Research Article

Relation between Tobacco Smoking/ Electronic Smoking and Albuminuria/ Vascular Stiffness in Young People without Cardiovascular Diseases

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Keywords

Smoking · Vaping · E-smoking · Albuminuria · Arterial stiffness

Abstract

Introduction/Objective: Tobacco smoking is a well-known risk factor for cardiovascular and renal diseases. In recent years, alternative types of smoking, including vaping, have been becoming popular. The contribution of vape to vascular and renal injury is not known. We studied the relation between smoking of traditional/electronic cigarettes and arterial stiffness and albuminuria, which is also a vascular dysfunction marker. **Methods:** We examined 270 young volunteers without significant clinical cardiovascular diseases (mean age: 21.2 ± 2.3 years). Twenty-seven percent of the subjects in the study group were smokers; 69.9% of them smoked traditional cigarettes and 30.1% smoked electronic cigarettes. The urine albumin level was assessed by a dipstick test, and the augmentation index was determined by photoplethysmography. A linear correlation test and multiple regression analysis were applied. **Results:** The study groups did not differ in basic characteristics. The smokers demonstrated generally higher blood pressure levels and were overweight. Most of the smokers were male. In the groups of smokers, albuminuria was more frequent, especially among vapers (94 vs. 79% in tobacco smokers and 29% in nonsmokers). AU values (median [quartile 25; quartile 75]) were significantly higher in vapers (160 mg/L [150; 207.5]) vs. tobacco smokers (115 mg/L [60; 200]) and vs. nonsmokers (20 mg/L [10; 50]) ($p < 0.05$). Photoplethysmographic results showed relevant higher augmentation indices among tobacco smokers (-4 , $[-6.6; -1.9]$) and vapers (-5.05 $[-13.4; -3.3]$) compared to nonsmokers (-16.2 $[-23.9; -7]$) ($p < 0.05$). Results of multiple regres-

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sion analysis demonstrate that smoking of both traditional and electronic cigarettes is related to an increase in the albuminuria level and the augmentation index. **Conclusions:** Smoking of both traditional and electronic cigarettes is related to albuminuria and an increase in the augmentation index, which is a noninvasive marker for arterial stiffness.

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Introduction

For decades, tobacco smoking along with arterial hypertension, obesity, excessive salt intake, and alcohol consumption have been the main risk factors for cardiovascular diseases (CVD) and related complications influencing the mean life duration of the population worldwide [1]. In spite of widespread antismoking campaigns, there are alternative smoking options [2], such as water pipes and electronic cigarettes (e-cigarettes); they are positioned as harmless and their popularity is rising, especially among youths. First, e-cigarettes entered the market in 2003–2004 and became so widespread that the word vape (literally an electronic cigarette) was the most frequent search request on the Internet in 2014 [2, 3].

In the past 10 years, owing to the efforts of public health authorities, there has been a decreasing trend in the spread of traditional tobacco smoking in the majority of countries. However, at the same time, e-cigarettes have been becoming more popular. The Global Adult Tobacco Survey that took place in 2016 showed that 91.2% of Russians aged 15–24 years were aware of e-cigarettes and 9.7% used them regularly [4]. The operating principle of e-cigarettes (electronic cigarette or vape) is based on the production of aerosol by heating of the solution, which the vaper inhales [2, 5]. The solution, apart from nicotine in e-cigarettes, is composed of propylene glycol and/or glycerol, glycerin, nitrosamine, ethanol, and propylene oxide (present even in nicotine-free e-cigarettes). The heating of these substances produces more than 30 chemical agents, many of which are potentially irritants and/or cancerogenic (glycidol, acrolein, aldehydes, etc.) [5]. An outbreak of acute lipoid pneumonia, including fatal cases, associated with e-smoking has been registered in the USA [6]. This condition is named e-cigarette, or vaping, product use-associated lung injury (EVALI).

The associations between traditional tobacco smoking and CVD development and their early symptoms – microcirculation disorders [7], endothelial dysfunction [8], deterioration of renal blood flow – have been studied thoroughly [9]. It is a result of the impact of both active and passive smoking on the functional status of the vascular endothelium, endothelium-dependent vasodilation, activation of a series of oxidative stress reactions [9], and antioxidant system suppression [9]. One of the clinical signs of microcirculation disorders among smokers from various age groups [10] is a reliably higher level of albuminuria (AU), an early predictor of microvascular injuries and endothelial dysfunction associated with a high risk of CVD and their complications [9–11].

As shown in a number of studies [7, 9], the nephrotoxic effects of tobacco smoking are mediated by generalized vasoconstriction and, as a consequence, by a decrease in renal blood flow. Tobacco smoking is a key factor for the increase in prevalence and the progression of both diabetic and nondiabetic nephropathy [9]. Moreover, AU onset and progression in arterial hypertension patients associated with tobacco smoking has been proven [9].

Thus, the relevant objective is to study the relationship between not only classical but also alternative tobacco smoking options such as vaping, along with early markers of microcirculation disorders such as AU and an increase in the augmentation index (Aip).

The objective of our study is assessment of AU levels and arterial stiffness, detected by the level of Aip, in young people without clinically significant CVD who practice classical or alternative smoking – vaping.

Table 1. Clinical profile of the study groups

	Smokers (n = 73)		Nonsmokers (n = 197)
	tobacco smoking (n = 51)	vaping (n = 22)	
Age, years	21.3±2.5	21.4±2.2	21.1±2.3
Male/female ratio (%)	61/39*	55/45*	27/73
Systolic BP, mm Hg	120.0±13.8	120.9±17.4	115.0±14.7
Diastolic BP, mm Hg	74.7±8.4	73.0±6.1	71.6±7.3
BP level			
Optimal (≤120/80 mm Hg)	75	65	84
Normal (121/81–130/85 mm Hg)	6	8	4
High normal (131/86–139/89 mm Hg)	4	12	3
Arterial hypertension (≥140/90 mm Hg), %	15	15	9
BMI	23.02±3.1	23.3±4.7	22.5±8.5
Overweight (25 < BMI <29.9), %	25.5*	20.0*	9.1
Obesity, %	3.4	5.0	3.5
AU, mg/L	115 (60; 200)*	160 (150; 207.5)*,§	20 (10; 50)
Alp, %	−4 (−6.6; −1.9)*	−5.05 (−13.4; −3.3)*	−16.2 (−23.9; −7)

Values are presented as means ± SD, medians (quartile 25; quartile 75), or numbers unless otherwise stated. * $p < 0.05$ vs. nonsmokers. § $p < 0.05$ tobacco smokers vs. vapers.

Materials and Methods

Our study enrolled 270 students from a medical university (96 males and 174 females) (mean age 21.2 ± 2.3 years) (Table 1). The inclusion criterion for the main group was an age of 18–35 years.

The exclusion criteria were clinical signs of any acute or chronic disease, systemic anti-hypertensive therapy, clinical signs of atherosclerosis (including coronary heart disease), cerebrovascular disease, diabetes mellitus type 1 or 2, inflammatory diseases of any localization, chronic renal and urinary tracts diseases, and administration of drugs affecting the urine albumin level.

Methods

We used a self-administered questionnaire to collect such data as age, gender, past medical history, medication history, smoking status (yes/no), type of smoking (cigarettes or vape), smoking duration, and smoking intensity (number of cigarettes per day, their strength, daily dose of e-fluid, and concentration of consumed nicotine). Initially 305 subjects filled out the questionnaire. Among them, 9 rejected to fill out the section about life behaviors, 3 had a history of chronic heart diseases, 9 had a known hypertension history, 2 were diabetic, 6 had chronic urinary tract infection, and 6 had chronic gynecology diseases. Those 35 subjects were not enrolled into this study and were not included in the final analysis.

Trained staff measured height, weight, pulse rate, and blood pressure (BP) according to the standard methodology. The body mass index (BMI) was calculated as weight divided by square of the height (kg/m^2).

To assess vascular wall status, photoplethysmography was conducted (AngioScan Professional 01; AngioScan-Electronics, Russia). The pulse wave and its components – the direct and reflected waves – were registered with further Alp calculation. During the investigation an optical detector was placed on the terminal phalanx of both middle fingers. The assessments were performed in the morning, after a 10-min rest, in a calm, warm room. The subjects

had not smoked or consumed alcohol, vasoactive drugs, or caffeine-containing drinks within the last 24 h. Measurements were taken with the subject seated with comfortable arm support at about heart level, with no tight clothing constricting the arm. The AIp was calculated as the difference between the first and second systolic peaks of the pulse wave via computer pulse wave analyses.

The urine albuminuria level was assessed in the morning urine portion using a semiquantitative dipstick test (Microalbu Phan; Erba Lachema, Croatia) according to the standard technic recommended by the manufacturer. Participants were required to delay the urine collection if they had a fever, a urinary tract infection, or menstruation. They were also informed to avoid heavy exercise within 24 h preceding urine collection. Participants were requested to keep the urine cold (at 4 °C) before the visit to the clinic but not for more than 2 days. Test strips were placed in the urine for 2 s, with further detection of urine albumin levels by comparison of the test strip color with the color scale on the package. Albuminuria was detected if the urine albumin level was $\geq 30\text{mg/L}$.

Statistical Analysis

Results are given as means $\pm$ SD or medians (quartile 25; quartile 75). One-way ANOVA and Mann-Whitney tests were used to compare numerical data. A χ^2 test was used to compare categorical variables. Spearman's rank correlation and multiple regression analyses were used to evaluate associations between smoking and other parameters, with adjustment for potential confounders. A two-tailed $p < 0.05$ was considered statistically significant. Statistical analyses were performed using Statistica 10.0 software (StatsSoft Inc., USA).

Results

All of the subjects included in this study were divided into the 2 groups: smokers ($n = 73$; 27%) and nonsmokers ($n = 197$; 73%). The smokers were divided into 2 subgroups; the first group included those who smoked traditional cigarettes ($n = 51$; 69.9%) (hereafter, tobacco smoking), and the second group was comprised of e-cigarettes smokers ($n = 22$; 30.1%) (hereafter, vaping). The clinical profile of the study groups is presented in Table 1.

The subgroups did not differ in mean age or BMI. The proportion of males among the smokers was greater (57.5 vs. 42.5% among females; <0.05). Frequency of smoking and other risk factors in the study population were the same as in the general Russian population [4]. The levels of both systolic and diastolic BP and the overweight rate were slightly higher in smokers, but these differences were not statistically significant. Nevertheless, higher BP levels, including arterial hypertension, were significantly more common among smokers ($\chi^2 = 13.263$; $p = 0.010$). Groups of smokers did not differ in the frequency of various BP categories ($\chi^2 = 5.000$; $p = 0.229$). There was no statistically significant difference between tobacco smokers and vapers in terms of their basic anthropometric characteristics ($p > 0.05$; Table 1).

The mean smoking duration in the group of tobacco smokers was 3 years (1.5; 7), and in the group of vapers it was 4 years (2; 6) ($p > 0.05$). It was impossible to assess the smoking index in vapers, while in tobacco smokers it was 0.9 pack-years (0.6; 3.5). The average consumption in the smoking group was 6 cigarettes a day (1.5; 20), and all of the smokers preferred superlight products with an average nicotine content of 0.5 mg per cigarette (0.3; 0.6). Vapers used Advanced Personal Vaporizers (APV) Mods with a tank volume of 1.5–2.0 mL and ultralight e-fluids with an average concentration of nicotine in consumed e-fluid of 1 mg (0.8; 1, 6). The average consumed e-fluid volume per day was 3.6 mL (2.5; 5). The average consumption of nicotine was 3 mg (0.75; 10) in smokers and 3.6 mg (2; 7.5) in vapers ($p > 0.05$).

Fig. 1. Albuminuria level in the study groups. Albuminuria was diagnosed when the urine albumin level was ≥ 30 mg/L.

The results of the AU level analysis in the study groups are presented in Figure 1. Subjects with high AU levels were significantly more frequently registered in both the tobacco smoking and the vaping subgroups (95 vs. 79% in smokers and 29% in nonsmokers).

AU values were significantly higher in vapers (160 mg/L [150; 207.5]) versus tobacco smokers (115 mg/L [60; 200]) and both types of smokers versus nonsmokers (20 mg/L [10; 50]) ($p < 0.05$; Table 1; Fig. 1).

Photoplethysmographic results showed significantly higher levels of AIp among tobacco smokers (-4 [-6.6 ; -1.9]) and vapers (-5.05 [-13.4 ; -3.3]) versus nonsmokers (-16.2 [-23.9 ; -7]) ($p < 0.05$; Fig. 2), which was expected as the marker of arterial stiffness increased.

A positive correlation was found between both tobacco smoking and vaping with AU ($r_s = 0.3$ and $r_s = 0.65$; $p < 0.05$). A similar positive correlation was detected between smoking duration and AU ($r_s = 0.6$; $p < 0.05$). AIp appeared to have a direct correlation with smoking ($r_s = 0.4$; $p < 0.05$), smoking duration ($r_s = 0.57$; $p < 0.05$) in the overall group of smokers (Fig. 2), number of cigarettes smoked daily ($r_s = 0.52$; $p < 0.05$), and tobacco smoking index ($r_s = 0.54$; $p < 0.05$), as well as vaping ($r_s = 0.38$; $p < 0.05$).

There were some differences in sex proportions in the study subgroups, with a predominance of males among smokers and those with a higher BP. Male sex and increased BP are significant risk factors for renal diseases and AU development as well as vascular stiffness. To assess the significance and reliability of the impact of such risk factors as smoking, BP level, age, sex, obesity, and BMI on AU and AIp levels, multiple linear regression analysis was used.

For model generation, the analysis included all potential confounders, i.e., smoking and its characteristics (smoking duration, number of cigarettes smoked, tobacco smoking index, consumed dose of nicotine per day), systolic and diastolic BP, age, sex, obesity, and BMI. Statistical processing of the results showed that only smoking and its characteristics accurately affected the AU level and the AIp, and the relationship correlated to a greater extent with smoking duration, the tobacco smoking index, and vaping for AIp (Table 2).

Fig. 2. Mean AIP among smokers and nonsmokers.

Table 2. Results of the multi-factor linear regression analysis of smoking and its characteristics as factors associated with albuminuria and the augmentation index

Parameter	AU B ± SE	AIP B ± SE
Smoking history	0.45±0.11*	0.46±0.097*
Smoking index	0.38±0.08*	ns
Vaping	ns	0.17±0.086*

Values are presented as B ± SE, standard error (adjusted for systolic and diastolic BP levels, BMI, obesity, age, and sex). * $p < 0.05$.

Discussion

Our results demonstrate changes in vascular stiffness and higher AU levels associated with both traditional tobacco smoking and vaping among young healthy individuals without subclinical or established CVD.

In our study we were focused on the investigation of arterial stiffness, which is supposed to be a universal marker for vascular damage regardless of the etiology. Arterial stiffness is increasingly being recognized as an important cardiovascular risk factor and an independent predictor of all-cause and cardiovascular death. Stiffness may be assessed indirectly by measuring pulse wave velocity, which is the golden standard for this purpose. Nonetheless, pulse wave velocity is characterized by low reproducibility and operator independency [12]. Pulse wave velocity has also been in a number of investigations in old smokers [13] and smoking adolescents [14]. Another indirect measure of arterial elasticity is pressure amplification, which is measured by AIP and was evaluated in our study during photoplethysmog-

raphy. This method allows detection of the pulse wave along with its components – the direct and reflected waves. The Alp is calculated as the difference between the first and second systolic peaks of the pulse wave and serves as the main parameter for quantification during pulse wave analyses. There are data showing that the arterial waveform, the size of the second, reflected wave, depends on the stiffness of the large arteries and the degree of endothelial dysfunction [15]. Therefore, Alp characterizes and quantifies the contribution of the reflected wave pressure to the central arterial pressure and an increase in the myocardial afterload. The normal value for the Alp in young apparently healthy people with preserved vascular elasticity is below zero. With increasing arterial stiffness, the reflected waves will reach the heart earlier, in the phase of cardiac systole. Thus, the Alp will have a near-zero value, reflecting equalization the pressures of the direct and reflected pulse waves. A further increase in arterial stiffness with a substantial elevation of the reflected wave velocity, which exceeds the maximum pressure of the direct wave, was accompanied by positive Alp values. Our results demonstrate significantly higher Alp levels in both smokers and vapers versus the nonsmoking group, which indicates subclinical vascular damage detected by a higher arterial stiffness in apparently healthy smokers and vapers. These data correspond to a number of papers dealing with traditional smoking [7, 9, 16, 17]. For instance, in his study Rose et al. [7] studied microcirculation disorders in healthy tobacco smokers, manifesting by significant deterioration of retinal blood flow and arteriolar spasm [7]. Other authors detected increases in stiffness, vessel wall inflammation, and free radicals levels and changes in pulse wave velocity, one of the CVD predictors among “healthy” smokers [9, 16]. Similar results were obtained in the study by Mahmud and Feely [18] in the group of young healthy smokers, where the Alp was measured by applanation tonometry. An increase in arterial stiffness was found in chronic smokers versus nonsmokers [18]. Another more cross-sectional population-based study (Circulatory Risk in Communities Study) from Japan evaluated the Alp by automated tonometry and revealed an increase in radial Alp in cigarette smokers [19]. However, we acknowledge that these results were obtained in cigarette smokers but not in vapers, in whom the vascular effects of e-smoking are still poorly understood.

According to the literature, pathological effects from vaping are associated with acute direct thermal and chemical irritation by vapors containing formaldehyde and products of its degradation [3] of the mucosa membrane of upper airways leading to mucosal inflammation, burns, and even scarring, strictures, and fistulas [3, 5]. There are data supporting a potential role of vitamin E acetate in EVALI [20]. The association of vaping with the development of chronic noninfectious diseases including CVD has been described in occasional studies mainly with small sample sizes [5, 11, 21]. According to the available data, chronic pathologic effects from vaping are related to the sympathomimetic effects of nicotine and other poorly studied chemical agents contained in vapor [22]. Data show that combustion results in the formation of acrolein, formaldehyde, and acetaldehyde which take part in oxidative stress reactions and have a proven cardiotoxic effect [21]. Besides, there is information on microvascular injuries and dysfunction from chronic vaping [22]. At the same time, some studies comparing cardiotoxic effects from traditional cigarette smoking and vaping have demonstrated a more significant negative impact of cigarette smoke on left ventricular myocardium functions due to lower concentrations of cardiotoxic substances in vape solutions versus cigarettes [21]. In a group of 25 healthy vape smokers e-cigarette vehicle vaporization did not alter micro- or macrovascular function or oxidative stress in an acute test, which differs from chronic use [23].

Our results showed statistically significantly higher AU levels associated with both traditional tobacco smoking and vaping (e-smoking) among young healthy subjects without any known CVD. Our data correspond to a number of studies [10–11] which mentioned

that smoking cessation is associated with a decrease in AU levels and an improved prognosis even in groups of patients with already diagnosed type 2 diabetes mellitus and chronic kidney disease [9]. Our data resulted from a semiquantitative dipstick test for albuminuria, which is less accurate than quantitative methods; this may be a limitation of our study. Our choice was based on the recommendation to use a urinary protein dipstick test as a routine laboratory test for the detection of kidney damage. On the other hand, a significant limitation of previously published studies is the enrollment of old patients [9] with various established CVD and even their complications [9, 10], which may have interacted with the studied parameters and hindered assessment of the relationship between smoking (an isolated risk factor) and AU levels. Along with this, most studies have assessed traditional tobacco (not vape) smoking as a factor in AU [9]. To overcome this problem, our study enrolled apparently healthy young subjects without any CVD and significant cardiovascular risk factors. Nonsmokers demonstrated normal mean levels of albumin excretion as the sign of a generally healthy population. Thus, high AU levels among smokers might be suspected as a consequence of the unfavorable effects of traditional tobacco smoking and vaping.

We found positive associations between cigarette smoking/vaping and AU and between AU and smoking duration. The results obtained on traditional tobacco smoking correspond with the data of other authors [9–10]. We underline that multiple regression analysis did not reveal relation between AU and obesity/BMI, which are significant confounders for kidney damage. The possible explanation for such a finding is the low rate of obesity in our group of young healthy subjects. It did not exceed 5%, which is much lower in comparison with the total population or patients with chronic kidney disease.

The associations between tobacco smoking, smoking duration, smoking index, and AU have been proven in numerous studies not only in groups of patients with diabetes mellitus and hypertension but also in healthy subjects [9–11, 16]. Currently AU is regarded as an early prognostically unfavorable marker not only for chronic kidney disease but also for CVD and their complications. According to Ninomiya et al. [16], the presence of AU is associated with a 3.3-fold increase in the risk of lethal renal outcomes. AU onset and progression caused by tobacco smoking are probably related to activation of oxidation and glycation of proteins and lipids associated with the increase in vascular permeability, microvascular injuries, and development of insulin resistance [10]. Besides, the increase in the glomerular filtration rate caused by various mechanisms of tobacco smoke has been noted in association with smoking, i.e., increase in sodium chloride excretion, catecholamine release activation, and increase in vasopressin levels [10–11]. We did not reveal any relation between AU.

Data on AU levels among vapers are not presented in the available literature. There is occasional information on alternative smoking options. One paper presents the data on AU in water pipe smokers; however, the enrolled group was quite heterogeneous and, despite the found relationships between AU and water pipe smoking, the contribution of other significant factors such as age and the presence of associated diseases was not excluded [11].

The reasons for the significantly higher AU levels revealed in our study in vapers versus tobacco smokers are still unclear. A possible explanation for this may be the high daily vaping rate versus traditional cigarette consumption [3, 5]. In contrast to these considerations, we did not find any significant differences between smokers and vapers in smoking intensity measured by the amount of consumed nicotine, and this parameter was not related to the AU and Alp according to the results of multiple regression. We can assume that this may be related to the relatively low level of nicotine consumption and the relatively short duration of smoking/vaping in our young study group. Another possible expla-

nation is that, even in spite of the lower nicotine concentrations in e-fluids, the vaso-, cardio-, and nephrotoxic properties of a wide range of various chemical agents, are insufficiently studied [3, 5, 11, 21, 22]. There is quite a common misconception, especially among the young population, that inhalation of vapors from water pipes or e-cigarettes coming through various solutions systems is, if not particularly harmless, less hazardous for the smoker's health in comparison with traditional tobacco cigarettes, since it is "being filtrated" through all of these solutions [11]. However, a number of studies have shown that even "filtrated" e-cigarettes vapors contain some chemical agents, the concentration of which is dozens of times higher than in cigarette smoke [3, 5, 11]. Thus, the existing uncertainty regarding the mechanisms of vascular damage induced by vaping justifies further research in this area.

Conclusion

Our results show the relationships between smoking of both traditional tobacco cigarettes and electronic cigarettes and albuminuria and higher levels of AIp, an arterial stiffness marker. It demonstrates the need for further study of the relationships between new smoking options, particularly vaping, which are quite widespread among the young healthy population, and microvascular injuries markers and the risk of CVD.

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Statement of Ethics

This study was conducted in accordance with the guidelines for human studies. The study protocol was approved by the Ethics Committee of Sechenov University. All of the subjects signed an informed consent form. The authors have no ethical conflicts to disclose.

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Disclosure Statement

The authors declare no competing interests.

Author Contributions

V.I. Podzolkov: senior author. A.E. Bragina: main author and corresponding author. N.A. Druzhinina, L.V. Vasil'eva, K.K. Osadchiy, A.E. Dubchak, and E.I. Khvalin: second authors.

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