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Response of some indicators of the respiratory system to dosed hypoxia in elderly people with impaired glucose tolerance

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Abstract. The response of the respiratory system to dosed hypoxia (breathing with a gas mixture of 12% oxygen for 20 min) in the elderly with impaired (n = 35) and preserved glucose tolerance (n = 33) was studied. It is shown that the increase in lung ventilation occurs regardless of the state of carbohydrate metabolism in hypoxia. In people with impaired glucose tolerance, changes in lung ventilation in hypoxia are less significant than in people with persistent glucose tolerance. In persons with impaired glucose tolerance, an inverse relationship was found between the increase in pulmonary ventilation during hypoxia and insulin resistance ($r = -0.26$, $p = 0.035$), as well as between the increase in pulmonary ventilation during hypoxia and plasma glucose concentration due to 2 hours of standard glucose tolerance test ($r = -0.31$, $p = 0.012$). It is concluded that there is a causal relationship between impaired glucose tolerance and insufficient response of pulmonary ventilation to hypoxia in the elderly.

Keywords: elderly; impaired glucose tolerance; hypoxia; ventilation.

With age, the frequency of detection of insulin resistance, impaired glucose tolerance, as well as type 2 diabetes [1]. This leads to a significant increase in the risk of cardiovascular disease and its complications in the elderly [2]. Given the pathogenesis of the cardiovascular disease, which is based on chronic hypoxia, it becomes clear the importance of hypoxic changes in the development of carbohydrate metabolism disorders. This is confirmed by Nyengaard J. R. and co-authors studies, 2004, according to which in diabetes there are common metabolic pathways in hypoxia and hyperglycemia, through which they mutually enhance their negative impact [3]. The respiratory system, the cardiovascular system, the oxygen transport system of the blood and others take part in ensuring the homeostasis of the organism in the conditions of hypoxia. Compensatory reactions of the body are aimed, on the one hand, to ensure the delivery of oxygen to tissues, and, on the other hand, to increase its utilization by tissues. But these reactions cannot always fully compensate for the lack of oxygen. This happens if the hypoxic effects are excessive, or the body's ability to adapt is limited. This is especially true for the elderly and senile, in whom morphofunctional changes in the body with ageing lead to the development of hypoxic changes in homeostasis. Quite often the elderly body already at rest operates in conditions of lack of oxygen, which can be significantly exacerbated by hypoxic stress due to limited functionality and compensatory mechanisms [4].

Among the adaptive mechanisms of response to hypoxia, an important role belongs, first of all, to changes in the functioning of the respiratory system, which response most rapidly to the development of arterial hypoxemia. In conditions of lack of oxygen, lung ventilation and bronchial patency increase. This process is regulated by a chemoreflex mechanism that responds to a decrease in oxygen in the arterial

blood. However, the specifics of the response to hypoxia of the respiratory system in the elderly with impaired glucose tolerance (IGT), which became the basis for the study, remain unclear.

Materials and methods

35 elderly people (60-74 years old) with IGT were examined, the presence of which was determined by the results of the standard glucose tolerance test (SGT) [5]. The control group consisted of 33 almost healthy elderly people (60-74 years), who according to the results of SGT had preserved glucose tolerance (PGT).

Participation in the study was voluntary, all respondents received detailed information about the study and signed an informed consent form. Research procedures, information for the patient, and the form of informed consent were approved by the Ethics Commission of the D. F. Chebotarev Institute of Gerontology Clinical Department. To determine the body's response to dosed hypoxic effects, a hypoxic test was performed by inhaling a hypoxic gas mixture with a content of 12% oxygen for 20 minutes with the help of automated software and hardware complex "Hypotron" (Research Institute "APRODOS" the National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute"). Blood saturation (SpO_2) was recorded using a UM-300 monitor from UTAS (Ukraine) for 5 minutes of breathing air, 20 minutes breathing a hypoxic mixture and 5 minutes after the transition to breathing air. The degree of reduction of SpO_2 during the hypoxic test reflects the body's ability to resist hypoxic effects, ie characterizes the resistance to hypoxia [6]. Indicators of lung ventilation function were determined using automated software and hardware complex "Hypotron" (Research Institute "APRODOS" the National Technical University of Ukraine "Igor Sikorsky Kyiv Polytechnic Institute"): VT - tidal volume, F – respiratory rate, VE - minute tidal volume.

Plasma glucose concentration was determined by the glucose oxidase method on a BTS-330 analyzer using Glucose reagents (Bio LATEST Lachema Diagnostica). Plasma insulin levels were determined by enzyme-linked immunosorbent assay using the DRG Insulin ELISA kit (DRG Instruments GmbH, Germany). The insulin resistance index (HOMA-IR) was determined by the conventional calculation method (Homeostasis Model Assessment for Insulin Resistance) [6].

The obtained data are processed by methods of variation statistics with the help of a computer program «Statistica 7.0 for Windows». The studied indicators had a distribution close to normal. The average values of indicators (M) and their errors (m) were calculated. Differences in mean values in the groups were evaluated by Student ratio. Pearson's correlation analysis was performed. The critical level of statistical significance was 0.05.

Results and discussion

The analysis of the obtained data showed that when breathing atmospheric air, the indicators of lung ventilation function did not differ between the groups of elderly people with PGT and IGT (Tab. 1). In response to dosed hypoxia, there was an increase in ventilation rates in both groups of subjects (Tab. 1).

Table 1.

Indicators of ventilation function of the lungs when breathing atmospheric air and dosed hypoxic test in the elderly with IGT and PGT (M±m)

Indicators	IGT group	PGT group
VT air, l	0.60 ± 0.04	0.59 ± 0.03
VT hypoxia, l	0.68 ± 0.05	0.63 ± 0.03
ΔVT, л	0.08 ± 0.008	0.04 ± 0.007*

F air, min^{-1}	13.09 ± 0.25	12.97 ± 0.28
F hypoxia, min^{-1}	14.31 ± 0.16	14.67 ± 0.15
Δ F, min^{-1}	1.22 ± 0.04	0.61 ± 0.08
VE air, l/min.	7.85 ± 0.27	7.65 ± 0.22
VE hypoxia, l/min.	9.73 ± 0.28	9.24 ± 0.32
ΔVE, l/min.	1.88 ± 0.17	1.59 ± 0.11
SpO_2, air, %	95.83 ± 0.15	95.48 ± 0.18
SpO_2, hypoxia, %	80.92 ± 0.14	78.15 ± 0.15*
Δ SpO_2, %	14.92 ± 0.12	17.33 ± 0.10*
$\Delta VE/\Delta SpO_2$	0.13 ± 0.003	0.09 ± 0.007*

Notes: all changes are valid, $p < 0.05$; * - differences are statistically significant compared to those with people with PGT, $p < 0.05$.

In addition, some differences in the response of the respiratory system to dosed hypoxia in the elderly with IGT and PGT. In those examined with IGT under conditions of hypoxia, the increase in VT is lower than in people with PGT, despite the development of more severe arterial hypoxemia in persons with IGT. In turn, the ratio $\Delta VE/\Delta SpO_2$, that characterizes the ventilatory response to hypoxia in the elderly with IGT is also lower than in people with PGT. Insufficient ventilation response to hypoxia in elderly people with IGT is probably one of the factors in their reduced resistance to hypoxia.

Does the question arise as to why the elderly with IGT have a reduced response to pulmonary ventilation in response to hypoxia? It is known that up to 70% of circulating glucose is consumed by the brain [7]. Our studies have shown that under conditions of hypoxia, the content of glucose in the blood decreases, especially in people with IGT (Tab. 2).

Table 2.

Indicators of plasma glucose levels during respiration of atmospheric air and dosed hypoxic test in the elderly with IGT and PGT (M±m)

Indicators	IGT group	PGT group
The concentration of glucose in blood plasma when breathing air, mmol / l	5.44 ± 0.27	4.76 ± 0.25
Plasma glucose concentration in hypoxia, mmol / l	5.11 ± 0.29	4.67 ± 0.22
Δ glucose concentration, mmol / l	-0.33 ± 0.08*	-0.09 ± 0.04

Notes: all changes are valid, $p < 0.05$; * - differences are statistically significant compared to those with people with PGT, $p < 0.05$.

To compensate for the energy supply of the brain in hypoxia, the transport of glucose to the brain is activated. This increases the level of insulin-independent glucose transporter GLUT-3 [8]. At the same time, it is known that with insulin resistance, cells lose the ability to respond to the metabolic activity of insulin and insulin-mediated processes in the brain. This is because insulin receptors are widely expressed in the hypothalamus, hippocampus and cerebral cortex [9]. In conditions of oxygen deficiency, despite not increasing glucose transport, defective insulin signalling leads to a deficiency in the energy systems of

neurons in the brain. Insulin resistance also increases the importance of activating free radical processes in the brain during hypoxia. This may contribute to excessive increases in the level of membrane lysophospholipids, which lead to impaired mitochondrial function and reduced synthesis of macroergic compounds [10].

The described processes reduce the energy supply of the brain and form a different nature of the activity of neurons of the respiratory centre. This can lead to delayed and insufficient response to hypoxia of respiratory centre neurons in elderly people with IGT. On the other hand, the mechanisms of regulation of ventilation, its response to hypoxia and carbohydrate metabolism may interact. The hypothesis between hypoglycemia and hypoxia supports this assumption. According to Nyengaard J. R. and co-authors studies, 2004, hyperglycemia and hypoxia may interact due to general metabolic imbalance [3]. Therefore, the functional insufficiency of ventilation regulation may contribute to the violation of carbohydrate metabolism. In turn, disorders of carbohydrate metabolism, which, in particular, develop in the elderly with IGT, adversely affect metabolism and can cause changes in the sensitivity of central and peripheral chemoreceptors. This leads to a decrease in the sensitivity of the chemoreceptor mechanism of compensation of arterial hypoxemia.

Respiratory centre response to hypoxia in the elderly with IGT may be reduced due to these complex mechanisms.

Relationship between pulmonary ventilation function response to hypoxia and impaired glucose tolerance in the elderly.

Constant oxygen tension in the tissues is essential for optimal cellular metabolism. Activation of ventilation under the influence of hypoxic stress is aimed at compensating for the lack of oxygen to meet the metabolic needs of the body. The activity of metabolic processes, in particular, carbohydrate metabolism in hypoxia directly depends on the adequacy of compensatory reactions of the body. It is hypoxia, namely, the inability of the body to meet the oxygen needs of metabolism leads to the development of pathological phenomena in violation of carbohydrate metabolism. For example, J. Ditzel 1975 proved the causal link between tissue hypoxia and diabetic retinopathy and glomerulosclerosis [11]. However, the relationship between changes in respiratory response to hypoxia and changes in blood glucose levels in a standard glucose tolerance test has not been studied. Clarifying this question may deepen our understanding of the mechanisms of impaired glucose tolerance in the elderly.

In the analysis of indicators of the respiratory system in hypoxia, we found their relationship with insulin resistance. In elderly people with impaired glucose tolerance, the response of pulmonary ventilation to hypoxia (ΔVE) had a statistically significant inverse relationship with the insulin resistance index (HOMA) ($r = - 0.26$, $p = 0.035$). An inverse correlation ($r = - 0.31$, $p = 0.012$) between VE shifts in hypoxia and changes in blood glucose levels after 2 hours SGT.

These data suggest a causal relationship between impaired glucose tolerance and insufficient response of pulmonary ventilation to hypoxia in the elderly.

Conclusions

1. Under conditions of dosed hypoxia, the indicators of pulmonary ventilation function increase in the elderly, regardless of the state of glucose tolerance.
2. In elderly people with impaired glucose tolerance, the response of pulmonary ventilation to hypoxia is less significant (insufficient) than in people with preserved glucose tolerance.
3. In elderly people with impaired glucose tolerance, an insufficient ventilatory response to hypoxia is associated with both insulin resistance and changes in blood glucose levels in a standard glucose tolerance test.

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