

E-cigarette Smoking (Vaping) and Markers of Vascular Wall Damage in Young Subjects without Cardiovascular Disease

Podzolkov V.I.¹, Bragina A.E.^{1*}, Druzhinina N.A.¹, Mohammadi L.N.²

¹I.M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

²University of California, San Francisco, San Francisco, California, USA

Aim: to investigate the effect of nicotine-containing vapes in comparison with traditional tobacco smoking on markers of vascular wall damage: high sensitivity C-reactive protein (hsCRP), albuminuria (AU), and ankle-brachial index (ABI).

Material and Methods: We examined 369 young subjects without cardiovascular diseases (age median 21 [20;21] years) (159 men and 210 women). The hsCRP levels in the serum were assessed by immunochromatographic express method. AU was investigated in daily urine by a quantitative reflex photometry. ABI was determined by plethysmography.

Results: All subjects were divided into groups: non-smokers (n=196, 53.1%), smokers of traditional cigarettes (n=83, 22.5%) and smokers of nicotine-containing vapes (n=90, 24.4%). The groups did not differ in main anthropometric data. Median hsCRP levels in smokers (14.30 [11; 16.5] mg/l in tobacco-smokers and 13.15 [9.65; 17.5] mg/l in vapers) were significantly higher vs nonsmokers (3.0 [2; 5.6] mg/l). In tobacco-smokers (33.0 [21.5; 60] mg) and vape smokers (45.0 [20; 115] mg), the median AU was statistically significantly higher than in non-smokers (12.0 [10; 20] mg). ABI levels were significantly lower in the groups of tobacco smokers (0.98 [0.91; 0.99]) and vapers (0.85 [0.79; 0.93]) when compared with nonsmokers (1.125 [1.01; 1.18]), and the median ABI in vapers was lower than in tobacco smokers ($p<0.001$). In the group of tobacco smokers, the hsCRP level correlated with the smoker's index ($r_s=0.31$, $p<0.05$), and AU ($r_s=0.54$, $p<0.05$) and ABI ($r_s=-0.28$, $p<0.05$) with a daily inhaled nicotine dose. In the group of vapers, CRP was associated with smoking experience ($r_s=0.338$, $p<0.05$), AU with a daily inhaled nicotine dose ($r_s=0.79$, $p<0.05$), and ABI with BMI ($r_s=-0.33$, $p<0.05$), heart rate ($r_s=-0.24$, $p<0.05$) and smoking experience ($r_s=-0.235$, $p<0.05$). According to the results of multivariate regression analysis the hsCRP level was related with only the smoking experience ($B=0.91\pm0.19$, $p=0.000005$), AU level with the daily inhaled nicotine dose ($B=1.59\pm0.7$, $p=0.0121$) and smoking experience ($B=3.07\pm1.23$, $p=0.0179$), and ABI level with only smoking experience ($B=-0.09\pm0.004$, $p=0.0419$).

Conclusion: In smokers, both traditional and vapers, the levels of hsCRP, AU are significantly higher, and the ABI is lower than in healthy young non-smokers. The most significant influence on the level of hsCRP is exerted by the experience of tobacco and vape smoking; to the AU level – the experience of tobacco and vaping and the daily inhaled nicotine dose, and by the value of the ABI – the experience of vaping.

Keywords: vaping, tobacco smoking, high sensitivity C-reactive protein, albuminuria, ankle-brachial index

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*Corresponding Author: anna.bragina@mail.ru

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Introduction

Alternative smoking options that appeared at the beginning of the 21st century, namely vapes, are especially popular among young people. Their rapid spread has reached the scale of an epidemic comparable and competing with tobacco smoking [1], from which more than 6 million people die every year in the world [1,2]. According to European studies, every third high school graduate smoked nicotine-containing vapes, not attaching particular importance to the harm of smoking [1]. Modern vapes are more and more different from classic cigarettes in fashionable design and versatility, which attracts not only young people, but also people of the middle and older age group [1]. Many consider vaping less harmful than cigarettes, despite the subject activating the device by heating and inhaling the same nicotine in combination with acrolein, formaldehyde, benzaldehyde, acenaphthylene, carbon monoxide, particulate matter and flavorings [1,3]. If the negative effects of nicotine, tar and carbon monoxide contained in cigarettes are well studied, proven in numerous studies and known to the general population [1,2,4], then the effect of smoking vape and its components on the body is still being studied. The negative effect of tobacco smoke, containing more than 100,000 free radicals and toxins, activating oxidative stress [3,4] and damaging endothelial cells and receptor systems of the bronchi and vascular endothelium, has been proven. This leads to the development of systemic inflammation [5], a decrease in the antiatherogenic fraction of high density lipoproteins, the formation of endothelial dysfunction and microvascular lesions [4-6], an increase in heart rate, the formation of blood clots and the development of cardiovascular complications [5]. Increasingly, reports on the negative effects of vaping smoking appear despite the widespread opinion among the population about the «safety» of vaping [1,7], but the long-term consequences of vaping smoking are not yet possible to assess. The study of the negative effects of vaping smoking is rather difficult, since many smokers combine different smoking options. Thus, the lack of certainty regarding the negative effect of vaping in relation to cardiovascular damage [6,8] was the reason for this study.

The aim of our study was to study the effect of an alternative smoking option, namely nicotine-containing vapes, on markers of vascular wall damage in comparison with traditional tobacco smoking: highly sensitive C-reactive protein (hsCRP), albuminuria (AU), and ankle-brachial index (ABI).

Materials and methods

369 young subjects (159 men and 210 women) were included in the study.

The study was conducted in accordance with the Declaration of Helsinki on Human Rights. All individuals included in the study signed a voluntary informed consent. Criteria for inclusion in the main group: age from 18 to 35 years, never smokers and chronic smokers of traditional cigarettes or nicotine-containing vapes for a period of > 12 months.

Exclusion criteria: pregnancy, clinical manifestations of any acute or chronic disease, cardiovascular diseases (CVD), type 1 and 2 diabetes mellitus, inflammatory diseases of any location, chronic kidney and/or urinary tract diseases, taking medications that affect albumin levels in the urine.

A questionnaire was conducted to assess the smoking status, which took into account data on smoking: type of smoking (cigarettes or vaping) indicating the nicotine content in 1 cigarette and a milliliter of liquid for vaping, smoking experience, smoking intensity (number of cigarettes or times vaping smoked, duration of vaping smoking), on the basis of which the average dose of inhaled nicotine per day in smokers of traditional cigarettes and vapes was assessed.

The assessment of the hsCRP level was carried out in the blood serum of the subjects on an empty stomach using the immunochromatographic express method using the Becman apparatus (USA). Albuminuria was studied in daily urine by quantitative reflex photometry using an Erba Lachema apparatus (Croatia).

The state of the vascular wall was assessed by determining the ankle-brachial index by plethysmography on the MESI ABPI MD apparatus (2019, Slovenia) according to the standard technique.

Statistical analysis

When statistically processing data using the Statistica 10.0 program (StatSoft Inc., USA) arithmetic mean (M) and standard deviation (σ) were calculated for variables with normal distribution; median, 25th and 75th percentiles – Me [25%, 75%] for variables with abnormal distribution. The statistical significance of the differences in mean values was assessed using: Student's t-test (p [t]) (with normal distribution) and Mann-Whitney's test (p [U]) – for variables with abnormal distribution. Comparison of frequency indicators for assessing statistical significance was carried out using the Pearson's χ^2 test. The identification and assessment of relationships between the studied indicators was carried out using the Pearson's correlation coefficient (r – with a nor-

mal distribution of the trait) and the Spearman's rank correlation coefficient (ρ – with an abnormal distribution of the trait). The assessment of the degree of influence on the investigated effective indicator of each of the factors introduced into the model with other factors fixed at the average level was carried out using multivariate regression analysis.

Results

All subjects included in the study were divided into non-smokers ($n=196$, 53.1%) and smokers ($n=173$, 46.9%). Smokers were divided into groups of people who smoke traditional cigarettes ($n=83$, 22.5%; further is tobacco smoking) or nicotine-containing vapes ($n=90$, 24.4%; further is vape smoking). The clinical characteristics of the examined groups are presented in Table 1.

The formed groups were comparable in terms of age, body mass index (BMI) and obesity frequency (Table 1). Men were in the groups of tobacco smokers and vape smokers more often than in the group of non-smokers ($p<0.05$). There were no significant gender differences between groups of smokers. Higher levels of systolic blood pressure and heart rate were observed in the group of tobacco smokers ($p=0.0022$) and vape smokers ($p=0.0002$). But heart rate was higher in the group of tobacco smokers than in the group of vape smokers ($p=0.0078$).

The smoking experience median in the group of tobacco smokers was 4 [2.5;6] years, and in the group of vape smokers – 4 [2;6] years ($p>0.05$). Evaluation of the smoker index in the group of vape smokers was not possible due to the lack of such calculated indices. In the group of tobacco smokers, it

was 2 [0.75;3.5] packs/years. According to the questionnaire, also the characteristics of cigarettes and nicotine-containing liquids of vapes, the median of the average daily inhaled dose of nicotine in the group of tobacco smokers were calculated – 3.05 [0.5;6.8] mg, and in the group of vape smokers – 3.4 [1.5;8.45] mg, which didn't differ statistically significantly ($p>0.05$).

The results of the study of hsCRP, AU, and ABI in the examined groups are presented in Table 2 and in Figure 1. The hsCRP and AU levels were statistically significantly higher in the groups of tobacco smokers and vape smokers, and the ABI level was statistically significantly lower than in the group of non-smokers (Table 2).

Evaluation of intergroup differences in hsCRP levels showed that no significant differences were observed between tobacco smokers and vape smokers, despite statistically significantly higher values in the groups of smokers compared with non-smokers (Fig. 1).

AU levels were statistically significantly higher in the groups of tobacco smokers and vape smokers median than in the group of non-smokers. The highest AU values were found in the group of vape smokers (Fig. 1).

In the groups of tobacco smokers and vape smokers, there were more patients with ankle-brachial index <0.9 when compared with the group of non-smokers (20.5%, 64.4% and 10.7%, respectively, $\chi^2=72.89$, $p<0.001$ when compared with vape smokers), and the medians of the ankle-brachial index in vape smokers were statistically significantly lower than in tobacco smokers (Fig. 1).

Table 1. Clinical characteristics of the examined groups

Parameter	Non-smokers (n=196)	Tobacco smoking (n=83)	Vape smoking (n=90)
Age, years	21.0 [20;21]	21.0 [20;22]	21.0 [20;21]
Men, n (%)	73 (37.2)	55 (66.3)*	39 (43.3)*
SBP, mm Hg	110 [110;120]	120 [110;120]*	121 [110;126]*
DBP, mm Hg	75 [70; 79]	75 [70;80]	75 [70;80]
Heart rate, per minute	75 [69;80]	88 [73; 95]*	79 [70;88]*†
BMI, kg/m ²	21.0 [19.7;23.4]	23.3 [20.6;26.2]	23.6 [21;29]
Overweight (25 kg/m ² <BMI<29.9 kg/m ²), n (%)	18 (9.2)	9 (10.8)	12 (13.3)
Obesity (BMI>30kg/m ²), %	9 (4.6)	3 (3.6)	5 (5.6)
Smoking experience, years	-	4 [2.5;6]	4 [2;6]
Inhaled nicotine dose, mg/day	-	2.05 [0.55;6.6]	3.3 [1.5;8.4]

Data are presented as Me [25%; 75%], unless otherwise indicated.

* $p<0.05$ compared with non-smokers, † $p<0.05$ compared with tobacco smokers

hsCRP – high sensitivity C-reactive protein, AU – albuminuria, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure.

Table 2. Results of the study of hsCRP, AU and ankle-brachial index in the examined groups

Parameter	Non-smokers (n=196)	Tobacco smoking (n=83)	Vape smoking (n=90)
hsCRP, mg/l	3.0 [2;5.6]	14.3 [11;16.5]***	13.2 [9.7;17.5]***
AU, mg/l	12.0 [10;20]	33.0 [21.5;60]***	45.0 [20;115]***†††
Ankle-brachial index	1.13 [1.01;1.18]	0.98 [0.91;0.99]***	0.86 [0.79;0.93]***†††

Data are presented as Me [25%; 75%]
 ***p<0.001 compared with non-smokers, †††p<0.001 compared with non-smokers.
 hsCRP – high sensitivity C-reactive protein, AU – albuminuria.

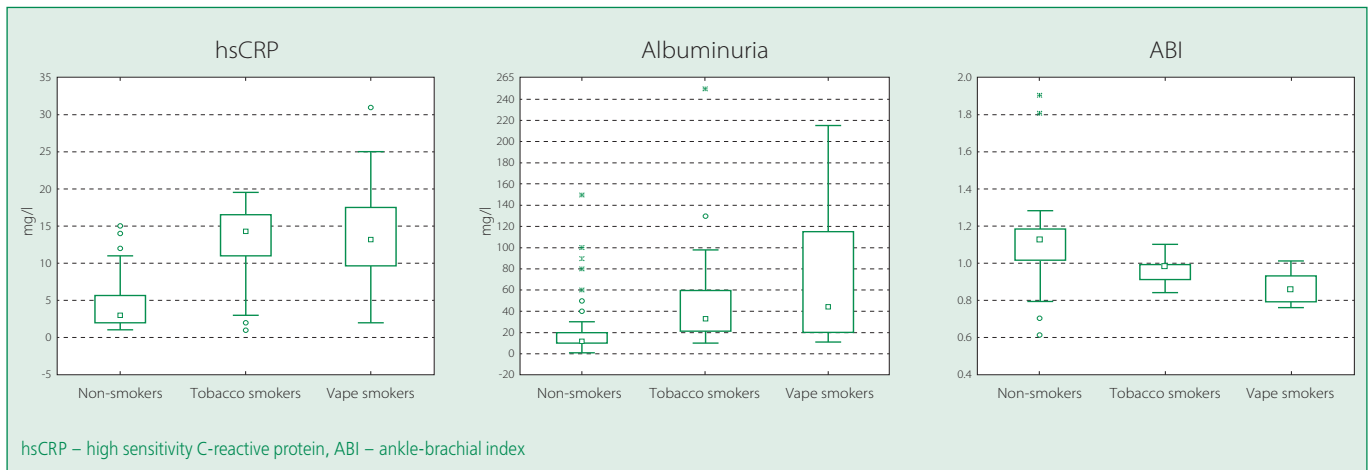


Figure 1. Medians of hsCRP, albuminuria and ABI in the study groups

The results of correlation analysis to assess the relationship of the studied parameters (CRP, AU and ankle-brachial index) by gender, age, SBP, diastolic blood pressure (DBP), BMI and smoking characteristics (experience, smoker index, daily dose of inhaled nicotine) are presented in Table 3. In the non-smoking group, statistically significant correlations between hsCRP, AU and ankle-brachial index with the main anthropometric indicators, blood pressure, heart rate and BMI levels were not obtained. Statistically significant correlations of BMI with SBP ($r_s=0.25$, $p<0.05$) and with DBP ($r_s=0.2$, $p<0.05$) were found, also gender correlation with SBP ($r_s=0.36$, $p<0.05$), DBP ($r_s=0.3$, $p<0.05$) and heart rate ($r_s=-0.2$, $p<0.05$). In the group of tobacco smokers, statistically significant correlations were found between the hsCRP level and the smoker's index, AU correlations and ankle-brachial index with the daily dose of inhaled nicotine. In the group of vape smokers, statistically significant correlations of hsCRP level with smoking experience, AU correlations with the daily dose of inhaled nicotine, as well as correlations of the ankle-brachial index with BMI, heart rate and smoking experience were found (Table 3).

Multiple linear regression analysis to assess the statistical significance of the effect was carried out

taking into account the existing differences in the relationships between risk factors (blood pressure, heart rate, body mass index, smoking and its characteristics) with the parameters under study.

During the construction of the model, all potential risk factors were included in the analysis: smoking and its characteristics (smoking experience, smoking index, average dose of inhaled nicotine), SBP level, DBP level, heart rate, age, gender, body mass index. Statistical processing of the obtained results showed that within the framework of this statistical model, only the smoking experience tobacco and the smoking experience vapes influenced the hsCRP level (Table 4). The average daily dose of inhaled nicotine (in the general group of smokers, tobacco smokers and vape smokers) and smoking experience (in the general group of smokers and the group of tobacco smokers) had a significant effect on the AU concentration, and the effect of the average daily dose of inhaled nicotine was significantly greater in the group of vape smokers (12.26 ± 1.6 ; $p=0.000001$) than in the group of tobacco smokers (1.65 ± 0.63 ; $p=0.0124$). The value of the ankle-brachial index in the general group of smokers was statistically significantly influenced only by the smoking experience (both tobacco and vaping). This relationship was also observed in the group of vape smokers (-0.02 ± 0.01 ;

Table 3. Results of correlation analysis in the examined groups

Parameter	hsCRP, r_s , p			AU, r_s , p			ABI, r_s , p		
	Non-smokers	Tobacco	Vape	Non-smokers	Tobacco	Vape	Non-smokers	Tobacco	Vape
Age	0.18; >0.05	0.07; >0.05	0.12; >0.05	0.11; >0.05	0.09; >0.05	0.07; >0.05	0.01; >0.05	-0.2; >0.05	-0.04; >0.05
Gender	0.08; >0.05	0.2; >0.05	0.03; >0.05	-0.123; >0.05	0.01; >0.05	0.04; >0.05	0.04; >0.05	0.05; >0.05	0.16; >0.05
BMI	0.04; >0.05	0.06; >0.05	-0.02; >0.05	-0.009; >0.05	0.18; >0.05	0.14; >0.05	0.03; >0.05	-0.02; >0.05	-0.33; <0.05
SBP	-0.03; >0.05	0.08; >0.05	-0.14; >0.05	0.02; >0.05	0.03; >0.05	0.03; >0.05	0.05; >0.05	-0.3; >0.05	-0.16; >0.05
DBP	-0.24; >0.05	0.2; >0.05	-0.15; >0.05	0.01; >0.05	0.05; >0.05	0.18; >0.05	0.06; >0.05	-0.07; >0.05	-0.19; >0.05
Heart rate	-0.00; >0.05	0.34; >0.05	0.16; >0.05	0.09; >0.05	0.01; >0.05	0.2; >0.05	-0.004; >0.05	-0.98; >0.05	-0.24; <0.05
Smoking experience	–	0.04; >0.05	0.338; <0.05	–	0.13; >0.05	0.23; >0.05	–	-0.11; >0.05	-0.235; >0.05
Dose of inhaled nicotine per day -0.125; >0.05		–	0.12; >0.05	0.15; >0.05	–	0.54; <0.05	0.79; <0.05	–	-0.28; <0.05
Smoker index	–	0.31; <0.05	–	–	0.19; >0.05	–	–	-0.14; >0.05	–

hsCRP – high sensitivity C-reactive protein, AU – albuminuria, ABI – ankle-brachial index, BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure.

Table 4. Results of multivariate linear regression analysis in the general group of smokers

Parameter	hsCRP	AU	ABI
	B±SE, p	B±SE, p	B±SE, p
Average daily dose of inhaled nicotine	>0.05	1.59±0.7, 0.0121	>0.05
Smoking experience	0.91±0.19, 0.000005	3.07±1.23, 0.0179	-0.09±0.004, 0.0419

hsCRP – highly sensitive C-reactive protein, AU – albuminuria, ABI – ankle-brachial index, B – regression coefficient, SE – standard error.

$p=0.002$), while in the group of tobacco smokers, only the average daily dose of inhaled nicotine influenced the ankle-brachial index (-0.04 ± 0.002 ; $p=0.0312$).

Discussion

The key link in the implementation of the negative effect of most of the known cardiovascular risk factors, including smoking, is the development of endothelial dysfunction (ED) [6,7]. A wide range of laboratory and instrumental methods for assessing endothelial dysfunction exists [6]. Our study assessed the hsCRP levels as a marker of systemic inflammation, AU, and ankle-brachial index, which are not only markers of ED and microvascular damage, but also predictors of cardiovascular disease.

The groups of smokers and non-smokers didn't statistically significantly differ in age and BMI in accordance with the design and preliminary selection of study participants, which excluded the contribution of these factors to the results obtained. The smoking groups were statistically significantly more likely to include men, which is consistent with population observations. Nevertheless, the results of multivariate analysis didn't reveal in any of the groups a

statistically significant effect of gender on the parameters assessed (CRP, AU, ankle-brachial index).

Important components of the formation of endothelial dysfunction (the initial stage of any cardiovascular disease) are peroxidation reactions, oxidative stress, activation of proinflammatory monocytes, which promote inflammation of the vascular wall and the development of microvascular lesions [9,10]. Kondo T. et al. found that endothelial dysfunction in smokers is manifested by impaired endothelium-dependent vasodilation and regenerative endothelial function with a decrease in the number and deterioration of mobilization of endothelial progenitor cells [4]. One of the well-studied markers of inflammation is hsCRP. According to our study, the hsCRP medians were statistically significantly higher in the groups of tobacco smokers and vape smokers compared with non-smokers. Statistically significant correlations of hsCRP with the smoker index in the group of tobacco smokers and smoking experience in the group of vape smokers were found during the correlation analysis. Our results of higher hsCRP levels against the background of tobacco smoking and vaping are consistent with the data of R. Carnevale et al., which showed an increase in markers of oxidative stress after smoking both traditional cigarettes and vaping [8]. In this study, slightly higher levels of markers of oxidative stress compared to vaping were found after smoking a cigarette. In our study, the hsCRP levels in the group of tobacco smokers and vape smokers didn't differ statistically significantly. These changes in vape smokers can be explained by the content of heavy metals, aldehyde and other components in the aerosol, which also have a significant oxidative potential [8]. The results of multivariate analysis in our study confirmed the significance of the effect of

smoking, namely, the smoking experience cigarettes and vapes, on the level of hsCRP.

Currently, AU is considered not only as an indicator of preclinical renal damage, but also as an early integral marker of ED and microvascular damage. Against the background of tobacco smoking, the level of proinflammatory cytokines increases, and the endothelial layer and basement membrane of the kidneys are damaged, which is manifested by an increase in the level of albumin in daily urine [4,11]. Our present and previous studies revealed statistically significantly higher AU median in tobacco smokers and vape smokers, when compared with non-smokers, and the AU levels in vape smokers were significantly higher than in tobacco smokers [12]. These results are consistent with some foreign studies, which also demonstrated high AU values in traditional smokers and vape smokers [13,14]. According to the results of the correlation analysis, in the group of smokers, AU was statistically significantly interrelated with the average daily concentration of inhaled nicotine, and it was more pronounced in the group of vape smokers. Multivariate analysis indicates a relationship between the smoking experience and the average daily dose of inhaled nicotine with the studied indicators. The dose of inhaled nicotine and smoking experience are the most important factors influencing the overall risk associated with smoking. A non-linear dose-effect relationship has been described for cigarette smoking, in which smoking just one cigarette per day corresponds to half the risk of coronary heart disease arising from smoking 20 cigarettes [15]. Smoking experience is also very important in assessing the risk of developing chronic diseases, including coronary heart disease and mortality from smoking. There is an opinion that smoking cessation within one year reduces the risk of coronary heart disease by 2 times, and the equalization of the risk of coronary heart disease with a comparable nonsmoking population occurs only after 5-15 years of smoking cessation [4,15].

In the group of tobacco smokers and vape smokers, the SBP and heart rate levels were statistically significantly higher than those of non-smokers. These results are consistent with numerous studies of the effect of smoking on blood pressure. Smoking even 1 cigarette leads to the activation of the sympathetic nervous system and, as a consequence, to an increase in blood pressure and heart rate [4]. Nevertheless, the blood pressure levels medians in smokers in our study didn't exceed the upper limit of the norm, which is most likely due to young age, short duration of smoking, and the absence of other risk factors other than smoking. An increase in blood pressure

and heart rate against the background of vaping smoking has also been demonstrated in several studies and is also explained by the activation of the sympathoadrenal system [16,17]. In addition, R.S. Mohemani et al. demonstrated an increase in heart rate variability against the background of vape smoking [18]. An increase in heart rate variability was observed in users of nicotine-containing and nicotine-free vapes [17].

The negative effects of smoking on the vascular wall, endothelial condition, and the development of atherosclerosis are well known. The most common integral marker of the functional state of the vascular wall is endothelium-dependent vasodilation, which, according to some studies, is significantly reduced against the background of traditional smoking [6] and vaping smoking [8,16,19-23]. Antoniewicz L. et al. demonstrated a significant increase in progenitor endothelial cells in response to smoking both cigarettes and nicotine-containing vapes, which reflects the degree of damage to the vascular endothelium against the background of various smoking options [19]. It has been shown that cigarette smoking increases the stiffness of the arterial wall, which persists for several years after smoking cessation [4]. Vlachopoulos C. et al. registered in their study an increase in the speed of the pulse wave, which reflects the increase in vascular stiffness equally when smoking cigarettes and nicotine-containing vapes [20]. In our study, we assessed the ankle-brachial index and obtained the lowest values of this marker of increased vascular stiffness in the group of vape smokers and tobacco smokers when compared with non-smokers. At the same time, the ankle-brachial index was significantly lower in the group of vape smokers than in the smoking patients. Multivariate analysis showed the significance of the effect on the ankle-brachial index only in the vaping experience in the general group of smokers and in the group of vape-smokers, while in the group of tobacco smokers only the average daily dose of inhaled nicotine influenced the level of the ankle-brachial index.

Conclusion

Our data indicate statistically significantly higher hsCRP and AU levels along with statistically significantly lower levels of the ankle-brachial index in chronic young smokers of traditional cigarettes and nicotine-containing vapes. At the same time, the AU level is higher in vape smokers, and the ankle-brachial index is lower than in cigarette smokers. The studied indicators depend on the smoking experience and the average daily concentration of inhaled nicotine, which should be taken into account when conducting

educational programs among young people who smoke. Thus, our results allow us to confidently assert that nicotine-containing vapes are not only comparable to traditional tobacco smoking in terms of the level of harm to the vascular wall, but they can also pose a great threat to the progression of vascular stiffness in healthy young people.

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About the Authors

Valery I. Podzolkov

eLibrary SPIN 8683-2155, ORCID 0000-0002-0758-5609

Anna E. Bragina

eLibrary SPIN 3753-5539, ORCID - 0000-0002-2699-1610

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Natalia A. Druzhinina

eLibrary SPIN 6842-0447, ORCID 0000-0001-8397-0210

Leila Mohammadi

ORCID 0000-0001-9586-1468