. Hipoksiya yak metod pidvyshchennya adaptatsiynoyi zdatnosti orhanizmu lyudyny [Hypoxia as a method of increasing the adaptive abilities of the human body]. Pryntsyp roboty aparata "HIPOTRON" [The principle of operation of the apparatus "GIPOTRON"], Slipchenko, V.G.; Korkushko, O.V., Eds. NTUU "KPI": Kyiv, 2011; pp 89-91.
10. Horanchuk, V.V.; Sapova, N.I.; Ivanov A.O. Hypoxia therapy. Ltd "Elbi-SPb": Moscow, 2003; p 536.