ORIGINAL ARTICLE

PECULIARITIES OF PULMONARY VENTILATION RESPONSE TO DOSED HYPOXIA IN ELDERLY PEOPLE WITH IMPAIRED GLUCOSE TOLERANCE

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ABSTRACT

The aim: To determine the peculiarities of the response of pulmonary ventilation to hypoxia in elderly people with impaired glucose tolerance
Materials and methods: Forty-three elderly people were examined, including 20 patients with impaired glucose tolerance and 23 healthy individuals with preserved glucose tolerance. Fasting plasma glucose and insulin concentrations were determined, and the HOMA-IR insulin resistance index was calculated. Under conditions of normoxia and during a dosed hypoxic test (12% oxygen, duration 20 min), blood saturation and lung ventilation parameters were monitored.
Results: Under conditions of normoxia, the indicators of lung ventilation function did not differ between the groups of elderly people with impaired and preserved glucose tolerance. Under conditions of hypoxia, elderly people with impaired glucose tolerance had a less significant increase in ventilation, despite the development of more severe arterial hypoxemia. This leads to a decrease in the ventilatory response to hypoxia in case of impaired carbohydrate metabolism.
Conclusions: In people with impaired glucose tolerance, a less significant ventilatory response to hypoxia is combined with more pronounced insulin resistance.

KEY WORDS: impaired glucose tolerance, aging, hypoxia, ventilation, insulin resistance

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INTRODUCTION

Disorders of glucose homeostasis are an important medical and social problem in the world. This is primarily due to their high prevalence, development of complications and economic losses. Thus, in 2015, there were about 415 million people in the world with disorders of glucose homeostasis (elevated fasting blood glucose level, impaired glucose tolerance), and according to the forecast, their number will increase to 642 million in 2040 [1]. Today, disorders of glucose homeostasis are considered an important risk factor for the development of cardiovascular disease and type 2 diabetes mellitus [2]. Epidemiological studies show that within a year, 3.6% to 8.7% of people with dysglycemia become patients with type 2 diabetes mellitus [3]. This gives grounds to consider impaired glucose homeostasis as an intermediate stage before the development of diabetes, i.e., as prediabetes [4].

Previous studies have shown a significant increase in the prevalence of glucose homeostasis disorders in older age: from 8.8% in men and 11% in middle-aged women to 24.3% in men and 34.7% in women over 85 years of age [5]. This indicates a link between age and carbohydrate metabolism disorders.

The causes of carbohydrate metabolism disorders in aging may include poor nutrition, reduced physical activity, decreased muscle mass, decreased insulin secretion, and the development of insulin resistance [6]. According to researchers, insulin resistance (IR) is the most important cause of impaired carbohydrate tolerance in the elderly [6].

Hypoxia plays an important role in glucose homeostasis disorders and in the development of diabetes complications [7]. Hypoxia controls the activation of HIF-1α, a hypoxia-inducible transcription factor, and through it VEGF, a vascular endothelial growth factor [8]. In the presence of elevated glucose concentrations, cells and tissues are exposed to elevated levels of glycation end products that inhibit HIF-1α function [7]. This leads to increased degradation of HIF-1α under conditions of hypoxia and hyperglycemia [7]. The consequence is a decrease in the adaptive capacity of cells and their survival [7, 8]. Tissue hypoxia also promotes the activation of proinflammatory cytokines, which can cause the onset and progression of carbohydrate tolerance disorders [9].

On the other hand, hypoxia and hypoxic shifts are the cause or characteristic feature of age-related decline in the body's functional capacity and adaptive capacity [10].

With aging, oxygen supply to tissues and oxygen tension in tissues decrease [11]. Studies have also shown that the body's resistance to hypoxia decreases with aging [11, 12].

Among the mechanisms of adaptation to hypoxia, the respiratory system plays a key role, as it responds most quickly to the development of arterial hypoxemia. Under conditions of oxygen deficiency, lung ventilation increases and bronchial patency increases [12].

At the same time, changes in pulmonary ventilation under hypoxia in elderly people with impaired glucose tolerance (IGT) remain unclear.

THE AIM

The aim of our study was to determine the peculiarities of the response of pulmonary ventilation to hypoxia in elderly people with impaired glucose tolerance (IGT).

MATERIALS AND METHODS

The study was conducted in accordance with ethical guidelines. Participation in the study was voluntary, all subjects received detailed information about the study and signed an informed consent. The study procedures, patient information, and the informed consent form were approved by the Ethics Committee of the Clinical Sector of the Dmitry F. Chebotarev Institute of Gerontology of the National Academy of Medical Sciences of Ukraine (Protocol 9 of June 11, 2013).

We examined 20 people aged 60-74 years with IGT, which was diagnosed on the basis of the results of an oral standard glucose tolerance test (OGTT) [2]. The criterion for IGT was a glycemic level of 7,8 to 11,1 $mmol*l^{-1}$ after 2 hours of OGTT. As a control group, 23 practically healthy people aged 60-74 years with preserved glucose tolerance (PGT) were examined, in whom the plasma glucose level after 2 hours of OGTT was less than 7.8 $mmol*l^{-1}$.

The index of insulin resistance (HOMA-IR - Homeostasis Model Assessment for Insulin Resistance) was calculated by the formula:

HOMA-IR = fasting plasma glucose * fasting plasma insulin / 22,5.

The glucose concentration was determined by the glucose oxidase method on a BTS-330 analyzer using Glucose reagents (Bio LATEST Lachema Diagnostica, Germany), and the plasma insulin concentration was determined by an enzyme-linked immunosorbent assay using a DRG Insulin ELISA kit (DRG Instruments GmbH, Germany).

A dosed hypoxic test was performed in a sitting position no earlier than 2 hours after breakfast using a standard certified gas mixture containing 12 % oxygen and 88 % nitrogen. The duration of the test was 20 minutes. During the hypoxic test, blood saturation (SpO_2) was recorded using the "UM-300" monitor (UTAS, Ukraine), respiratory volume (VT) and respiratory rate (F) using the "Hypotron" apparatus (Scientific Research Institute "APRODOS" of National technical university of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute", Ukraine). SpO_2 and pulmonary ventilation were recorded under normoxia conditions (before the hypoxic test for 5 minutes), then during the hypoxic test and for 5 minutes after the hypoxic test. The degree of SpO_2 decrease during the hypoxic test reflects the body's ability to withstand hypoxic exposure, i.e., characterizes resistance to hypoxia [13]. It is worth noting that inhalation of a hypoxic gas mixture containing 12 % oxygen for 20 minutes is completely safe for humans, as evidenced by the widespread use of hypoxic tests in both healthy and sick people [14].

The obtained data were processed by the methods of variational statistics using the computer program "Statistica 7.0 for Windows". The studied indicators had a distribution close to normal. Average values of indicators (M), their errors (m) were calculated. Differences in the average values of the indicators in the groups were evaluated according to the Student's test. Pearson's correlation analysis was performed. The critical level of statistical significance was 0.05.

RESULTS

Under conditions of normoxia, the indicators of lung ventilatory function did not differ between groups of elderly people with IGT and PGT (table I).

In response to dosed hypoxia, ventilation rates increased in both patients with PGT and patients with IGT (table I).

At the same time, certain differences in the response of pulmonary ventilation to dosed hypoxia in elderly people with PGT and those with IGT were found. In subjects with IGT under hypoxia, the increase in VT and, accordingly, VE was less than in subjects with PGT, despite the development of more severe arterial hypoxemia. As a result, under hypoxia, the ratio ΔVE/ΔSpO2, which characterizes the ventilatory response to hypoxia, decreased to a lesser extent in patients with IGT than in patients with PGT (table I).

The insufficient ventilatory response to hypoxia in elderly people with IGT is likely to be one of the factors in reducing their resistance to hypoxia.

In the study of the relationship between ventilation response to hypoxia and the insulin resistance index, the following was found. In patients with IGT, changes in minute ventilatory volume (ΔVE) during hypoxia

Table I. Indicators of ventilation function of lungs in elderly people with IGT and PGT, M ± m

Indicator	Group with PGT	Group with IGT
VT in normoxia, l	0,61 ± 0,02	0,59 ± 0,03
VT in hypoxia, l	0,69 ± 0,03	0,63 ± 0,03
ΔVT, l	0,08 ± 0,007	0,04 ± 0,007*
F in normoxia, min-1	13,10 ± 0,23	13,01 ± 0,25
F in hypoxia, min-1	14,32 ± 0,15	14,71 ± 0,15
ΔF, min-1	1,22 ± 0,09	1,70 ± 0,07
VE in normoxia, l*min-1	7,99 ± 0,26	7,68 ± 0,22
VE in hypoxia, l*min-1	9,88 ± 0,28	9,27 ± 0,30
ΔVE, l*min-1	1,89 ± 0,08	1,59 ± 0,06*
SpO2 in normoxia, %	95,74±0,15	95,50 ± 0,17
SpO2 in hypoxia, %	80,74 ± 0,16	78,13 ± 0,14*
ΔSpO2, %	-15,00 ± 0,14	-17,37 ± 0,11*
ΔVE/ΔSpO2	-0,126 ± 0,003	-0,092 ± 0,005*

Notes: all shifts are significant, $p < 0.05$; * - differences are significant compared with the indicators of elderly people with VT, $p < 0.05$; VT - respiratory volume, F - respiratory rate, VE - minute respiratory volume, Δ - shift in hypoxia

correlated with the HOMA-IR index of insulin resistance ($r = - 0,37$, $p = 0,0012$). The regression analysis showed an inverse linear relationship between these parameters.

The analysis also revealed an inverse correlation ($r = - 0.36$, $p = 0,0019$) between VE shifts during hypoxia, on the one hand, and changes in glucose levels after 2 hours of OGTT, on the other hand, in patients with IGT.

DISCUSSION

The question arises: why do elderly people with IGT have a reduced ventilatory response to hypoxia? It is known that up to 70% of circulating blood glucose is consumed by the brain [15]. Our previous studies have shown that hypoxia reduces blood glucose levels, especially in people with IGT [16]. In order to compensate for the energy supply of the brain under hypoxia, glucose transport to the brain is activated. Thus, the level of the insulin-independent glucose transporter GLUT-3 increases [17]. At the same time, it is known that in IR, cells lose the ability to respond to the metabolic activity of insulin and insulin-mediated processes in the brain, in particular in the hypothalamus, hippocampus and cerebral cortex [18]. Under conditions of oxygen deficiency, despite increased glucose transport, defective insulin signaling leads to a shortage of energy substrates in brain neurons. In IR, the importance of activation of free radical processes in the brain during hypoxia also increases. This can contribute to an excessive increase in the level of membrane lysophospholipids, which leads to a violation of the functional activity of mitochondria and a decrease in the synthesis of macroergic compounds [19].

The described processes reduce the energy supply of the brain and form a different pattern of the activity of the neurons of the respiratory center. This can lead to a delayed and insufficient response to hypoxia of the respiratory center neurons in elderly people with IGT.

On the other hand, the mechanisms of ventilation regulation, its response to hypoxia, and carbohydrate metabolism may interact [20]. Therefore, it is possible that functional insufficiency of ventilation regulation contributes to carbohydrate metabolism disorders. In turn, disorders of carbohydrate metabolism, which, in particular, develop in elderly people with IGT, negatively affect metabolism and can cause changes in the sensitivity of central and peripheral chemoreceptors. This leads to a decrease in the sensitivity of the chemoreflex mechanism of compensation for arterial hypoxemia. As a result of these complex mechanisms, the respiratory center's response to hypoxia in elderly people with IGT is reduced.

RESPIRATORY RESPONSE TO HYPOXIA AND INSULIN RESISTANCE

It is known that a constant oxygen tension in tissues is essential for optimal cellular metabolism. The activation of ventilation under the influence of hypoxic stress is aimed at compensating for oxygen deficiency to meet

the body's metabolic needs. The activity of metabolic processes, in particular, carbohydrate metabolism under hypoxia, directly depends on the adequacy of the body's compensatory reactions. It is hypoxia, that is, the inability to meet the oxygen needs of the body, that leads to the development of pathological changes in carbohydrate metabolism. However, the relationship between changes in pulmonary ventilation to hypoxia and insulin resistance in elderly people with IGT is still unclear.

These data suggest the existence of a cause-and-effect relationship between IGT and insufficient response of lung ventilation to hypoxia in the elderly. The identified dependencies do not allow us to determine what is the cause and what is the effect. However, they show an important role of lung ventilation in the development of adaptive reactions to hypoxia in elderly people with IGT.

CONCLUSIONS

1. Ventilatory function of the lungs under condition of normoxia does not differ in elderly people with preserved and impaired glucose tolerance.
2. In elderly people with impaired glucose tolerance, the ventilator response to dosed hypoxia is less than in healthy people with preserved glucose tolerance.
3. In elderly people with elevated glycemia and insulin resistance, the ventilator response to hypoxia decreases, which leads to a limitation of the body's adaptive capacity in hypoxic conditions.

REFERENCES

1. Khetan AK, Rajagopalan S. Prediabetes. Can J Cardiol. 2018;34(5):615-623. doi: 10.1016/j.cjca.2017.12.030.
2. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. Diabetes Care. 2021;44(1):S15-S33. doi: 10.2337/dc21-S002.
3. Lin X, Xu Y, Pan X et al. Global, regional, and national burden and trend of diabetes in 195 countries and territories: an analysis from 1990 to 2025. Sci Rep. 2020;10(1):14790. doi: 10.1038/s41598-020-71908-9.
4. Rett K, Gottwald-Hostalek U. Understanding prediabetes: definition, prevalence, burden and treatment options for an emerging disease. Curr Med Res Opin. 2019;35(9):1529-1534. doi: 10.1080/03007995.2019.1601455.
5. Stolk RP, Pols HA, Lamberts SW et al. Diabetes mellitus, impaired glucose tolerance, and hyperinsulinemia in an elderly population. The Rotterdam Study. Am J Epidemiol. 1997;145(1):24-32. doi: 10.1093/oxfordjournals.aje.a009028.
6. Chow HM, Shi M, Cheng A et al. Age-related hyperinsulinemia leads to insulin resistance in neurons and cell-cycle-induced senescence. Nat Neurosci. 2019;22(11):1806-1819. doi: 10.1038/s41593-019-0505-1.
7. Ramalho AR, Toscano A, Pereira P et al. Hyperglycemia-induced degradation of HIF-1α contributes to impaired response of cardiomyocytes to hypoxia. Rev Port Cardiol. 2017;36(5):367-73. doi: 10.1016/j.repc.2016.09.018.
8. Ferreira JV. Diabetes, hypoxia and cardiovascular disease: From molecular mechanism to treatment. Rev Port Cardiol. 2017;36(5):375-6. doi: 10.1016/j.repc.2017.03.003.
9. Mansor LS, Mehta K, Aksentijevic D et al. Increased oxidative metabolism following hypoxia in the type 2 diabetic heart, despite normal hypoxia signalling and metabolic adaptation. J Physiol. 2016;594(2):307-20. doi: 10.1113/JP271242.
10. Halim M, Halim A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). Diabetes Metab Syndr. 2019;13(2):1165-1172. doi: 10.1016/j.dsx.2019.01.040.
11. Richalet JP, Lhuissier FJ. Aging, Tolerance to High Altitude, and Cardiorespiratory Response to Hypoxia. High Alt Med Biol. 2015;16(2):117-24. doi: 10.1089/ham.2015.0030.
12. Asanov EO, Dyba IA, Asanova SO et al. Hypoxia resistance among the aged patients with chronic obstructive lung disease: possibilities of using hypoxic trains. Ageing & Longevity. 2020;1:11-17. doi:10.47855/jal9020-2020-1.
13. Korkushko OV, Asanov EO, Pisaruk AV, Chebotarev ND. Izmeneniya ventilyatsii pri gipoksii u pozhilykh lyudey s fiziologicheskim i uskorennym stareniyem dykhatel'noy sistemy. [Changes in ventilation during hypoxia in patients with manifestation and accelerated aging of the respiratory system]. Ukr Pulmonol Zh. 2009; 3:33-5.
14. Bradi AC, Faughnan ME, Stanbrook MB et al. Predicting the need for supplemental oxygen during airline flight in patients with chronic pulmonary disease: a comparison of predictive equations and altitude simulation. Can Respir J. 2009;16(4):119-24. doi: 10.1155/2009/371901.
15. Silver I, Erecińska M. Oxygen and ion concentrations in normoxic and hypoxic brain cells. Adv Exp Med Biol. 1998; 454:7-16. doi: 10.1007/978-1-4615-4863-8_2.
16. Havalko AV, Asanov EO, Shatylo VB et al. Peculiarities of the organism's reaction to dosed hypoxia in elderly people with impaired glucose tolerance. Problems of endocrine pathology. 2022; 3:7-13.
17. Leão LL, Tangen G, Barca ML et al. Does hyperglycemia downregulate glucose transporters in the brain? Med Hypotheses. 2020;139:109614. doi: 10.1016/j.mehy.2020.109614.

18. Boucher J, Kleinridders A, Kahn CR. Insulin receptor signaling in normal and insulin-resistant states. Cold Spring Harb Perspect Biol. 2014;6(1):a009191. doi: 10.1101/cshperspect.a009191.
19. Yaribeygi H, Farrokhi FR, Butler AE, Sahebkar A. Insulin resistance: Review of the underlying molecular mechanisms. J Cell Physiol. 2019;234(6):8152-8161. doi: 10.1002/jcp.27603.
20. Nyengaard JR, Ido Y, Kilo C, Williamson JR. Interactions between hyperglycemia and hypoxia: implications for diabetic retinopathy. Diabetes. 2004;53(11):2931-8. doi: 10.2337/diabetes.53.11.2931.

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The Authors declare no conflict of interest.

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