Hypoxia Caused by General Cooling of the Body in Citizens from the Polar Region

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Abstract

The aim of the study is to discover the process of hypoxia development at bronchial asthma due to the long exposure of the body to severe climatic conditions that affect airways; to reveal the character of the influence of low temperatures of the inhaled atmospheric air on the receptors of epithelium of tracheobronchial airways at the first stage of bronchial asthma formation, which intensifies the development of hypoxic state of the body and involves the vascular system and erythrocytes of the peripheral blood into this process.

Keywords: Low Temperature; Receptors to Cold in Bronchi

Introduction

Breathing in cold conditions decreases the ventilation function of lungs, which leads to the development of hypoxia [2]. Long exposure to low temperature inhaled air during a year results in the decrease of active ventilation as adaptive abilities of the body are always in severe climatic conditions. There happens the worsening of processes of oxygen transition through aero-hematic barrier and this in its turn causes severe morpho-functional changes both in aeriferous and in respiratory parts of lungs. For the air, not warm enough to penetrate into bronchioles and respiratory part of the lungs, it is necessary to have an increased ventilation performance of lungs, as a result of which a bronchospasm inducing reaction develops [10,11].

The decrease of PaO₂ is likely to occur as a result of the necessity to protect the airways from cold and restrictions of heat losses under constant penetration of cold atmospheric air into the lungs. This leads to the decrease of alveolar ventilation as a result of which there is the decrease of oxygen tension in alveoli PaO₂ [16]. The hypoxia state develops in the body [9-11].

Materials and Methods of the Research

108 asthmatics were examined, including 25 patients with mild persistent course of asthma, 45 with moderate bronchial asthma and 38 with severe asthma. Diagnosis and the severity degree of the disease were found according to Federal Standards and International Consensus Papers (GINA).

The examination of patients was done in the pulmonologic department in Chukotskaya county hospital in the branch office of the Center of Physiology and Pathology of Respiration of the Siberian Branch of Academy of Medical Sciences at the exacerbation of the disease under the decrease of clinical symptoms and achievement of the partial pharmacotherapeutic control over asthma.

The research protocol was approved by the Committee of Biomedical Ethics of the institution. The criterion for the patients’ selection became the absence of general negative side effects for the conductance of functional and endoscopic studies, of severe concomitant pathology of other organs and systems as well as an agreement of patients and their awareness of the examination aim.

The control group included 30 almost healthy volunteers. At the selection of the control group there were used the following criteria: they did not complain about pulmonary or cardiovascular system, did not have pulmonary diseases in anamnesis, did not have functional data proving pulmonary and cardiovascular pathology, did not have any changes in the lungs according to large picture frame photofluorography and they had standard parameters of spirometry.

The study of the respiratory function was done at the device “Ultrascreen” (Erich Jaeger, Germany). Pulmonary ventilation function was assessed by the data of the curve “flow-volume” of the forced expiration. The following parameters were used: vital capacity (VC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), maximal volumetric flow rate at the level of 25, 50, 75% of the exhaled VC (MOC25, MOC50, MOC75). All the parameters were evaluated in percentage in ratio to due values. Visual examination of tracheobronchial tree was done with the help of bronchoscopy which was done under local anesthesia. Biopsy sampling from middle lobe bronchus and segmentary bronchi of the basal pyramid of the low lobe of the right lung was done through the bronchoscope forceps aperture.

Biopsy sampling was studied at semifine sections (fixation with glutaraldehyde with further embedding) as well as after fixation in formalin ethyl-acetate with further embedding in paraffin. The sections were stained with Bemer’s hematoxylin-eosin by Van Gieson methodology and cation proteins into fast green by Pigarevsky [8]. Fatty acids peroxides were found by Schulz Winkler methodology, and histamine by Shampi.

The contents of 2,3-bisphosphoglycerate (2,3-BPG) and ATP were found by Luganova and Blinova method. Acid-alkaline condition of blood gases was studied at the analyzer “IRMA Tru Point” (USA). Myoglobin peroxidase in the unstriated muscles was found by the method of Drews G.A.

The constitution of erythrocytes membrane was studied with the help of vertical disk of electrophoresis in polyacrylamide gel. Identification of electropherograms was done at the length of the wave in 590 - 600 nm with the help of the device “Bio Doc Analize” (Germany).

The measurement of microviscosity of erythrocyte membranes lipid bilayer was done with the method of lateral diffusion of hydrophobic fluorescent bougie of pyrene at spectrofluorimeter “Hitachi” (Japan). For determination of the microviscosity of the zone of protein-lipid contacts, the excitation of wavelength was 286 nm, monomers wavelength was 395 nm, eximers wavelength was 470 nm. The assessment of microviscosity is based on the calculation of the coefficient of pyrene eximerization which is equal to the ratio of eximers fluorescence intensiveness to monomers fluorescence intensiveness. The coefficient of pyrene eximerization is in the inverse dependence on microviscosity. The erythrocyte membrane density was studied under microscope by the program ”BioVision” (USA) with the help of digital camera “Pixera” (Figure 5).

The Obtained Data

One of the adaptations of the body to cold is the change in the links of thermoregulatory reflex [3,4]. The influence of cold stimulates the release of noradrenaline by the adrenaline gland into the blood [4]. The effect of the mediator at oxygen consumption (E") can be presented with the formula:

\[ E" = N \times M \]
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where $E_m$ – is the effect of the mediator, the increase of oxygen consumption induced by it; $N$ – is the number of receptors in the system under consideration (bronchi); $M$ – is the mean number of mediator quanta interacting with the receptor per time unit; $e$ – is the elementary effect caused by the interaction of one mediator quantum with one receptor [6,7].

At the adaptation of the body to cold during a long time there happens the increase of adrenoreceptors [12-14].

**Figure 1: Bronchi mucosa. Ciliated cells in a healthy person or under mild bronchial asthma. At the cilia of ciliary cells, a big number of adenylate cyclase receptors is concentrated.**

*Electronic-histamine reaction.*

Under long cold exposure the contents of noradrenalin is constantly very high in the body. It can be proved that the ratio between the activation of adenylate cyclase and noradrenaline dependent increase of ionic penetration of plasmatic membrane and activation of membrane (Na$^+$ + K$^+$) – ATPase is a thermogenic constance for the body. Adenylate cyclase supports and changes the conformation of the complex of ATPase restoration and provides the optimal level of cAMP. It was found out that the influence of cold activates a phosphodiesterase link in the regulation of cAMP exchange [17].

The breathing trouble under cold exposure of the body is limited by the concentration of cAMP which depends on the activity of adenylate cyclase. While using adenylate cyclase (for example, at the cilia of ciliary cells) the activity of cAMP decreases due to its damage by phosphodiesterase.

It becomes clear that the long effect of the inhaled cold air is the cause of the suppression of the complex of cAMP- phosphodiesterase action on the cilia of the ciliary cells and it decreases ATPase in the cells cilia.

Ciliary cells under long adaptation to cold are the first to be damaged; as a result, the mucociliary clearance is disturbed. The substitution of cAMP for cGMP increases the action of adrenergic receptors, which leads to the narrowing of the lumen of the microcirculatory system vessels both in bronchi and respiratory part.

Under influence of adrenergic receptors there is the increase in the traction of unstriated muscles of the terminal parts of the bronchial tree; besides, it leads to the growth in the mucosa the muscles of myoglobin peroxidase that intensifies this process.

The conductance of terminal bronchi decreases, which violates gas exchange in aero-hematic part of lungs.

**Figure 2:** Myoglobinperoxidase in the control of unstriated muscles of the terminal parts of the bronchial tree (control). Reaction to myoglobin peroxidase by Drews G. A Amplification 10 х 100.

**Figure 3:** Myoglobinperoxidase at the growth of noradrenalin in the blood. In the unstriated muscles there is the increase of myoglobin peroxidase. Reaction to myoglobin peroxidase by Drews G. A Amplification 10 x 100.
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Capillary component of microcirculatory channel narrows. The conductance of erythrocytes to the working organ and the process of gas exchange in target-organs worsens. The system Hif-1α signals about the disturbance in gas exchange and provision of target organs with oxygen.

Figure 4: At the growth of noradrenaline in the body there is the narrowing of the lumen of microcirculatory channel capillaries in the bronchial mucosa and respiratory part of lungs.

a – the primary stage of inflammation.
b – the growth of noradrenalin.
Gallocyanine stain. Amplification 10 х 40.

The decrease of PO$_2$ in the gas environment of the inhaled air is the cause of hypoxic hypoxia. The oxygen delivery to the tissues of the body is determined by its diffusion from the microcirculatory channel which contacts with it. The efficiency of diffusion depends on the value of diffusion gradient at different parts of oxygen transport. The fall of PO$_2$ in intercellular fluid lower than it is necessary to keep the cell alive leads to oxygen deficiency, the energy metabolism disturbance; and its excess leads to the generation of reactive substances that damage proteins and nucleic acids [5].

Homeostasis of the oxygen is supported with the hypoxia inductor factor - Hif’s [17]. Hif-1α и Hif-2β control the delivery of the oxygen to the tissues through the regulation of expression of gene products that participate in the cellular energetic metabolism. Hif-1α binds with the protein of von Hippel-Lindau (VHL) which has a capability to degradation of Hif-1α. When the level of oxygen is low, Hif-1α makes an active complex with β-subunit and becomes stable as a result of it [12,14]. It was found out that the increase of Hif-1α, Hif-2β proves the development of severe bronchial asthma which is followed by morphofunctional disorders in bronchi. In mucosa, there are serious disturbances in the composition of the microcirculatory channel. The vessels of the microcirculatory channel in the conjunctive tissue narrow (Figure 4b), and the development of new capillaries progressively decreases as a result of the drop of the level of vascular endo-

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This explains the disturbance of metabolic processes in bronchi mucosa which is revealed through long inflammatory process leading in the end to the formation of hypoxic hypoxia which in its turn breaks metabolic processes including the production of secretion by goblet cells and the motion activity of the ciliated epithelium.

A sharp decrease of capillaries diameter makes it very difficult for erythrocytes to move towards aero-hematic barrier of the respiratory part of lungs. In these conditions, there is a deformation of erythrocyte membranes in the narrowest parts of the capillary bed.

A detailed study of this process shows that the membrane of erythrocytes under sudden deformation loses its elasticity, that is to say, the process of microviscosity and induration of erythrocytes membrane layer density develops. Coefficient of pyrene eximerization decreases till 0.67 ± 0.07 of relative units (in control it was 1.29 ± 0.05 of relative units; p(t) < 0.01), which characterized the increase of microviscosity of erythrocyte membranes. The displacement of protein scaffold of erythrocyte membranes and the increase of microviscosity disturb the elasticity of α and β-spectrin, band 3 and 4 protein, which excludes the erythrocyte membrane from gas transport function.

Deoxygenation of hemoglobin is spent under active circulation; the contents of fatty acids peroxides grow in erythrocytes (Figure 6), the quantity of 2,3 BPG binds with hemoglobin in bigger quantities than in the norm (2,3 BPG in the norm should be 5.1 mkmole/ml, under oxygenation disturbance the number of 2,3 BPG increases till 6.2 mkmole/ml).

Figure 5: The growth of protein-lipid composition density and erythrocyte membrane fluidity.

Figure 6: The erythrocyte membrane from capillaries with a lowered diameter (figure 5 – degenerative form). Control – figure 5 normocyte. The reaction to fatty acids peroxides by Winkler –Shultz. Amplification 10 x 90.

Conclusion

Thus, the long exposure to low temperatures of the environment results in hypoxic condition development and damaging vitally important functions of the airways:

1. It decreases the ventilation function of the bronchial tree.
2. It stimulates the growth of smooth muscle tissue and mechanically intensifies the conductance of the inhaled air into the respiratory part.
3. The activity of cAMP is disturbed and cGMP increases, which stimulates the growth of noradrenaline in the circulating blood narrowing the lumen of the capillaries of the vascular bed.
4. In unfavorable conditions, the advancement of erythrocytes is followed by the growth of erythrocytes deformation; membrane microviscosity and gas transport function of erythrocyte membranes increase.
5. In erythrocytes, the hemoglobin oxygenation decreases under the growth of fatty acids peroxides.

The patients with severe bronchial asthma have hypoxia well developed by many ingredients, it severely disturbs metabolism of cardio-vascular and neuro-endocrine function of the body.

Bibliography


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