Effects of smoking on the level of SP-A and SP-D surfactant proteins in the blood of patients without bronchopulmonary diseases

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ABSTRACT

Every year, about six million people die from tobacco use. Respiratory epithelium is the first line of defense against exogenous invasion, in particular, harmful inhaled particles, pathogens and allergens. However, the epithelium of the respiratory tract is also a regulator of immunological and inflammatory reactions through secretion of inflammation and immune cell recruitment mediators. An important component of the pulmonary immune system is the surfactant, and, in particular, its proteins SP-A and SP-D, synthesized mainly by type II pneumocytes.

Aim. To assess the levels of surfactant proteins SP-A and SP-D in the blood of smoking patients without bronchopulmonary diseases.

Materials and methods. The study included 59 patients admitted to the department of internal medicine with hypertension. The general group was divided into subgroups: non-smoking patients (n = 31) and healthy smokers (n = 28). All patients underwent clinical, functional, diagnostic and laboratory tests. The content of surfactant proteins SP-A and SP-D in the blood was determined by enzyme immunoassay.

Results. The subgroups did not differ in sex, age, height, body weight, blood pressure, heart rate, respiratory rate, and the distribution of comorbidities. The subgroups differed in the platelet level; in other main parameters of complete blood count and blood biochemistry no differences were revealed. It was found that the blood levels of surfactant proteins SP-A and SP-D in the subgroup of healthy smokers were significantly higher in comparison with the subgroup of non-smoking patients. The correlation analysis revealed a direct relationship between surfactant proteins SP-A and SP-D and smoking (R = 0.360, p = 0.006, R = 0.274, p = 0.037), a negative correlation between SP-D protein and age (R = -0.315, p = 0.016), and a direct relationship between SP-A protein and diastolic blood pressure (R = 0.271, p = 0.039). In the non-smoking subgroup, a negative correlation between SP-D and age (R = -0.438, p = 0.016) and between SP-D and systolic blood pressure (R = -0.433, p = 0.017) was identified.

Conclusions. The direct relationship between higher levels of the surfactant proteins SP-A and SP-D and smoking in the group of healthy smokers is justified (inflammatory changes, structural abnormalities in the lung parenchyma under the influence of cigarette smoke). The SP-D protein is more significant in comparison with the SP-A protein in vascular wall remodeling, lung tissue matrix, oxidative lung tissue damage, and apoptosis, which explains its negative correlation with age and systolic blood pressure.

Key words: surfactant, surfactant protein A, surfactant protein D, biomarker, smoking.

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Влияние курения на уровне сурфактантных белков SP-A и SP-D в крови у пациентов без бронхолегочных заболеваний

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РЕЗЮМЕ

Актуальность. Ежегодно около 6 млн человек умирают из-за употребления табака. Дыхательный эпителий – первая линия защиты против экзогенной инвазии, в частности вредных вдыхаемых частиц, патогенов и аллергенов. Однако эпителий дыхательных путей является не просто физическим барьером, но и регулятором иммунологических и воспалительных реакций посредством секреции медиаторов воспаления и рекрутинга иммунных клеток. Важным компонентом легочной иммунной системы является сурфактант, в частности его белки SP-A и SP-D, синтезируемые в основном пневмоцитами II типа.

Цель. Оценить уровень сурфактантных белков SP-A и SP-D в крови у курящих пациентов без наличия бронхолегочных заболеваний.

Материалы и методы. В исследование включены 59 пациентов, госпитализированных в терапевтическое отделение по поводу гипертонической болезни. Общая группа разделена на подгруппы: некурящие пациенты (n = 31) и «здоровые курильщики» (n = 28). Всем пациентам проведены клиническое, функционально-диагностическое и лабораторное исследования. Содержание сурфактантных белков SP-A и SP-D в крови определяли методом иммуноферментного анализа.

Результаты. Подгруппы не различались по полу, возрасту, росту, массе тела, уровню артериального давления, частоте сердечных сокращений, частоте дыхательных движений, а также по распределению сопутствующей патологии. Сравниваемые подгруппы достоверно отличались по уровню тромбоцитов, по остальным основным параметрам общего анализа крови, биохимического анализа различий не отмечено. В подгруппе некурящих пациентов выявлены обратная связь SP-D с возрастом и систолическим артериальным давлением (R = –0,438; p = 0,016) и систолическим артериальным давлением (R = –0,433; p = 0,017). В подгруппе некурящих по- лучена обратная связь SP-D с возрастом (R = –0,315; p = 0,016) и систолическим артериальным давлением (R = –0,433; p = 0,017).

Заключение. Отмечены более высокий уровень сурфактантных белков SP-A и SP-D в группе курящих пациентов, их прямая связь патогенетически обоснована (воспалительные изменения, структурные аномалии в паренхиме легких при воздействии сигаретного дыма). Белок SP-D более значим в сравнении с SP-A при ремоделировании сосудистой стенки, матрикса ткани легкого, при окислительном повреждении ткани легкого и апоптозе, что объясняет его обратную связь с возрастом и систолическим артериальным давлением.

Ключевые слова: сурфактант, сурфактантный белок А, сурфактантный белок D, биомаркер, курение.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.
INTRODUCTION

Despite the efforts aimed at decreasing prevalence of smoking, approximately six million people die due to tobacco consumption worldwide annually [1]. Cigarette smoking contributes greatly to the pathogenesis of chronic obstructive pulmonary disease (COPD), hypertension, cardiovascular and oncological diseases with inflammatory components, such as atherosclerosis, Crohn’s disease, rheumatoid arthritis, psoriasis, Grave’s ophthalmopathy, and non-insulin-dependent diabetes mellitus [2–5]. Apart from this, smokers show elevated sensitivity to microbial infections (respiratory tract infections, bacterial meningitis and periodontitis) and wound healing disorder [6]. Respiratory epithelium is the first line of defense against exogenous invasion including inhaled noxious particles, pathogens and allergens. However, respiratory epithelium is not merely a physical barrier, but also a regulatory mechanism for immune and inflammatory responses through secretion of inflammation and immune cell recruitment mediators [7, 8, 9]. An important component of the immune system is the surfactant and, in particular, its proteins SP-A and SP-D, mainly synthesized by type II pneumocytes [10].

Physiologically, small amounts of surfactant proteins SP-A and SP-D are found in blood. Tobacco smoke promotes increased alveolar-capillary leakage of surface-active proteins into the blood, and their level may facilitate assessment of damage to the lungs caused by smoke. The potential to use surfactant proteins as markers of alveolar epithelium damage against the background of smoking has not been studied previously and only rare investigations regarding SP-A and SP-D levels in patients with COPD have been conducted. Therefore, studying these mechanisms is relevant in modern medical science for identification of smoking individuals exposed to the risk of COPD.

The aim of the study was to assess the levels of surfactant proteins SP-A and SP-D in the blood of smoking patients without bronchopulmonary diseases.

MATERIALS AND METHODS

A total of 59 patients admitted to the department of internal medicine with hypertensive disease were enrolled in the study. The inclusion criteria were: worsening of hypertensive disease progression (the mean index of systolic arterial pressure (SAP) ≥140 mmHg during automatic evaluation of arterial blood pressure at the doctor’s office), patients of both genders aged 18 to 75 years, absence of acute and chronic bronchial and pulmonary diseases, absence of changes in spirometry previous/active pulmonary tuberculosis; clinically significant (according to judgment of the researcher) unstable cardiologic disease, e.g. uncontrolled symptomatic arrhythmia, atrial fibrillation, cardiac insufficiency with congestion phenomena of 3rd or 4th grades according to the NYHA classification; severe renal insufficiency di and presence of a known life-threatening comorbidity type 1 diabetes mellitus (DM); pregnancy or lactation; presence of oncological diseases; previous chemotherapy or radial therapy; immunodeficiency disorders; previous/active pulmonary tuberculosis; clinically significant (according to judgment of the researcher) unstable cardiologic disease, e.g. uncontrolled symptomatic arrhythmia, atrial fibrillation, cardiac insufficiency with congestion phenomena of 3rd or 4th grades according to the NYHA classification; severe renal insufficiency diagnosed through evaluation of eGFR calculated using the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration) with consideration for creatinine concentration in the serum below 15 ml/min/1.73 m²; type 1 diabetes mellitus (DM); pregnancy or lactation; and presence of a known life-threatening comorbidity with life expectancy < 18 months from the moment of enrollment into the study. The general group was divided into two subgroups: non-smoking patients (n = 31) and healthy smokers (n = 28). “Healthy smokers” is a
term used in modern literature meaning absence of respiratory symptoms or minimal respiratory symptoms (cough, expectoration, shortness of breath after insignificant physical loads) that may only be revealed using a clinical survey [11]. The subgroup of healthy smokers only included patients with the minimal smoking index of 2 packs/year.

All patients underwent clinical, functional, diagnostic, and laboratory assessment. Laboratory diagnosis (complete haemogram, blood biochemistry) was carried out using the biochemical analyzer Beckman Coulter AU 480 (Beckman Coulter, USA) and the haematology analyzer Siemens advia2120i, BC 5300 (Germany). The levels of the surfactant proteins SP-A and SP-D in the blood serum were evaluated by the method of immune-enzyme analysis using the Multiscan EX analyser (Finland) and the ELISABioVendor test system (R&D, USA). X-ray examination of thoracic organs was conducted using the TeleKoRD-MT device (a remotely operated diagnostic X-ray complex, Russia). The external respiration function was evaluated using the Spirolab I spirometer (Italy).

Statistical processing of the data obtained was performed using the SPSS 10.05 program package. The pattern of quantitative attribute distribution was determined using the Kolmogorov–Smirnov method. In case of normal distribution, the mean value ($M$) and standard deviation ($SD$) were calculated. The Student’s $t$-test was used to compare normally distributed samples. In case of non-Gaussian distribution, the median ($Me$), and the 25 and 75 percentiles were calculated. Interrelations between the attributes were evaluated through calculation of the Spearman’s correlation coefficient ($R$). The $\chi^2$ criterion was used for qualitative attributes. The critical level of statistical significance in the null hypothesis tests was assumed to be 0.05. The study protocol was approved by the local Ethics Committee at the research site.

**RESULTS**

The clinical characteristics of the patients are presented in Table 1.

The subgroups did not differ in sex, age, height, body mass, arterial blood pressure level, heart rate, respiratory rate or distribution of comorbidities.

The characteristics of patients’ laboratory data (complete blood count, blood biochemistry, SP-A and SP-D surfactant protein levels) are presented in tables 2 and 3.

The compared subgroups were significantly different in thrombocyte levels; no difference was revealed in the remaining parameters of complete blood count and biochemistry.

| Table 1 Clinical characteristics of the patients |
|-----------------------------------------------|
| **Parameter**                          | **General group of patients, $n = 59$** | **Subgroup of healthy smokers, $n = 28$** | **Subgroup of non-smoking patients, $n = 31$** | $p$ |
| Sex, men/women, $n$ (%)               | $32 (54.2) / 27 (45.8)$               | $17 (60.7) / 11 (39.3)$                  | $15 (48.4) / 16 (51.6)$                 | $0.421$ |
| Age, years, $Me$ (25%; 75%)           | $55 (47; 68)$                        | $53 (48; 65)$                            | $61 (44; 68)$                           | $0.543$ |
| Height ($M \pm SD$), cm               | $169.2 \pm 9.0$                      | $170.6 \pm 9.6$                          | $168.0 \pm 8.3$                        | $0.113$ |
| Body weight, $Me$ (25%; 75%), kg      | $79 (69; 85)$                        | $80 (71; 83)$                            | $75 (65; 86)$                           | $0.101$ |
| Systolic blood pressure ($M \pm SD$), mmHg | $157 \pm 26$                       | $162.7 \pm 26.8$                         | $152.3 \pm 24.3$                      | $0.343$ |
| Diastolic blood pressure ($M \pm SD$), mmHg | $89 \pm 12$                        | $91.8 \pm 12.7$                          | $86.3 \pm 10.5$                        | $0.320$ |
| Respiratory rate ($M \pm SD$), beats per minute | $17.6 \pm 4.8$                     | $17.3 \pm 6.4$                           | $18.0 \pm 2.6$                         | $0.716$ |
| Heart rate ($M \pm SD$), beats per minute | $84.2 \pm 10.2$                    | $83.4 \pm 10.1$                          | $83.8 \pm 10.4$                        | $0.113$ |
| Number of patients with type 2 diabetes, $n$ (%) | $8 (13.6)$                        | $4 (14.3)$                               | $4 (12.9)$                              | $0.885$ |
| Number of patients with obesity, BMI $\geq$ 30, $n$ (%) | $21 (35.6)$                       | $10 (35.7)$                              | $11 (35.4)$                              | $0.933$ |

Note. $p$ – significance of differences between the subgroups of non-smoking patients and healthy smokers. BMI – body mass index.
It was revealed that the blood level of surfactant proteins SP-A and SP-D in the subgroup of healthy smokers was significantly higher than in the subgroup of non-smokers.

Significant correlations in the general group of patients are presented in table 4. A direct correlation was found between SP-A and SP-D surfactant proteins and smoking. An inverse correlation was revealed between the SP-D protein and age. Additionally, a positive correlation was found between the SP-A protein and systolic arterial blood pressure. While investigating the correlations in the subgroups separately, a negative correlation was found between SP-D and age (Spearman \((R)\) \(-0.438\), \(p = 0.016\)) and SP-D and diastolic blood pressure (Spearman \((R)\) \(-0.433\), \(p = 0.017\)) in the subgroup of non-smokers.

### Table 2

| Parameter                              | General group of patients, \(n = 59\) | Subgroup of healthy smokers, \(n = 28\) | Subgroup of non-smoking patients, \(n = 31\) | \(p\)  |
|----------------------------------------|--------------------------------------|----------------------------------------|---------------------------------------------|------|
| White blood cells, \(Me (25\%; 75\%), *10^9/l\) | 8.1 (6.6; 10.1)                      | 9.0 (6.5; 10.5)                         | 7.6 (6.6; 9.7)                              | 0.427|
| Red blood cells \((M \pm SD), *10^9/l\) | 4.5 ± 0.7                            | 4.5 ± 0.9                              | 4.5 ± 0.5                                  | 0.737|
| Hemoglobin \((M \pm SD), g/l\)         | 135.3 ± 22.7                         | 135.8 ± 27.7                           | 134.8 ± 17.4                               | 0.762|
| Platelets, \(Me (25\%; 75\%), *10^9/l\) | 225 (176; 267)                       | 184 (150; 236)                         | 249 (202; 268)                             | 0.016|
| Erythrocyte sedimentation rate, \(Me (25\%; 75\%), mm/hr\) | 8 (5; 13)                            | 8 (4; 13)                              | 9 (6; 12)                                  | 0.816|
| Alanine aminotransferase, \(Me (25\%; 75\%), ME/l\) | 18.5 (12.0; 29.2)                    | 21.5 (14.1; 33.7)                      | 15.0 (11.3; 23.2)                          | 0.069|
| Aspartate aminotransferase, IU \((25\%; 75\%), IU/l\) | 21.3 (17.1; 35.0)                   | 22.0 (18.3; 46.2)                      | 20.5 (17.0; 30.1)                          | 0.349|
| Total protein \((M\pm SD), g/l\)       | 71.0 ± 26.5                          | 72.6 ± 7.3                             | 69.9 ± 5.7                                | 0.146|
| Total bilirubin, \(Me (25\%; 75\%), mmol/l\) | 13.7 (10.8; 17.4)                   | 13.4 (9.8; 17.3)                       | 14.2 (11.5; 17.4)                          | 0.611|
| Cholesterol \((M \pm SD), mmol/l\)     | 4.8 ± 1.3                            | 4.7 ± 1.1                              | 4.8 ± 1.4                                  | 0.902|
| Creatinine, \(Me (25\%; 75\%), mmol/l\) | 99.0 (80.9; 216)                     | 100.0 (81.2; 133.4)                    | 98.0 (78.0; 108.0)                         | 0.237|
| Glucose, \(Me (25\%; 75\%), mmol/l\)  | 5.2 (4.6; 5.9)                       | 5.3 (4.9; 6.0)                         | 5.0 (4.4; 5.8)                             | 0.221|
| Urea, \(Me (25\%; 75\%), mmol/l\)     | 6.1 (5.4; 8.5)                       | 5.9 (4.8; 8.9)                         | 6.3 (5.5; 8.1)                             | 0.809|

Note. \(p\) – significance of differences between the subgroups of non-smoking patients and healthy smokers.

### Table 3

| Parameter                              | General group of patients, \(n = 59\) | Subgroup of healthy smokers, \(n = 28\) | Subgroup of non-smoking patients, \(n = 31\) | \(p\)  |
|----------------------------------------|--------------------------------------|----------------------------------------|---------------------------------------------|------|
| SP-A, \(Me (25\%; 75\%), (ng/ml)\)    | 34.19 (26.97; 45.96)                 | 44.60 (28.35; 61.56)                   | 29.26 (21.25; 39.46)                        | 0.007|
| SP-D, \(Me (25\%; 75\%), (ng/ml)\)   | 274.06 (173.95; 484.22)              | 333.99 (232.32; 593.35)                | 242.37 (145.51; 356.80)                      | 0.039|

Note. \(p\) – significance of differences between the subgroups of non-smoking patients and healthy smokers.

### Table 4

| Correlation pair                      | General group of patients, \(n = 58\) |
|---------------------------------------|---------------------------------------|
|                                       | Spearman \((R)\) \(p\)                |
| SP-A – Smoking                        | 0.360                                 | 0.006                                 |
| SP-D – Smoking                        | 0.274                                 | 0.037                                 |
| SP-A – Diastolic blood pressure       | 0.271                                 | 0.039                                 |
| SP-D – Age                            | \(-0.315\)                            | 0.016                                 |
DISCUSSION

The obtained results regarding higher blood levels of SP-A and SP-D surfactant proteins in the group of healthy smokers in comparison with the subgroup of non-smoking patients comply with the results obtained by Sorensen G.L. et al. (2006), Mazur W. et al. (2011), Behera D. et al. (2005), Helen Ilumets et al. (2011), Moazed F. et al. (2016), and Nida, Lone (2018) [12–17]. Non-smokers usually demonstrate inflammatory changes and structural abnormalities in respiratory ways and parenchyma caused by cigarette smoke and leading to passage of SP-A and SP-D surfactant proteins into blood [18]. This is associated with loss of blood–air barrier integrity against the background of smoking, which is responsible for the leak of the secreted pulmonary proteins into the blood channels through the vessels [19]. It has been demonstrated in experiments that the gradient of SP-A and SP-D concentration makes it possible for proteins synthesized in the respiratory tract to leak into the blood flow against the background of exposure to cigarette smoke [16, 20, 21]. In certain circumstances, including acute exposure to cigarette smoke, the level of surfactant proteins may decrease in the bronchoalveolar lavage fluid while simultaneously increasing in the blood serum. The smoking status is a strong predictor of such translocation [16, 22–24].

In our study, a strong association between SP-D and SABP in the subgroup of non-smoking patients is worth noting. In the literature available to us, there was no reference to the association between surfactant proteins SP-A and SP-D and systolic or diastolic arterial blood pressure. It is known that hypertensive angiopathy essentially involves vascular remodeling: a complex structural and spatial modification of small arteries, including lung tissues [25–27]. Wall remodeling is a multi-layer interaction including hypertrophy, hyperplasia, apoptosis, hyalinosis, and fibrinoid necrosis of smooth muscle cells as well as deposition of extracellular matrix [28, 29]. An important role of SP-A and SP-D proteins in apoptosis regulation, further digestion of cell debris by phagocytes and subsequent remodeling of extracellular matrix has been proved in experiments. However, SP-D is a more potent modulator of pulmonary cell apoptosis in comparison with SP-A [30]. Therefore, not only impairment of alveolar-capillary permeability in the lungs is observed against the background of higher arterial blood pressure, but also active participation of SP-D in vessel wall remodeling, which may affect downregulation of this protein in blood.

In our study, the inverse correlation of SP-D blood level and age was shown, while there was no correlation between obesity and SP-D or SP-A. Research in this field is rare and inconsistent. Thus, according to the study by Sorensen G.L. et al. (2006), age and obesity were outlined as important determinants of constitutional SP-D circulation levels [12]. This is explained by the experimentally demonstrated association between the alveolar SP-D level elevation and increased oxidative damage to lung tissue [31]. Studies by Betsuyaku T. et al. (2014) and Zhao X.M. et al. (2007) devoted to the alveolar SP-D level in humans showed no significant change in it with age [32, 33]. These findings comply with the data by Moliva J.I. (2014) revealing that no alveolar SP-D induction was observed with increasing age alongside with cytokine and oxidant induction [34].

Thus, a positive correlation between higher indices of SP-A and SP-D surfactant proteins in the group of smokers was pathogenetically substantiated. The SP-D protein is more important than the SP-A protein for remodeling of the vessel wall and lung tissue matrix as well as oxidative damage to lung tissue and apoptosis, which explains its inverse correlation with age and systolic arterial blood pressure.

CONCLUSION

The levels of SP-A and SP-D surfactant protein in smoking patients without bronchopulmonary diseases were significantly higher in comparison with non-smoking patients. The SP-A protein level has inverse correlation with the age and systolic arterial blood pressure of the patient.

Further research is required in order to determine whether SP-A and SP-D could be used as markers for early identification of smokers exposed to the risk of COPD.

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Kharlamova O.S. – collection and processing of the materials, statistical processing, analysis and interpretation of data, drafting of the manuscript. Nikolaev K.Yu., Voevoda M.I. – conception and design, analysis and interpretation of data, editing of the manuscript. Ragino Yu.I. – conception and design, collection of data for analysis, analysis and interpretation of data, editing.

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