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TOPICAL ISSUE

DOI 10.25789/YMJ.2020.69.14

УДК 613.84(571.56)

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Physiological and biochemical aspects of smoking in Yakutia

The article reports the influence of tobacco smoking on the indices of pulmonary function testing and on the biochemical indices (including the some indices of antioxidant system) of the organism of the inhabitants of Yakutsk. The indices of pulmonary function testing (PFT) were determined in accordance with the recommendations of the Russian society of pulmonologists (M., 2003, 2016). The intensity of the peroxide lipids oxidation (PLO) was determined on the concentration in the blood of malonic dialdehyde (MDA). The state of the antioxidant protection of organism was evaluated according to the activity of superoxidedismutase (SOD), catalase and total antioxidant activity of the blood plasma. The concentration of uric acid, total bilirubin and cholesterol in the blood serum was determined on the automatic biochemical analyzer Cobas mira plus of the firm La Roche.

Keywords: smoking tobacco, the chronic obstructive diseases of lungs (COPD), the pulmonary function testing (PFT), malonic dialdehyde (MDA), superoxidedismutase (SODAS), catalase.

Introduction. The respiratory system, being an open one, is one of the first to protect the body from the adverse effects of environmental factors. Smoking as an aggressive risk factor contributes to the development of bronchopulmonary, oncological and cardiovascular diseases. Tobacco smoke is one of the most aggressive smokes, so-termed "pro-oxidant pollutants". It contains a number of chemically active components: nicotine, formaldehyde, benzopyrenes, nitrogen oxide, cadmium, urethane, vinyl chloride, etc. All these components have a direct effect not only on the surface layer of the bronchoalveolar secretion and epithelial cells of lungs, but also on the internal milieu of the body, causing an increase of free-radical oxidation [11, 15, 17, 25].

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It is known that the death rate from lung cancer among smokers is 20 times higher than among non-smokers. Smokers are 13 times more likely to suffer from angina and 10 times more likely to have peptic ulcers than non-smokers. Alveolar macrophages of smoker uptake insoluble particles of tobacco smoke and undergo characteristic morphological changes, which allow them to be classified as biomarkers of a smoker. Another marker is an increased blood nicotine level. Nicotine is a thrombogenic factor that causes damage to the endothelial cells of both large and small vessels. The chemical reaction of nicotine and nitrogen oxide leads to the formation of N-nitrosamines, which have significant carcinogenic properties. Urethane, benzopyrenes, and vinyl chloride are also classified as carcinogens [23]. A smoker has a high percentage of hemoglobin associated with carbon monoxide (CO). With the formation of the CO-hemoglobin complex, the main function of hemoglobin, the transport of oxygen to the tissues, is disrupted.

In the North, the cold factor plays a significant role in the impact on the bronchopulmonary system along with smoking. Inhalation of cold air often causes deterioration of bronchial patency even in healthy people [3]. Data on the effect of smoking on the bronchopulmonary system under the Far North conditions are available only in a few works [8].

The purpose of the research: assessment of the effect of tobacco smoking on the function of external respiration and biochemical indices that characterize the state of antioxidant defense in men in Yakutsk.

Research material and methods: We examined a total of 237 men aged 24 to 50 years. The control group consisted of 140 apparently healthy non-smoking men, mean age 45.28±2.43 (Me-45). Among them, there were 70 men of Yakut nationality mean age 45.71±2.32 (Me-44), and 70 men of Russian nationality with a period of residence in the North of at least five years, without a history of lung diseases mean age 44.86±2.21 (Me-44). There were 97 men with smoking history, mean age 46.78±3.56 (Me-46). Indices of the pulmonary function were estimated by spirometry. The evaluation of the results of pulmonary function, pneumotachometry and respiratory quotient was carried out in accordance with the recommendations of the Russian Respiratory Society [6, 14]. The concentration of malondialdehyde (MDA) in blood serum was estimated by colorimetric method using thiobarbituric acid [28]. The total antioxidant activity of blood plasma was determined using G.I. Klebanov's method [9]. Chemiluminescent methods for estimating the activity of superoxide dismutase (SOD) and catalase were used to evaluate the enzymatic system of the body's antioxidant defense [13]. The content of uric acid, total bilirubin and cholesterol in the blood serum

was estimated using an automatic biochemistry analyzer Cobas Mira Plus, manufactured by La Roche.

The results were processed using the SPSS 8.0 computer software for Windows 95. The data in the tables are presented as M±m, where M is the average, and m is the error of the average. The statistical significance was evaluated using Student's t-Test.

Results and discussion. According to the obtained data, the actual vital capacity (VC) in men of Russian nationality slightly exceeded the upper limit of the norm (85-90%) and was statistically significantly higher than in men of Yakut nationality. Tiffeneau index (the ratio of the volume of forced expiration to vital capacity, i.e. FEV1/FVC) and maximal voluntary ventilation (MVV) were also higher in Russians, and the respiratory reserve was lower than in Yakuts ($p<0.05$). At the same time, the MVV in the indigenous population of the Far North corresponded to the lower limits of the European norm, and the Tiffeneau index even slightly exceeded the generally accepted standards, indicating that there was no disruption of bronchial patency or changes in the elasticity of the pulmonary tissue (Table 1).

The analysis of the PFT results in the two main ethnic groups of the population of Yakutsk indicates the presence of morphological and functional differences in the pulmonary tissue. Differences are associated with maintaining effective respiratory airway in the conditions of permafrost. Thus, the increasement of MV and breathing reserve in Yakuts, compared to the Russians, is related to the reduction in respiratory rate. Pneumotachometry data also confirm this fact. With such pulmonary mechanics' indices, the residual air increases and the contact time of cold air with the respiratory tract reduces. Higher values of the VC, MVV, and Tiffeneau index in men of Russian nationality may be related to an increase in the pulmonary alveolar surface area during the process of adapting to the conditions of the Far North. Literature has evidence that the morphometry of the pulmonary alveolar surface area of the northerners revealed a significant increase in comparison with residents living in Central Russia. The main reason for increasing the alveoli area under the influence of cold climate is their hypertrophy and additional disclosure of previously non-functioning alveoli. According to some researchers, the morphological and functional changes related to physiological defense reactions in response to the low temperature of the inhaled air are developing in two directions. The first direction relates to the compensation of alveolar hypoxia and provides a significant increase in the respiratory lining of the number of type II alveoli. They produce surfactant, which enhances the airiness of the pulmonary tissue. The second direction is related to the development of hypervolemia in response to the decrease of the oxygen partial pressure in alveoli. It is provided by an increased diameter of capillary, size of capillary loops, and a decreased thickness of the endothelium [7, 16].

Comparative analysis of the data in table 1 shows that the surveyed apparently healthy men of Yakut nationality were found to have more effective respiratory airway, despite the decrease in VC, MVV and Tiffeneau index (compared to men of Russian nationality). That is since RQ in Yakut men was higher than in Russians. A. P. Milovanov's fundamental research (1981) showed that the Northern aboriginal people's essential adaptive traits of aero-hematic barrier to the effects of low temperatures is the increasement of the respiratory airway's working zone. Another adaptive trait is structural features of the pulmonary vascular system. In particular, the expansion of pulmonary circulation's arteries [7]. Our results do not contradict the literature data [3, 5, 7, 15, 16].

We analyzed the indices of pulmonary function in 97 men who abused smoking and had smoking history. Many of those subjects started smoking at the age of 16 (30%), and the majority started smoking from 18-19 years old (70%), so people in their 50s had about 30 years of smoking history. All the subjects considered themselves apparently healthy, although in the mornings they were disturbed by coughing with a slight sputum discharge.

According to the obtained data, grouped by smoking history, indices of pulmonary ventilatory function in smokers were significantly reduced (Table 2). Thus, the vital capacity (VC) in young smokers (5 years of smoking history) was statistically significantly lower ($P<0.05$), compared to the control group of healthy non-smokers. With an increase in smoking history (10 years or more), the VC decreased even more, while the average value of this indicator was 84.4±6.2 % ($P<0.05$). The values of the Tiffeneau index, MVV, and FEV1 also decreased with increasing smoking history. Men with smoking history of more than 10 years had worsened indices of pneumotachometry: up to 2.4±0.5 L/sec on an inhale compared to the control group of 3.8±0.1 L/sec ($P<0.001$), on exhalation up to 3.3±0.8 l/sec with the value of the indicator in the control group of 4.3±0.1 l/sec ($P<0.001$). It should be emphasized that in this group of smokers, all indices were significantly reduced. We examined smokers with a smoking history of 5 to 10 years, and they can be considered patients with stage 1 (mild severity) chronic obstructive pulmonary disease (COPD). At this stage of the disease, according to the classification adopted by the Russian Respiratory Society, FEV1 varies from 70% to 80% of the required value. Smokers with more than 10 years of smoking history have signs of stage 2 COPD, since the main symptom of COPD at this stage is that FEV1 is less than 70% of the required value. Thus, all people who abuse smoking need doctor's closest attention, particularly to create a strong motivation for them to quit smoking. The results obtained by us confirm the literature data that smoking has a negative impact on the pulmonary function, which worsens with the age of the smoker and with the number of cigarettes smoked [4,15].

Table 1

Indices of pulmonary function in apparently healthy residents of ethnically different groups of Yakutsk

PF Indices	Groups	
	Yakuts (n=70)	Russians (n= 70)
MV in %	144.6 ± 5.0	142.8 ± 4.8
VC in %	90.8 ± 1.6	96.31.4*
Tiffeneau index in %	81.8 ± 1.9	86.8 ± 0.5*
MVV in %	103.9 ± 3.2	127.6 ± 1.7*
Breathing reserve in %	91.6 ± 0.6	87.6 ± 1.0*
Pneumotachometry L/sec Inhalation Exhalation	 4.31 ± 0.10 4.310.12 ± 0.12	 3.38 ± 0.04 4.52 ± 0.06
RQ ml/L	29.5 ± 1.3	28.9 ± 1.2

* $p<0.05$, statistical significance

Table 2

Indices of pulmonary function in men depending on their smoking history

Показатель	Healthy n=90	Smoking history		
		5 years n= 30	More than 5 years n= 31	10 years and more n= 36
VC, %	94.3 ± 1.3	86.1± 5.0*	88.4 ± 6.1	84.4 ± 6.2*
FEV1, %	80.3 ± 3.4	71.4 ± 6.6	71.2 ± 6.6	63.8 ± 5.8*
Tiffeneau index, %	84.8 ± 0.5	74.8 ± 7.7	71.1± 4.8*	70.5 ± 3.4*
MVV, %	118.6 ± 1.7	87.3 ± 9.1*	84.6 ± 10.4*	87.6 ± 5.8*
Breathing reserve, %	89.6 ± 0.9	79.0 ± 4.4	83.2 ± 3.9	80.8 ± 4.0*
Pneumotachometry Inhalation 1/sec	3.8 ± 0.1	2.9 ± 0.5	3.3 ± 0.8	2.4 ± 0.5*
Exhalation 1/sec	4.3 ± 0.1	3.7 ± 0.7	4.0 ± 0.7	3.3 ± 0.8*
RQ, ml/L	29.1 ± 1.2	15.0 ± 4.0*	18.6 ± 2.4*	10.7 ± 2.1*

* $p<0.05$ compared to healthy subjects

It should be noted that the inverse relationship of pulmonary ventilatory function on smoking history is the most likely cause of an increase in COPD incidence rate among men with age.

It is shown that under the influence of tobacco smoke, alveolar macrophages are destroyed with the release of oxidative substances and lysosomal enzymes from them. Those contribute not only to pulmonary tissue's damage, but also to their infection. A study of bronchoalveolar lavage in smokers showed a 2-3-fold increase in neutrophils. At the same time, the time of their transport through the capillaries increased as a result of reducing the ability to deform under the influence of tobacco smoke oxidants. A big number of polymorphonuclear neutrophils adhered in places of damage to pulmonary blood vessels. Neutrophilia of lavage fluid in smokers plays a pathogenetic role in the development of obstructive bronchitis and pulmonary emphysema due to the increased content of neutrophilic elastase. Its proteolytic effect leads to the development of pulmonary fibrosis and loss of elasticity of the alveolar walls. Moreover, the thin elastic fibers of the interalveolar septum are destroyed faster than their bundles in the bronchial walls. As a result, there is a narrowing of the respiratory tract's lumen, especially pronounced in bronchioles devoid of cartilage. An obstructive syndrome occurs, which is not based on a spasm of the bronchial muscles, but on a disbalance of elastic tension between the pulmonary parenchyma and the bronchi. At the same time, unlike bronchial asthma, the airway obstruction is not paroxysmal, it increases gradually.

Young smokers were found to have squamous cell metaplasia in the respiratory tract's epithelium, chronic inflammatory infiltrates, and small increases in connective tissue in the respiratory tract's walls. Atypical squamous cell metaplasia was also found in older age groups. This is not surprising, considering that tobacco smoke contains substances that damage cell membranes, which was confirmed by experiments with pulmonary fibroblast's culture. When inhaling tobacco smoke, there is a decrease in the synthesis of surfactant phospholipids necessary for the synthesis of surfactant. Prolonged exposure to the chemical components of tobacco smoke leads to metaplasia of epithelial cells, which can become precursors of cancer cells. Dysfunction of muco-ciliary clearance contributes to the bacterial colonization. With the addition of a respiratory infection, the pathological process of the respiratory tract leads to the appearance of typical clinical signs of obstructive bronchitis. A sharp decrease in RQ under the influence of tobacco smoke is the result of a respiratory airway dysfunction, which inevitably leads to tissue hypoxia and disruption of intracellular metabolism, and above all are metabolic processes associated with oxidative phosphorylation reactions.

Therefore, smoking is an important risk factor for developing chronic respiratory diseases. The results of the pulmonary function's study in active smokers indicate significant airways obstruction.

Tobacco smoke is one of the most aggressive, so-termed "pro-oxidant pollutants". It contains a number of chemically active components: nicotine, formaldehyde, benzopyrenes, nitrogen oxide, cadmium, urethane, vinyl chloride, etc. All these components have a direct effect not only on the surface layer of the bronchoalveolar secretion and epithelial cells of lungs, but also on the internal milieu of the body, causing an increase in free radical oxidation.

According to the obtained data, the decrease in all indices of pulmonary function was combined with the intensification of free-radical reactions in the examined men. This is indicated by an increase in the concentration of malondialdehyde (MDA), which is a marker of lipid peroxidation. The count of MDA in the blood of smokers was increased by 30% compared to healthy non-smokers. Hypoxia can also contribute to the intensification of lipid peroxidation, since according to the obtained data, the RQ in smokers was significantly reduced compared to non-smokers (Table 3).

The toxic effect of lipid peroxidation is manifested in the antiproteases inactivation. In this case, oxidative inactivation of α_1-antitrypsin precedes elastase-dependent tissue damage in vivo. This has been demonstrated by studies showing that prior treatment with a small non-damaging dose of hydrogen peroxide significantly increases the sensitivity of isolated lungs to damage caused by perfusion with neutrophilic elastase. Activation of free-radical reactions is accompanied by a decrease in the activity of β-adrenergic and an increase in α-adrenergic and cholinergic receptors, which often leads to the development of bronchospasm in smokers with long history [20].

The intensification of lipid peroxidation in smokers is accompanied by compensatory activation of the endogenous antioxidant body system. The common antioxidant activity of blood plasma, as well as the activity of antioxidant enzymes, was higher in smokers than in non-smokers (Table 3). The level of uric acid (low-molecular endogenous antioxidant) in the blood of smoking men was statistically significantly increased. Bilirubin also has an inhibitory effect at the lipoperoxidation's chain branching stage, the concentration of which also increased in people who abused smoking.

The analysis of the obtained data shows that PFT indices are associated not only with the processes of respiratory airway and oxygen transport blood function, but also with the antioxidant defense of the body. Tissue metabolism, particularly the intensity of free-radical lipid oxidation, depends on the supply of oxygen to tissues. The obtained data on a decrease in pulmonary function indices with a parallel increase in the

Table 3

The impact of smoking on the antioxidant defense indices

Parameters	Healthy	Smokers (smoking history of more than 5 years)
Antioxidative activity, %	51.3 ± 0.7	55.6 ± 1.2
MDA, MDA/ml	1.26 ± 0.06	1.76 ± 0.10*
Superoxide dismutase (SOD), mcg/g, Hb	1.50 ± 0.03	1.96 ± 0.08*
Catalase, mcg/g, Hb	7.36 ± 0.10	7.98 ± 0.36
Uric acid, mmol/L	161.3 ± 7.5	226.5 ± 16.5*
Total bilirubin, mmol/L	5.74 ± 0.30	6.07 ± 0.48
Total cholesterol, mmol/L	4.32 ± 0.05	4.42 ± 0.12

*p 0.05, compared to healthy non-smokers

concentration of MDA in the blood, and an increase in the activity of SOD and catalase in red blood cells, suggest that people who smoke form a higher stationary level of lipid peroxidation. Higher level of LP activates the enzymatic system of antioxidant defense and drains the pool of natural antioxidants. The results of our study are consistent with the literature data. J. Kalra's research [21] showed a spontaneous increase in the generation of hydrogen peroxide from monocytes of smokers in vitro. Alveolar macrophages obtained from the lavage fluid of healthy smokers released more superoxide anion than alveolar macrophages obtained from the lavage fluid of healthy non-smokers.

Conclusion. Human adaptation to the Northern conditions causes morphological and functional changes in the pulmonary tissue, associated with physiological defensive mechanisms responding to the effect of the inhaled air's low temperature. The results of our study indicate that in the process of long-term adaptation to cold climate, the respiratory organs of the two main ethnic groups of the population of Yakutsk acquired some morphological and functional differences that affected the indices of pulmonary function. Thus, in apparently healthy men of Yakut nationality, there was a statistically significant decrease in the VC, Tiffeneau index, and MV, as well as an increase in the breathing reserve and RQ, compared to men of Russian nationality. Features of PFT indices in apparently healthy men of Yakut nationality are probably associated with an increase in the pulmonary airway's working zone and with the expansion of the pulmonary circulation's arteries.

Smoking is an important risk factor for developing chronic respiratory diseases. The results of the pulmonary function's study indicate significant airway obstruction in smokers. There are certain effects due to smoking, such as increased hypoxia, the disruption of blood oxygenation and oxygen transport to the tissues. The effects are evidenced by statistically significant decrease in the value of RQ in smokers, compared to non-smokers.

Tobacco smoke is one of the most aggressive "pro-oxidant pollutants". Our obtained data on the decrease of pulmonary function's indices with a parallel increase of MDA, increase of the contents of SOD and catalase in erythrocytes, suggests that smokers form a higher stationary level of lipid peroxidation. Higher level of LP increases the risk of damaging membrane structures, developing inflammatory process in the pulmonary tissue and forming chronic obstructive pulmonary disease (COPD). The degree of airway obstruction in smokers increases in direct proportion to smoking history. The examined men with smoking history of 5 to 10 years already show signs of stage 1 (FEV1 71.2±6.6%) COPD, and smokers with more than 10 years smoking history have signs of stage 2 (FEV1 63.8±5.8%) COPD. Thus, all smokers need doctor's closest attention, particularly to create a strong motivation for them to quit smoking.

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