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Acute health effects of Heated Tobacco Products - comparative analysis with traditional cigarettes and electronic cigarettes in young adults.

Paulina Majek[1], Mateusz Jankowski[2], Grzegorz Marek Brożek[1]

I. Department of Epidemiology, School of Medicine in Katowice, Medical University of Silesia, 40-752 Katowice, Poland.
II. School of Public Health, Centre of Postgraduate Medical Education, 01-826 Warsaw, Poland.

Abstract:

Background: Heated Tobacco Products (HTPs) were designed to deliver nicotine by heating the tobacco instead of burning it.

Aim: The study aimed to examine the acute health effects on the respiratory and cardiovascular systems during the use of HTPs and compare these effects with acute health effects evoked by cigarette smoking or electronic cigarettes.

Methods: The study group comprised 160 healthy young adults (age 23 [Q1 21; Q3 26] years), both sexes divided into groups according to their smoking status: 40 HTPs users (H-group), 40 traditional cigarette smokers (T-group), 40 e-cigarette users (E-group), 40 non-smokers (C-group). The measurements of heart rate, blood pressure, O2 saturation, the concentration of FeNO, CO, temperature of exhaled air, and spirometry were performed thrice: initially, immediately after the exposure, and after 30 minutes. The exposure differed depending on smoking status: heating HTP, smoking a cigarette, using an e-cigarette, and simulation of smoking.

Results: After 5 minutes of exposure, a significant decrease in FeNO was observed in H and E groups, from 12.8±5.5ppb to 11.2±5.3ppb and from 16.9±6.5 to 14.2±6.8, $p<0.01$; respectively. A slight, but statistically significant, increase in the temperature of exhaled air after 30 minutes was observed in groups T and E (from 34.1[33.6;34.4]°C to 34.4[34.1;34.6]°C, $p=0.02$ and from 34.2 [33.9;34.5]°C to 34.4 [33.8;34.6]°C $p<0.01$; respectively). In C, E and H groups, a significant increase in heart rate and blood pressure was observed. Only cigarette smoking increased CO levels ($p<0.01$).

Conclusions: The use of HTPs elicits acute respiratory and cardiovascular health effects.

Key words: heated tobacco products; IQOS; tobacco; health effects

I. INTRODUCTION

It has been estimated that globally, a quarter of the adult population are tobacco users [1]. Cigarettes are the most common tobacco products used, but new forms of tobacco products such as heated tobacco products (HTPs) are gaining popularity [1]. The challenge of today's science is to determine the impact of HTPs on human health [2].

The first HTPs were launched in 1988 but their popularity did not match that of traditional cigarettes at that time [3]. However, the next generations of HTPs created almost 30 years later achieved international popularity and sales globally [4,5].

When using HTPs, dedicated tobacco sticks are placed on the heating blade or inside the heating chamber and after the process of warming (temperature below 350 °C) the aerosol with nicotine is inhaled by the user. Products can be used for 4-6 minutes or up to 14 puffs at once [6-10]

Tobacco sticks used in HTPs contain processed tobacco, water, glycerin, guar gum, and cellulose fibers [8]. Aerosol generated during the use of HTPs has a chemical compound comparable to traditional cigarettes, includes a comparable level of nicotine, presence of propylene glycol, glycerol, acetol, carbonyls, ammonia, N-nitrosoanabasine, aldehydes, volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide [11]. Findings from toxicological studies confirmed that the aforementioned substances are harmful to human health [12-13]. It is believed that due to the chemical composition of the aerosols generated during the use of HTPs, HTPs may evoke similar health effects to cigarettes. However, due to the growing prevalence of HTP use [14] and limited scientific data on its health consequences, the assessment of the HTPs' impact on human health is a new challenge for public health. The objectives of this study were to examine the acute health effects on the respiratory and cardiovascular systems during the use of HTPs as well as to compare these effects with acute health effects evoked by cigarette smoking or the use of electronic cigarettes.

II. MATERIAL & METHODS

Study design and population

This was a laboratory-based intervention study performed at the Respiratory Function Laboratory at the Department of Epidemiology, Medical University of Silesia in Katowice, Poland. The study population was recruited from young healthy adults (18-30 years) living in the Silesian voivodeship (one of 16 administrative regions in Poland). Participants were assigned into one of four groups according to their self-reported smoking status: T-group – 40 exclusive traditional cigarette smokers, H-group – 40 exclusive heated tobacco users and E-group – 40 exclusive users of electronic cigarettes; C-group (control) – 40 non-smokers (current and in the past). The population size was calculated based on previous research on a given topic using a similar set of measures [2]. The inclusion and exclusion criteria and detailed description of the study procedures are presented in Supplementary Materials.

The study protocol was approved by the Ethics Committee of the Medical University of Silesia in Katowice (decision number: PCN/0022/KB1/59/I/19). All participants provided written informed consent.

Measures

Basic cardiological measures, fractional exhaled nitric oxide (FeNO), carbon monoxide (CO) exhaled air temperature and spirometry tests were performed two or three times, depends on the smoking status. The study flow is presented in Figure1. The details about measurements are described in Supplementary Materials.

Figure 1. The study flow.

Procedures

After the baseline measurements were made, subjects underwent the exposure phase of testing based on their smoking status. One non-flavor cigarette from the common brand (0.5 nicotine per cigarette) was given to each participant from the T-group to smoke with the intensity and frequency of puffs consistent with their personal habits. H-group used the IQOS 2.4. The device was new, used only for research purposes, and cleaned following recommendations by the manufacturer. One non-flavor tobacco stick was given to each participant from H-group and was used according to the time dedicated by the device. E-group was examined while using their own e-cigarette devices, but they were asked to clean them before the examination day. They were provided with a non-flavoured e-liquid containing 12 mg/ml of nicotine. They were asked to use the e-cigarette for 5 minutes with their usual intensity and frequency of vaping. 5 minutes of e-cigarette use based on puffing topography is equivalent to smoking one cigarette [15-17]. C-group was asked about the 5-minutes simulation of smoking using a hollow paper tube the length of a regular cigarette (to imitate a smoking behavior).

Directly after the exposure, the second phase of the experiment was performed (Post-exposure Values I). All groups had the same measurements taken as before the exposure. T, H, and E-groups were asked to wait 30 minutes and after that time all the measurements were performed for the third time (Post-exposure Values II). C-group did not complete second post-exposure measurements. Details are presented in Figure 1.

Statistical analysis

Data analysis was performed using Statistica 13 (TIBCO Software Inc., Palo Alto, CA, USA) and IBM SPSS Statistics, version 28 (IBM, Armonk, NY, USA). Detailed description of statistical analysis is presented in Supplementary Materials.

III. RESULTS

Participants

The study group consisted of 160 young adults, including 75 women (46.9%) and 85 men (53.1%), with a median age of 23 [Q1 21; Q3 26] years. The characteristics of the test groups by smoking status are presented in Table 1.

Table I. Demographic and anthropometric characteristics by study group

	Overall n= 160	**HTP users n=40**	**Traditional Cigarette smokers n=40**	**E-cigarette users n=40**	**Control group n=40**	**p**
Male, n; %	85; 53.1	18; 45	18; 45	20; 50	19; 52.5	0.9*
Female, n; %	75; 46.9	22; 55	22; 55	20; 50	21; 47.5	

Age, median [Q1;Q3]	23 [21;26]	24 [23;26,5]	23 [21;24,5]	21 [20;22]	25,5 [22;28]	<0.01**
Height, m ± SD	1.7 ± 0.1	1.7 ± 0.1	1.8 ± 0.1	1,7 ± 1.9	1.7 ± 0.1	0.4***
Weight, kg ± SD	71.5 ± 15.2	70.8 ± 13.4	71.9 ± 15.4	72.8 ± 15.1	70.6 ± 17.1	0.9***
SD standard deviation Q1, Q3 - quartiles *Chi-square test **Kruskal-Wallis ***one-way ANOVA						

The baseline values

The baseline values of the tested parameters were analyzed by smoking status. The diastolic blood pressure in the T group was significantly higher than in the E group (p = 0.01). There was a difference in the baseline FeNO level (p <0.01) between groups C and T (p=0.04), C and E (p = 0.01), T and E (p <0.01), and H and E (p <0.01). The baseline value of CO in exhaled air was also significantly higher in the T group compared to all other groups (p <0.01). In the remaining variables, no differences in the initial measurements were visible (Supplementary Figure S1-S3).

The post-exposure values

The results from the analysis of acute effects on the respiratory and cardiovascular systems according to smoking status at the 3-time points is presented in Table II. Within each smoking group, there was a decrease in FeNO value at the post-exposure value I followed by an increase in FeNO value for post-exposure value II where the last measurement was consistently the highest. However, this was statistically significant only for the H and E groups. There was no change in FeNo within the C-group (p=0.7). A slight, but statistically significant, increase in the temperature of exhaled air was observed in groups T and E. In both cases, the increase was progressive showing the highest values in half an hour after using a cigarette/e-cigarette (from 34.1[33.6;34.4]°C to 34.4[34.1;34.6]°C, p=0.02 and from 34.2 [33.9;34.5]°C to 34.4 [33.8;34.6]°C p<0.01; respectively). Changes in exhaled CO were shown in the case of the use of traditional cigarettes with a significant increase from 6 [4;10] ppm to 11 [8;15] ppm immediately after smoking (p<0.01) with a slow decrease 30 minutes after - 9 [7;14], without return to the baseline value (p <0.01). An upward trend, which was not statistically significance, was also seen in the group of HTPs' users where a small increase 30 minutes after use was observed (p = 0.07). There were no changes in exhaled CO in the C and E groups. The measurement of O2 saturation showed no statistically significant differences, but in the case of HTPs, there was a statistical trend (p = 0.05) in the decrease of SpO2 from 99 [98;99]% at baseline to 98 [97;99]% at 30 minutes after exposure. For heart rate and blood pressure, the changes observed in each group were statistically significant (p <0.01). In the control group, after simulating smoking, a decrease in heart rate, systolic blood pressure, and diastolic blood pressure was shown (p<0.01). This was opposite to what was observed in the groups of traditional cigarette smokers, HTP users, and e-smokers, where each of those parameters showed an increase immediately after use (p<0.01) with a subsequent decrease to values close to the initial value after half an hour (p>0.01).

Table II. Changes in nitric oxide in exhaled air (FeNO), airway temperature, CO in exhaled air, O2 saturation, systolic and diastolic blood pressure and heart rate after exposure to traditional cigarettes, HTPs, e-cigarettes and after exposure simulation.							
Group	I. Baseline values	II. Post-exposure values I	III. Post-exposure values II	p	p I-II*****	p I-III*****	p II-III*****
Fractional exhaled Nitric Oxide FeNO [ppb]							
HTPs users, mean ± SD	12.8 ± 5.5	11.2 ±5.3	14.3 ± 6.2	<0.01****	<0.01	<0.01	<0.01
Traditional cigarette smokers, mean ± SD	10.3 ± 5.7	9.5 ± 6.3	12.7 ± 7.8	<0.01****	0.1	<0.01	<0.01
E-cigarette users, mean ± SD	16.9 ± 6.5	14.2 ± 6.8	17.3 ± 7.1	<0.01****	<0.01	0.4	<0.01
Control group, mean ± SD	13.2 ± 5.9	13.1 ± 5.8	-	0.7***	-	-	-
Temperature of exhaled air [°C]							
HTPs users, mean ± SD	34.1 ± 0.7	34.2 ± 0.5	34.2 ± 0.5	0.1****	0.09	0.1	0.9
Traditional cigarette smokers, median [Q1;Q3]	34.1 [33.6;34.4]	34.3 [33.7;34.5]	34.4 [34.1;34.6]	0.03**	0.05	0.02	0.7
E-cigarette users, median [Q1;Q3]	34.2 [33.9;34.5]	34.3 [34.1;34.6]	34.4 [33.8;34.6]	<0.01**	<0.01	<0.01	0.7
Control group, median [Q1;Q3]	34.0 [33.6;34.4]	34.1 [33.7;34.4]		0.3*	-	-	-
Exhaled carbon monoxide CO [ppb]							
HTPs users, median [Q1;Q3]	4 [3;5]	4 [3;5,5]	4 [3;7]	0.07**	0.1	0.2	0.9

Traditional cigarette smokers, median [Q1;Q3]	6 [4;10]	11 [8;15]	9 [7;14]	<0.01**	<0.01	<0.01	0.02
E-cigarette users, median [Q1;Q3]	3 [2;4]	3 [2;4]	3 [3;4]	0.9**	0.8	0.9	0.9
Control group, median [Q1;Q3]	3 [2;5,5]	3 [2,5;5]	-	0.4*	-	-	-
O2 Saturation [%]							
HTPs users, median [Q1;Q3]	99 [98;99]	98 [97;99]	98 [97;99]	0.049**	0.1	0.05	0.8
Traditional cigarette smokers, median [Q1;Q3]	98 [98;99]	98 [98;99]	98 [97;99]	0.1**	0.4	0.08	0.3
E-cigarette users, median [Q1;Q3]	99 [98;100]	98 [98;99]	98 [97;99]	0.1**	0.4	0.08	0.3
Control group, median [Q1;Q3]	98.5 [98;99]	99 [98;99]	-	0.4*	-	-	-
Heart rate [bpm]							
HTPs users, mean ± SD	74.9 ± 12.0	87.5 ± 12.6	73.9 ± 9.6	<0.01****	<0.01	0.8	<0.01
Traditional smokers, mean ± SD	79.3 ± 12.2	93.7 ± 15.1	80.5 ± 11.9	<0.01****	<0.01	0.7	<0.01
E-cigarette users, mean ± SD	79.6 ± 11.6	89.9 ± 13.9	80.4 ± 12.0	<0.01****	<0.01	0.5	<0.01
Control group, mean ± SD	76.9 ± 10.2	72.7 ± 10.5	-	<0.01***	-	-	-
Systolic blood pressure [mmHg]							
HTPs users, mean ± SD	120.3 ± 13.4	129.3 ± 17.2	120.7 ± 14.5	<0.01****	<0.01	0.8	<0.01

Traditional cigarette smokers, mean ± SD	125.4 ± 13.0	133.0 ± 13.2	123.7 ± 12.0	<0.01****	<0.01	0.3	<0.01
E-cigarette users, mean ± SD	126.1 ± 14.2	134.3 ± 13.2	128.4 ± 12.4	<0.01****	0.01	0.3	0.1
Control group, mean ± SD	122.5 ± 11.0	117.4 ± 13.8	-	0.01***	-	-	-
Diastolic blood pressure [mmHg]							
HTPs users, mean ± SD	76.3 ± 10.9	81.7 ± 10.4	76.3 ± 11.0	<0.01****	<0.01	0.9	<0.01
Traditional cigarette smokers, mean ± SD	80.5 ± 8.5	84.8 ± 8.9	79.0 ± 8.6	<0.01****	0.01	0.2	0.01
E-cigarette users, mean ± SD	74.6 ± 10.6	80.4 ± 8.0	77.1 ± 8.6	0.01****	0.01	0.1	0.09
Control group, mean ± SD	78.0 ± 7.0	74.6 ± 9.2	-	0.01***	-	-	-
*Wilcoxon signed-ranked test **Friedman ANOVA ***t-test for repeated measurements ****one-way ANOVA with repeated measurements *****post hoc tests							

Changes in spirometry results are presented in Table III. Slight differences were found in the case of electronic cigarette users where there was an increase of FVC from 4.8 ± 1.1 to 4.7 ± 1.2 L (p=0.02) and increase of FEV1 from 3.9 ± 0.8 to 3.8 ± 0.9 L, p=0.01. In the remaining groups, no changes were noticed.

Table III. Changes in the spirometry results after exposure to a traditional cigarette, HTPs, e-cigarette and simulation of exposure

Variable	I. Baseline values, mean ± SD	II. Post-exposure values I, mean ± SD	III. Post-exposure values II, mean ± SD	p	p I-II*****	p I-III*****	p II-III*****
HTP users, n=40							
FVC [l]	4.8 ± 0.9	4.7 ± 0.9	4.7 ± 1.0	0.1 ***	0.6	0.1	0.5
FEV1 [l]	3.9 ± 0.7	3.9 ± 0.7	3.8 ± 0.8	0.3 ***	0.9	0.4	0.2
FEV1/FVC	0.8 ± 0.7	0.8 ± 0.7	0.8 ± 0.5	0.2 ****	0.7	0.8	1.0
PEF [l/s]	7.9 ± 1.8	7.7 ± 1.8	7.7 ± 2.0	0.3 ***	0.4	0.3	1.0
MEF75 [l/s]	6.9 ± 1.6	6.7 ± 1.3	6.7 ± 1.7	0.5 ***	0.6	0.5	1.0
MEF50 [l/s]	4.6 ± 1.1	4.6 ± 1.1	4.5 ± 1.3	0.8 ***	1.0	0.8	0.8
MEF25 [l/s]	1.8 ± 0.6	2.0 ± 0.6	2.0 ± 0.7	0.05 ***	0.2	0.3	1.0
Traditional smokers, n=40							
FVC [l]	5.1 ± 1.1	5.0 ± 1.2	4.9 ± 1.1	0.2 ***	0.6	0.2	0.8
FEV1 [l]	4.1 ± 0.9	4.1 ± 0.9	4.1 ± 0.9	0.4 ***	0.5	0.4	1.0
FEV1/FVC [%]	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.7 ***	1.0	0.8	0.7
PEF [l/s]	7.7 ± 2.0	7.9 ± 2.1	8.0 ± 2.2	0.5 ***	0.7	0.5	1.0
MEF75 [l/s]	7.0 ± 1.9	7.0 ± 1.8	7.1 ± 2.1	0.5 ***	0.8	0.9	0.5
MEF50 [l/s]	4.8 ± 1.4	4.8 ± 1.3	4.7 ± 1.3	0.3 ***	1.0	0.5	0.4
MEF25 [l/s]	2.1 ± 0.7	2.0 ± 0.6	2.1 ± 0.7	0.4 ***	0.4	0.7	0.9
E-cigarette users, n=40							
FVC [l]	4.8 ± 1.1	4.7 ± 1.1	4.7 ± 1.2	0.02 ***	0.3	0.02	0.4
FEV1 [l]	3.9 ± 0.8	3.9 ± 0.8	3.8 ± 0.9	0.01 ***	0.5	0.01	0.2
FEV1/FVC [%]	0.8 ± 0.1	0.8 ± 0.1	0.8 ± 0.1	0.5 ***	1.0	0.6	0.6
PEF [l/s]	7.7 ± 1.9	7.7 ± 1.8	7.6 ± 1.9	0.6 ***	1.0	0.7	0.7
MEF75 [l/s]	6.7 ± 1.5	6.9 ± 1.6	6.7 ± 1.7	0.7 ***	0.8	1.0	0.7
MEF50 [l/s]	5.0 ± 1.3	4.7 ± 1.2	4.7 ± 1.2	0.04 ***	0.1	0.06	0.9
MEF25 [l/s]	2.2 ± 0.6	2.1 ± 0.6	2.1 ± 0.9	0.1 ***	0.4	0.7	0.9
Control group, n=40							
FVC [l]	4.7 ± 1.1	4.7 ± 1.0	-	0.4 *	-	-	-
FEV1 [l]	3.8 ± 0.8	3.8 ± 0.8	-	0.8 *	-	-	-
FEV1/FVC [%]	0.8 ± 0.1	0.8 ± 0.1	-	0.1 **	-	-	-
PEF [l/s]	8.0 ± 2.2	8.1 ± 2.1	-	0.3 *	-	-	-
MEF75 [l/s]	6.8 ± 1.9	6.8 ± 1.8	-	0.9 *	-	-	-
MEF50 [l/s]	4.4 ± 1.3	4.4 ± 1.3	-	1.0 *	-	-	-
MEF25 [l/s]	1.9 ± 0.7	1.8 ± 0.8	-	1.0 *	-	-	-

* t-test for repeated measurements; ** Wilcoxon signed-ranked test; *** one-way ANOVA with repeated measurements; ****Friedman ANOVA; *****post-hoc tests

Relative differences

Mean relative differences between baseline values vs post-exposure values I and II according to smoking status are shown in Tables IV and V (Supplementary Table S1-S2). Differences in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were statistically significant in all groups between the first and second examination; however, increases in SBP, DBP, and HR were similar between groups T, H, E (all experimental groups). Exhaled CO had increased much more in the T-group than in any other group ($p<0.01$). Level of FeNO 30 minutes after exposure had exceeded the initial level much more in the T group than in the E group. Exhaled CO had increased, in 30minutes after exposure, much more in the T-group than in any other group.

IV. DISCUSSION

This study is one of the first designed to assess the acute health effects of HTPs. In this study, eight different parameters were analyzed. Findings from this study showed that immediately after the use of HTPs, a significant change in various respiratory health parameters and cardiovascular indicators was observed. Particular attention should be given to fractional exhaled nitric oxide which showed a statistically significant decrease after the use of HTPs. This was also detected after the use of e-cigarettes and traditional cigarettes. Contrary to cigarette or e-cigarette use, the use of HTPs did not evoke an increase in exhaled air temperature. As expected, an increase in carbon monoxide levels was found only after cigarette smoking. An increase in heart rate and blood pressure was observed in all groups where nicotine-containing products was used.

As findings from longitudinal observational studies on HTP use and its health effects are not available, findings from interventional studies on HTP use may provide evidence for policymakers to strengthen tobacco regulation as well as physicians to develop up-to-date guidelines on nicotine and tobacco. This is the most comprehensive study on the acute health effects of HTP use on human health (carried out among regular HTP users), so direct comparisons with other studies are difficult.

Fractional exhaled nitric oxide is a free radical gas produced in humans among others in the respiratory tract which role includes neurotransmission, vasodilation, bronchial dilatation, and immune enhancement (host defense) [18-19]. However, FeNO has a paradoxical role in inflammatory diseases such as asthma. In low concentrations, FeNO induces a bronchodilation effect opposite at higher concentrations where NO seems to act as an inflammatory agent. 14,19].

Previous studies have shown that smoking traditional cigarettes can evoke a decrease in FeNO levels, as well as the base concentration level of FeNO [20-22]. This decrease has been hypothesized to be attributable to decreasing inducible FeNO synthase mRNA transcription [23]. Since endogenous NO is important in defending the respiratory tract against infection, smoking traditional cigarettes may contribute to the increased risks of chronic respiratory and cardiovascular disease [24]. In this study, the use of HTPs evoked a decrease in FeNO levels. A similar effect was observed after traditional smoking and e-cigarettes. Findings from the cell-based studies confirmed the cytotoxic effects of HTP use and its impact on the induction of oxidative stress [25]. Similarities between this human-based study and previous cell-based studies suggest that the use of HTPs results in oxidative stress that is associated with a higher risk for numerous diseases [11].

Currently, exhaled breath temperature (EBT) is an indicator available for monitoring the presence of inflammation in the airways [26]. Modulation of the caliber of the airways and the blood flow through the vast vascular network of the bronchial tree influences the EBT [26]. The tissue inflammation leads to hyperemia and elevated tissue temperature and ultimately to elevated EBT [27]. A similar pathophysiological process may be present when smoking traditional cigarettes, which is confirmed by the results of this study, where the increase in exhaled air temperature was observed 30 minutes after the use of traditional tobacco. An even greater increase in the temperature of exhaled air was observed with the use of e-cigarettes, where the warm water vapor is heated instead of smoke. No increase in breath temperature in the HTP group can be a result of the lower temperature used in HTP devices compared to burning traditional tobacco (350 °C vs up to 900 °C) [8,28].

Cigarette smoke (which contains around 4% CO by volume) is a well-documented source of ambient CO, which may reach up to 20 mg of CO per cigarette [29]. There are numerous studies, which have shown associations between CO levels and various health conditions [29-31]. Findings from the studies on the chemical composition of heated tobacco sticks and smoke generated during the use of HTPs revealed the presence of the combustion process during the use of HTPs, as well as confirmed the presence of CO [11]. However, the concentration of CO emitted during the use of HTPs was approximately one-hundredth of that emitted by conventional combustion cigarettes [33]. It is believed that the lower concentrations of CO in the mainstream smoke of HTPs were due to its heating mechanism and operation in lower temperatures [33]. In the study by Pataka et al. (50 males; 25 traditional smokers, and 25 non-smokers) a statistically significant increase in CO levels were observed both after cigarette smoking and HTP use ($p<0.001$), wherein the increase in CO levels was more pronounced after cigarette use [34]. Differences between our study and the study by Pataka et al. [34] may result from different research methodologies and exposure conditions. However, the impact of HTPs use on CO levels requires further investigation.

The use of nicotine-containing products such as cigarettes is associated with elevated heart rate and blood pressure [35-36]. Chronic exposure to nicotine is associated with a higher risk of cardiovascular diseases [37-39].

In this study, a significant increase in blood pressure and heart rate was observed immediately after the use of heated tobacco, cigarette, or e-cigarette. The similar increase in blood pressure and heart rate after the use of HTPs and traditional tobacco may result from the fact that the level of nicotine is similar in the two products [15]. An increase in heart rate and blood pressure after the use of HTPs is in line with previous experimental studies [40-41].

Interestingly, in the control group, a statistically significant decrease in heart rate and blood pressure was observed directly after the smoking simulation. Changes in these parameters may be related to the “white coat effect” and the stress associated with participation in the experimental study [42]. A decrease followed the time after the simulation of smoking, which coincided with the time needed to become familiar with the site and the researcher who performed the study.

Spirometry is one of the most common respiratory tract examinations [43]. In this study, no changes in spirometry parameters were observed among H and T groups. The lack of changes in spirometry values may result from the fact that the measures were carried out after smoking only one cigarette / using one tobacco stick. Such short-term exposure may be insufficient to evoke changes in spirometry values. Previously published data showed that long-term tobacco smokers have decreased values of forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), Tifeneau index, and forced expiratory flow at 25–75% FVC [FEF25–75] [44]. Other publications have revealed a decrease in FEV1/FVC directly after smoking traditional

cigarettes [45-46]. Moreover, previous studies on the acute health effects of e-cigarettes have shown statistically significant decreases in MEF75 directly after the use of e-cigarettes and a decrease in FVC 30 minutes after the session of smoking [2]. Our study revealed changes in FVC and FEV1 directly after the use of e-cigarettes. Changes in the spirometry values, only among e-cigarette users may result from a different mechanism of nicotine inhalation, which seems to have a greater effect on bronchial responsiveness [47].

Practical implications and further research needs

The long-term health effects of HTPs are unknown. Because of their short time on the market, research has been limited to studying the composition of aerosol and its potential harmfulness. Our findings, as one of the first, have shown that acute health effects of HTPs use are present. These findings may be a prelude to the implementation of the ban on advertising HTPs as a less harmful product by tobacco companies. They can also be the basis for introducing changes in the anti-tobacco policy. Particular attention should be paid to the effect of HTP aerosol on passive smokers, something we have not done yet.

Study limitations

There are several limitations related to this study. First, the study population was relatively small (40 subjects per group). However, this study is one of the first human-based studies on the acute health effects of HTP use and the number of participants seems to be high among published papers. Participants were divided into groups according to their own declaration of daily use of nicotine products. Also, the amount of daily smoking/use differed between participants. Finally, subjects were selected as current exclusive users of products, but their history of smoking could include other types of tobacco use, for example, most HTP and e-cigarette users had a history of traditional cigarette smoking.

V. CONCLUSIONS

The use of HTPs evoked acute respiratory and cardiovascular health effects. After 5 minutes of exposure, a significant decrease in exhaled nitric oxide levels was observed in heated tobacco users, cigarette smokers, and e-cigarette users. In all three groups, an increase in heart rate and blood pressure was observed. Contrary to cigarette smoking, HTPs use did not increase carbon monoxide levels and exhaled air temperature. These findings suggest that the regular use of heated tobacco use may increase the risk of chronic respiratory and cardiovascular diseases.

VI. ACKNOWLEDGEMENTS

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VII. CONFLICT OF INTEREST

The authors declare no conflict of interests.

VIII. REFERENCES

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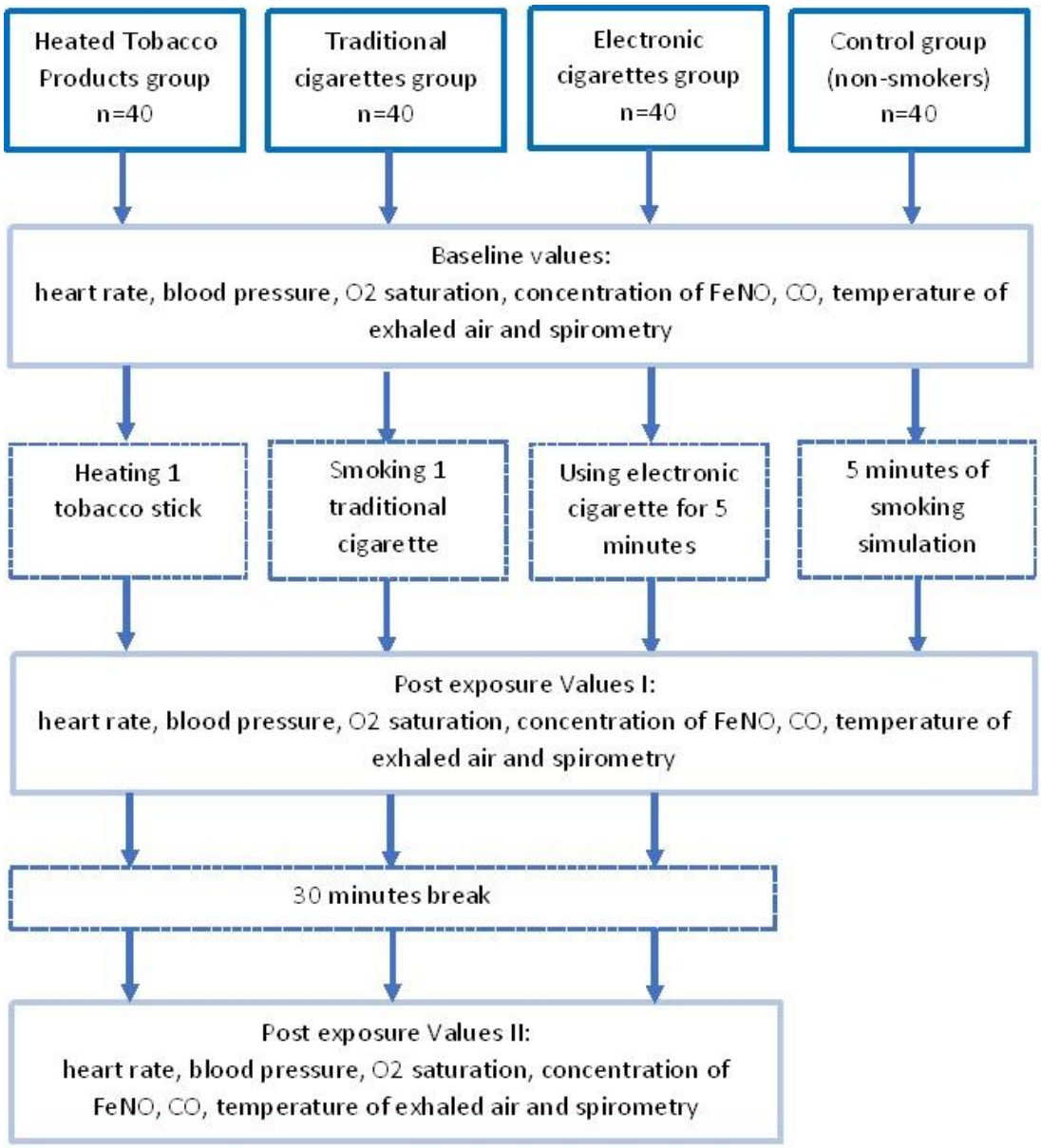


Figure 1. The study flow.

SUPLEMENTARY MATERIALS

Inclusion and exclusion criteria: The inclusion criteria were age between 18-30, written consent to participate in the study, tobacco use (T-group), HTPs use (H-group), e-cigarette use (E-group), or no history of smoking/vaping in the past (C-group). The exclusion criteria are the presence of chronic diseases, respiratory infection in the last 2 weeks, ophthalmic surgery in the last 8 weeks, pregnancy and lactation, and active allergy.

Study procedures: All smoking participants (T, H and E groups) were asked not to smoke for at least 6 hours before the examination and all subjects were asked to fast (no food and drink) at least 2 hours before. Additionally, no bronchial reactivity reducing medicines were to be taken for at least 12 hours before the test. Subjects who expressed their willingness to take part in the study and met the criteria were invited to the Respiratory Function Laboratory at the Department of Epidemiology, Medical University of Silesia in Katowice where the experiment proceeded under the supervision of a trained physician. Subjects were informed about the study procedures and a written informed consent form was collected. All participants provided written informed consent prior to participating. Subjects then completed a set of questionnaires (health form and questionnaire about smoking behavior and habits). Moreover, a short physical examination was performed.

Measurements description:

1. Non-invasive measurement of blood pressure (presented in millimeters of mercury – mmHg) and heart rate (presented in beats per minute -bpm) were measured with an automatic blood pressure monitor. O2 saturation was measured with a pulse oximeter (PULSOX 2, presented in %).

2. Non-invasive measurement of the concentration of fractional exhaled nitric oxide (FeNO) was made using a standard procedure in a seated position using the Bosch Vivatmo pro. The subjects were instructed to breathe as long as possible through the mouthpiece to achieve maximum lung filling, and then deliver a 50ml/s exhalation for 10s. Three measurements were taken 30 seconds apart. Results of FeNO measurements are presented in part per billion (ppb).

3. Non-invasive measurement of carbon monoxide (CO) concentration in exhaled air - with Pico Smokerlyzer respecting length and strength requirements of the exhalation. Results of CO measurements are presented in part per billion (ppb).

4. Non-invasive measurement of exhaled breath temperature were made using a standard seated procedure with the X-Halo Breath Thermometer, CE compliant. The measured temperature of the exhaled air is expressed in degrees Celsius (°C).

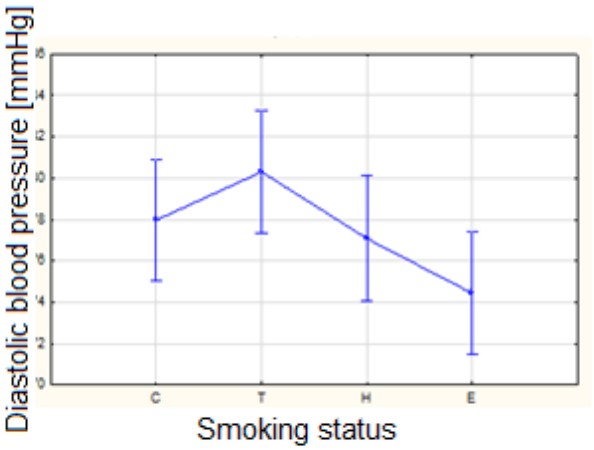
5. Flow and volume of the lungs was measured through spirometry in the sitting position according to the guidelines of the Polish Association of Pulmonary diseases. Measurements were made using the EasyOne 2001 (Switzerland, ISO quality certification) and following the American Thoracic Society (ATS)/European Respiratory Society (ERS) recommendations. The following parameters were measured: Forced vital capacity (FVC), Forced expiratory volume in 1 second (FEV1), FEV1%FVC ratio, Peak expiratory flow (PEF), Maximum Expiratory Flows at different lung volume levels (MEF75, 50, 25). Each maneuver was repeated until a minimum of three technically correct, reproducible measurements were obtained.

Statistical analysis:

Data analysis was performed using Statistica 13 (TIBCO Software Inc., Palo Alto, CA, USA) and IBM SPSS Statistics, version 28 (IBM, Armonk, NY, USA). Data were described using

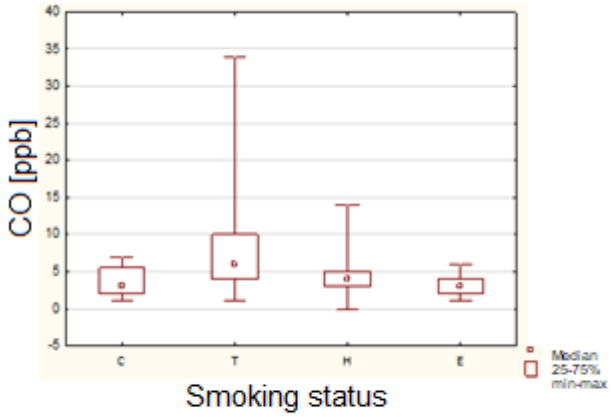
means, standard deviations, medians, and quartiles for contiuous variables and percentages for categorical variables. The normality of distributions of continuous variables was assessed by the Shapiro–Wilk test. The statistical significance of differences between continuous repeated variables, the paired Student-t-test and Wilcoxon test (for non-parametric distributions) were used. Comparisons involving more than two groups for quantitative variables were assessed using the analysis of variance (ANOVA). In the case of non-repeated variables, the one-way ANOVA or ANOVA of Kruskal-Wallis was used, depending on the normality of the distribution. While the repeated variables were analyzed – one-way ANOVA with repeated measurements or Friedman ANOVA were used. The post-hoc Dunn's and Scheffe's tests were used to control for multiple comparisons. Statistical testing to compare between categorical variables was completed using the independent samples Chi-square test. Changes in blood pressure, heart rate, O2 saturation, spirometry' values, FeNO levels, exhaled CO levels and temperature of exhaled air were assessed by calculating relative differences (in %) according to the formula: ((Post-exposure Value – Baseline Value)/Baseline Value) * 100%. Relative differences were calculated separately for post-exposure values I (immediately after exposure) vs baseline measurements and for post-exposure values II (3 minutes after exposure) versus baseline measurements. II post-exposure measurements in T, H and E-groups were not compared with control group, which have ended their examination after I post-exposure measurement. Statistical significance was based on the criterion $p < 0.05$. A similar analytical approach was used in a previous study on the acute health effects of e-cigarettes carried out using a comparable research method [Brożek GM, Jankowski M, Zejda JE. Acute respiratory responses to the use of e-cigarette: an intervention study. Sci Rep. 2019; 9:6844].

Supplementary Figure S1. The differences in baseline diastolic blood pressure according to smoking status; mean ± SD; $p<0.01$.



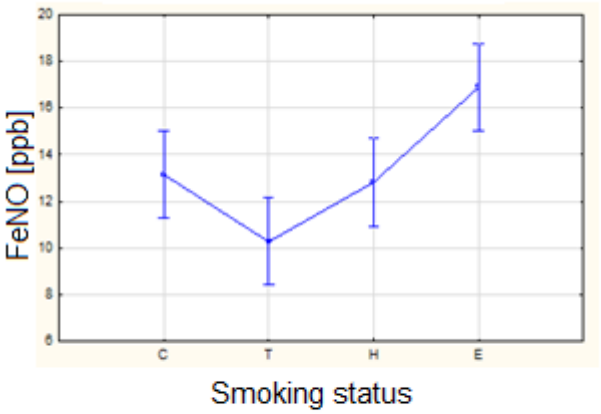
*C-control group; H- HTPs users; T-tobacco users; E-electronic cigarette users

Supplementary Figure S2. The differences in baseline Carbon monoxide according to smoking status; median, 25-75%; p<0.01



*C-control group; H- HTPs users; T-tobacco users; E-electronic cigarette users

Supplementary Figure S3. The differences in baseline Fractional Exhaled Nitric Oxide according to smoking status; mean ± SD; p<0.01



*C-control group; H- HTPs users; T-tobacco users; E-electronic cigarette users

Supplementary Table S1. Mean relative differences (%) of tested variables: baseline values vs post-exposure values I.

	Control group; mean ± SD	**Traditional smokers;** mean ± SD	**HTP users;** mean ± SD	**E-cigarette users;** mean ± SD	**p***
SBP	-4.1 ± 9.0	6.6 ± 10.3	7.6 ± 9.6	7.8 ± 17.1	<0.01
DBP	-4.3 ± 8.7	5.7 ± 8.9	7.8 11.1	10.4 25.6	<0.01
Heart rate	-5.2 ± 8.2	19.1 ± 17.3	18.1 ± 15.9	13.6 ± 12.8	<0.01
O2 saturation	-0.1 ± 1.1	-0.3 ± 1.4	-0.7 ± 1.8	-0.5 ± 1.8	0.6
FVC	0.03 ± 0.2	-0.2 ± 1.2	-0.1 ± 0.3	-0.0 ± 0.0	0.2
FEV1	0.09 ± 5.8	-5.8 ± 22.5	0.1 ± 4.2	-0.9 ± 5.1	0.2
FEV1/FVC	-1.0 ± 4.2	-5.3 ± 22.6	0.7 ± 3.1	0.1 ± 3.8	0.3
PEF	2.5 ± 9.9	-3.3 ± 25.5	-3.0 ± 11.5	2.2 ± 17.2	0.2
MEF75	1.6 ± 15.2	-6.2 ± 23.7	-1.5 ± 11.4	4.1 ± 22.1	0.5
MEF50	3.1 ± 25.0	-3.9 ± 26.0	0.7 ± 14.7	-2.6 ± 14.3	0.5
MEF25	5.1 ± 40.0	-7.2 ± 28.8	9.2 ± 19.3	-3.8 ± 16.5	0.01
FeNO	2.2 ± 21.0	-7.6 ± 58.2	-14.5 ± 20.9	-15.2 ± 25.5	<0.01
CO	0.3 ± 25.1	97.0 ± 105.1	18.9 ± 39.2	9.1 ± 42.4	<0.01
Temperature	0.2 ± 1.5	0.4 ± 1.9	0.4 ± 1.4	0.5 ± 1.0	0.6
* ANOVA of Kruskal-Wallis					

Supplementary Table S2. Mean relative differences (%) of tested variables: baseline values vs post-exposure values II.

	Traditional smokers; mean ± SD	**HTP users;** mean ± SD	**E-cigarette users;** mean ± SD	**p***
SBP	-3,5 ± 17,2	-2,7 ± 16,6	2,8 ± 13,5	0.4
DBP	-3,9 ± 19,0	-2,1 ± 19,7	5,2 ± 19,2	0.2
Heart rate	-0,6 ± 21,8	-2,3 ± 18,8	1,5 ± 10,7	0.8
O2 saturation	-2,9 ± 15,8	-3,1 ± 16,0	-0,6 ± 1,6	0.9
FVC	-6,3 ± 22,6	-9,9 ± 26,9	-7,1 ± 22,4	0.6
FEV1	-5,8 ± 22,4	-9,3 ± 27,7	-7,6 ± 22,5	0.3
FEV1/FVC	-4,5 ± 22,9	-6,8 ± 27,9	-5,6 ± 22,8	0.1
PEF	-3,2 ± 26,1	-9,9 ± 29,8	-5,8 ± 26,4	0.2
MEF75	-7,3 ± 29,6	-8,9 ± 30,7	-3,9 ± 29,2	0.8
MEF50	-5,5 ± 24,8	-8,2 ± 33,4	-8,8 ± 26,5	0.3
MEF25	-5,7 ± 29,7	0,9 ± 39,5	4,8 ± 24,4	0.2
FeNO	26,6 ± 73,6	11,7 ± 26,7	4,8 ± 24,4	0.02
CO	7,6 ± 9,9	1,5 ± 5,1	0,8 ± 3,2	<0.01
Temperature	-1,5 ± 16,1	-4,6 ± 22,2	-2,2 ± 15,9	0.3
* ANOVA of Kruskal-Wallis				