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Acute effects of heated tobacco smoking: a single-center study

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Abstract

The idea of heated tobacco products (HTPs) is to deliver nicotine to the consumer by heating the tobacco rather than burning it, possibly causing less release of many harmful and potentially harmful chemical constituents, including carbon monoxide (CO). This prospective observational study targets studying the acute effects of HTPs regarding exhaled CO, serum cotinine level, and pulmonary function. A total of 91 participants were included; 46 current traditional cigarette smokers were instructed not to smoke for a minimum of 12 hours before the study (not following the smoking cessation program) and then divided into two groups. Group 1 contained 23 participants who smoked their usual cigarette brands, and Group 2 consisted of 23 participants who smoked the I-Quit-Ordinary-Smoking tobacco sticks. Group 3 is the control group, including 45 normal healthy non-smoker participants. All participants were subjected to the subsequent thorough medical history and clinical examination, followed by assessment of the following parameters before smoking as well as 5 minutes after smoking (either heated tobacco or traditional cigarettes according to their groups): oxygen saturation (SpO2), heart rate (HR), measurement of exhaled CO, spirometry, and blood sample for serum cotinine level (which was assessed 5 minutes as well as 30 minutes after smoking). The study's findings showed that after smoking cigarettes, the amount of CO in the air was higher (mean 32.83±16.73 standard deviation) than after smoking heated tobacco, which was statistically significant. Serum cotinine levels also went up after smoking in both groups, but they were slightly higher after HTPs than after conventional cigarettes (CCs). Spirometry and SpO2 levels went down after smoking in groups 1 and 2, while HR levels went up after smoking in both groups, with a p-value of less than 0.001. We concluded that the HTPs have acute respiratory and cardiovascular effects similar to CCs but with less exhaled CO.

Key words: heated tobacco, exhaled CO, serum cotinine, IQOS.

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Introduction

Tobacco smoke, which arises from usual cigarettes, contains several dangerous chemical components like nicotine, arsenic, benzene, carbon monoxide (CO), heavy metals, and tobacco-derived nitrosamines. Tobacco smoking is greatly accompanied by the development of lung inflammation of the airways and lung parenchyma, leading to respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), interstitial lung disease, and lung cancer. Also, it is accompanied by oxidative stress and cardiovascular diseases like stroke and myocardial infarction [1]. The idea of heating tobacco without combustion and smoke is called "heat-not-burn" tobacco. IQOS is one of the recent heat-not-burn tobacco products, first introduced in Italy and Japan. IQOS is known as a new mixed product between conventional and electronic cigarettes (EC), and it provides another method to decrease the quantity of harmful constituents in comparison to conventional cigarettes (CCs) by its new technology [2]. In CCs, tobacco combustion leads to the release of nicotine with other harmful and potentially harmful chemical constituents (HPHCs), including CO.

On the contrary, products that do not need combustion to deliver nicotine (such as nicotine replacement therapies - NRTs, smokeless tobacco, EC) release less HPHCs, including CO. So, non-combustible nicotine devices are offered for reducing harm from smoking [3]. Our research intends to assess the acute effects of heated tobacco smoking regarding exhaled CO level, serum cotinine level, and pulmonary functions.

Materials and Methods

This is a prospective observational analytical study that was carried out from November 2021 to October 2022. A total of 91 participants were included with simple randomization using a table created by a computer software program, and divided into three groups as follows: group 1 included 23 subjects of current cigarette smokers who were instructed not to smoke for a minimum of 12 hours before the study, then after assessment, were allowed to smoke one cigarette of their usual brands. Group 2 included 23 subjects of current cigarette smokers who were instructed not to smoke for at least 12 hours before the study, then,

after assessment, were allowed to smoke one IQOS tobacco stick. Group 3, as a control group, included 45 normal healthy subjects with no history of any type of smoking. The study was approved by the ethics committee with IRB Code No. (MD-337-2021) in 20/2/2022. Written informed consent was obtained from all participants before enrollment in the study. The inclusion criteria were: i) both sexes, ii) above 20 years old, iii) current regular traditional cigarette smokers who are defined as subjects who smoke ≥1 cigarette/day during the last 30 days with at least 5 pack-years (Brinkman index) [4]. The exclusion criteria were: i) any subjects using IQOS or EC, any shisha smokers, ii) any subjects with uncontrolled comorbidities such as renal failure or heart failure, iii) any current active infectious lung disease. All participants were evaluated as regards complete medical history with special concern to personal history (demographics such as age, and sex), smoking index, exposure history (second-hand smoking), history of any chronic diseases or comorbid conditions, physical examination, oxygen saturation (SpO_2) and heart rate (HR), CO level measured by CO Check Pro device which is a handheld portable battery-operated device used for assessing the concentration of CO in the exhaled breath and calculating the percentage of % COHb in the blood, it requires a single exhaled breath into the device to display CO results in parts per million (ppm) and %COHb, and spirometry by Master Screen PFT 2012, CareFusion 234 GmbH, Germany (V-781267-057 version 03.00). During the test, the patients sat upright, and a clip was placed on their nose. They were then instructed to insert the mouthpiece, clamp it between their teeth, and close their lips tightly around it to form a proper seal. The patient was asked to breathe normally through the transducer, achieving tidal breathing, before taking in a deep, full breath and exhaling as forcefully and quickly as possible for as long as they could [5]. A blood sample was taken for serum Cotinine level as a baseline value; the kit used is an enzyme-linked immunosorbent assay. Cotinine is added to the wells pre-coated with the cotinine monoclonal antibody. After incubation, a biotin-conjugated anti-human cotinine antibody is added and binds to human cotinine. Then, participants of group 1 smoked their usual brand of cigarettes, while those of group 2 smoked the IQOS tobacco cigarette for up to 14 puffs (around 5-6 minutes). For each subject, a new tobacco cigarette was used as IQOS includes a charger, a holder, and tobacco sticks (heets). The tobacco stick is "heated" with an electronically controlled heating blade (less than 350°C). The participants of group 3 were controllers. After that, all participants of (groups 1 and 2) were exposed again to the above steps (including measurements of serum cotinine level 5 minutes and 30 minutes after smoking).

Statistical analysis

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Analysis included mean, standard deviation, median, minimum, and maximum in quantitative data, and used frequency (count) and relative frequency (percentage) for categorical data. The non-parametric Mann-Whitney test was used for comparing quantitative variables. For assessing serial measurements within each patient, the non-parametric Friedman fort and the Wilcoxon signed rank test were applied [6]. For comparing categorical data, a Chi-square (c2) test was performed. An exact test was used instead when the expected frequency was less than 5 [7]. The Spearman correlation coefficient was used to evaluate correlations between quantitative variables [8]. A p-value below 0.05 was considered statistically significant.

Results

The age range of the participants was from 21 to 71 years with a mean age of 47.54 years [±10.89 standard deviation (SD)], 46 males (100%), and all of them were cigarette smokers, while the age range of the control group was from 22 to 66 years with a mean age of 43.44 years (±13.06 SD), males (91.1%) and most of them with no special habits of medical importance (94.3%), 3 of them were exposed to secondhand smoke.

A statistical significance was found in the pre-smoking measurements of spirometry between groups 1 and 2 (Table 1). The post-smoking exhaled CO (Table 1) was more elevated in group 1 than in group 2, with a statistical significance. HR also increased, and SpO_2 decreased in both groups post-smoking compared to the pre-smoking values, but with no statistical significance.

Also, our study shows an increase in post-smoking cotinine after 5 minutes and after 30 minutes in both groups, with no statistical significance. The percentage of change % in serum cotinine level from the baseline after 5 minutes (mean 22.19±39.08) and after 30 minutes (36.98±63.84) was higher in those who smoked the heated tobacco products (HTPs) than those who smoked the cigarettes (mean 9.79±24.75 after 5 minutes and mean 8.73±23 after 30 minutes) but with no statistical significance.

In Table 2, the measurements of spirometry decreased post-CC smoking without statistical significance, except for peak expiratory flow (PEF). The exhaled CO level increased post-CC smoking, SpO_2 decreased, and HR increased, all with statistical significance.

Spirometry measurements decreased post-HTP smoking without statistical significance, except for PEF and forced expiratory flow (FEF) of 25%, which were decreased with statistical significance. Table 2 also shows that the exhaled CO level did not increase after HTP smoking (pre-smoking mean of 10.74±5.70), (post-smoking mean of 10.30±5.23), decreasing SpO_2, and increasing HR with statistical significance.

There was a negative correlation between smoking index (pack/year) and spirometric measures, but with no statistical significance except with forced vital capacity (FVC) ($p=0.029$), and a positive correlation with exhaled CO without statistical significance.

Discussion

The study included 46 male smokers (100%), as all our cases were males with a mean age of 47.54 (±10.89 SD). The predominance of the male sex among the participants may be attributed to the habits and traditions of our society. This was also found by Pataka *et al*., who evaluated 50 male non-smokers, healthy and current smokers with no co-morbidity, regarding the acute effects of IQOS on pulmonary function, and all subjects in that study were males with a mean age of 38.8 (±11.09 SD) [2]. However, our study participants were not in line with the studies conducted by Rabenstein *et al.* [9], Vukas *et al.* [10], and Majek *et al*. [11], in which both sexes were included with a mean age of 26.5, 32, 30, and 23, respectively.

The exhaled CO level increased post-CC smoking with statistical significance, with $p<0.001$ (pre-smoking mean of 9.83±4.41 SD and post-smoking mean of 32.83±16.73 SD), which was more than group 2 (who smoked HTPs) with a mean of 10.74 (±5.70 SD) as described in Table 1. This is in line with Pataka *et al.*, as in both groups, after IQOS use, the amount of exhaled CO was found within the range of CO exposure found in non-smokers (4.12±1.66 in the non-smoker group and 4.9±3.6 in the smoker group) and was lower

than the announced levels of smokers in the study by Deveci *et al*. [2,12]. Also, in Majek *et al*. [11], there was a significant rise in exhaled CO in the T group (traditional cigarette smokers), from 6 ppm to 11 ppm just following smoking, with a slow decline 30 minutes after to 9, with no return to the baseline value ($p<0.01$). While in the H group (HTP users), the baseline value was 4 ppm, and it was 4 ppm immediately after smoking.

Along the same line, the observations from studies on the chemical composition of heated tobacco cigarettes and the smoke they produce revealed not only that combustion occurs when using HTP, but also the presence of CO [13]. However, the concentration of CO emitted during the use of HTPs was approximately one-hundredth of that emitted by conventional combustion cigarettes.

The same findings were found by Maloney *et al.*: own-brand cigarettes increased exhaled CO concentration [14], but IQOS did not. Also, Zhang *et al*. concluded that levels of exhaled CO among HTP users were lower than those of CC users [15].

Serum cotinine level increased post-CC smoking with statistical significance, and the rate of increase in the first 5 minutes was more than that in the remaining 25 minutes, as shown in the curve in Figure 1; however, in Figure 2, it increased post-HTP smoking with statistical significance, and the rate of increase in the first 5 minutes is almost the same in the remaining 25 minutes.

The slope of the nicotine curves in the initial phase of consuming nicotine-containing products indicates their addictive potential. It is assumed that cigarettes are addictive due to the quick delivery of nicotine into the bloodstream and subsequently to the brain. So, if other nicotine delivery products exhibit similar kinetics, they could potentially be just as addictive, although other factors play important roles as well. Nicotine addiction is recognized as a complex issue, with psychosocial and biogenic factors, for example, that should also be taken into consideration.

Another study shows that the nicotine delivery by HTPs was significantly less than that by traditional cigarettes. [10]

Also, in the study by Hardie *et al*. [16], which estimated nicotine pharmacokinetics and subjective effects of two HTPs compared with traditional cigarettes, it was found that nicotine uptake was much higher for the cigarette [maximum nicotine concentration (Cmax)= 22.7 ng/mL] than for either HTP (8.6 and 10.5 ng/mL). In the same line as the previous one, Phillips-Waller *et al*. found that IQOS delivers less nicotine (median Cmax 8.3) than cigarettes (median Cmax 12.9) [17].

Table 1. Comparison between groups 1 and 2 regarding pre-smoking and post-smoking pulmonary function test, exhaled carbon monoxide, serum cotinine level, oxygen saturation, and heart rate.

	Group 1					Group 2					p
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Pre- smoking											
FEV1/FVC	72.06	12.97	75.93	43.43	88.97	76.28	8.84	79.57	53.84	84.74	0.258
FEV1 %	60.36	26.81	57.00	15.30	105.00	78.79	18.89	84.00	42.30	106.00	0.018*
FVC %	66.51	24.13	64.00	28.40	110.00	84.23	15.73	86.00	46.90	118.00	0.018*
PEF L/s	54.89	20.83	56.00	19.00	101.00	66.41	21.06	64.00	28.80	114.00	0.119
FEF25 %	47.28	26.15	47.00	5.00	104.00	65.38	26.06	63.00	20.70	116.00	0.032*
FEF50%	48.36	31.22	45.00	6.20	110.00	71.40	31.06	77.00	21.10	119.00	0.021*
FEF75%	47.41	31.63	47.00	9.00	134.00	61.41	25.23	64.00	18.50	97.00	0.030*
MMEF25-75%	49.01	30.89	48.00	7.80	114.00	67.93	28.26	70.00	18.60	109.00	0.032*
Exhaled CO-level ppm	9.83	4.41	9.00	5.00	22.00	10.74	5.70	10.00	3.00	22.00	0.643
Serum Cotinine level(pg/mL)	7.49	4.65	6.90	1.80	21.40	11.51	14.05	7.00	1.50	55.40	0.725
SpO_2%	96.83	1.37	97.00	93.00	98.00	97.43	0.90	98.00	95.00	99.00	0.141
HR	77.74	12.26	76.00	62.00	110.00	72.04	8.43	71.00	56.00	90.00	0.134
Post-smoking											
FEV1/FVC	70.07	14.62	74.40	40.00	90.35	75.11	10.93	76.83	47.49	88.89	0.231
FEV1%	59.33	27.75	54.00	14.70	108.00	76.56	22.53	81.50	29.20	104.00	0.035*
FVC%	66.28	22.89	64.60	30.60	112.00	82.83	19.47	87.10	43.00	119.00	0.010*
PEF L/s	50.90	22.38	49.00	13.00	88.00	60.07	21.46	61.00	20.00	102.40	0.218
FEF25%	44.83	26.08	44.00	6.00	95.00	59.28	25.55	61.00	14.00	109.40	0.085
FEF50%	46.96	30.72	43.00	5.80	106.00	70.10	36.86	69.00	12.00	133.00	0.040*
FEF75%	51.99	40.75	41.00	6.90	160.00	60.37	31.24	62.00	11.90	129.00	0.166
MMEF25-75%	48.59	32.37	44.00	8.30	111.00	65.64	31.92	66.10	11.30	120.00	0.059
Exhaled CO-level ppm	32.83	16.73	27.00	15.00	74.00	10.30	5.23	9.00	3.00	21.00	<0.001*
Serum cotinine level after 5 minutes of smoking (pg/mL)	8.03	4.97	7.00	1.70	21.40	12.43	14.22	8.30	1.60	53.50	0.356
Serum cotinine level after 30 minutes of smoking (pg/mL)	8.11	5.73	6.20	2.10	28.20	13.29	14.32	7.80	1.60	54.50	0.121
SpO_2	96.30	1.72	96.00	91.00	98.00	96.65	1.07	97.00	94.00	98.00	0.664
HR	92.00	13.08	88.00	72.00	117.00	87.65	10.38	88.00	68.00	110.00	0.415

SD, standard deviation; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF25%, forced expiratory flow of 25%; FEF50%, forced expiratory flow of 50%; FEF 75%, forced expiratory flow of 75%; FEF25-75%, forced expiratory flow of 25-75%; MMEF, maximum mid expiratory flow; CO, carbon monoxide; HR, heart rate; ppm, parts per millio; SpO_2, oxygen saturation. This table shows that there was statistical significance in the pre-smoking measurements of spirometry (FEV1, FVC%, FEF25%, FEF50%, FEF75%, MME F25-75%) between groups 1 and 2. Regarding the post-smoking finding, the post-smoking exhaled CO was elevated in group 1, with a mean of 32.83 (±16.73 SD), more than group 2, with a mean of 10.3 (±5.23 SD), with statistical significance. Also, there is an increase in post-smoking cotinine after 5 minutes and after 30 minutes in both groups, but with no statistical significance between the groups. The heart rate also increased in both groups post-smoking, but with no statistical significance between the two groups. The post-smoking SpO2 in both groups decreased in relation to the pre-smoking values, but with no statistical significance between the two groups. *significant $p<0.05$.

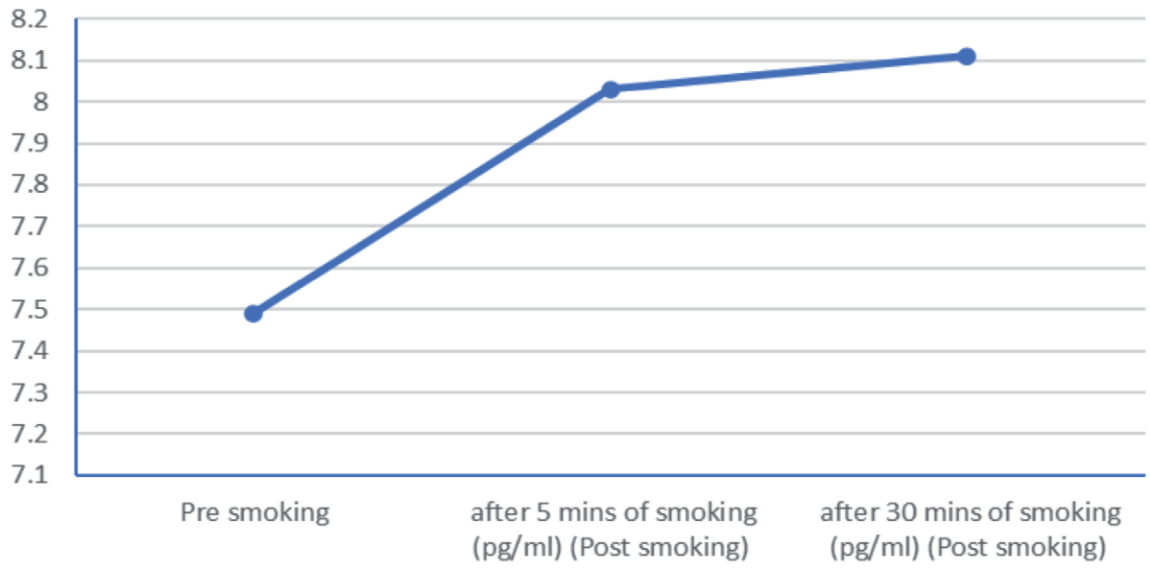

Figure 1. Serum cotinine level group 1 (pg/mL). Serum cotinine level increased post-conventional cigarette smoking with statistical significance, and the rate of increase in the first 5 minutes was more than that in the remaining 25 minutes.

Table 2. Comparison of pre and post-smoking pulmonary function test, exhaled carbon monoxide, oxygen saturation, and heart rate in group 1 and group 2.

	Pre-smoking					Post-smoking					p
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Group 1											
FEV1/FVC	72.06	12.97	75.93	43.43	88.97	70.07	14.62	74.40	40.00	90.35	0.068
FEV1 %	60.36	26.81	57.00	15.30	105.00	59.33	27.75	54.00	14.70	108.00	0.248
FVC%	66.51	24.13	64.00	28.40	110.00	66.28	22.89	64.60	30.60	112.00	0.782
PEF L/s	54.89	20.83	56.00	19.00	101.00	50.90	22.38	49.00	13.00	88.00	0.021*
FEF25% (L/sec)	47.28	26.15	47.00	5.00	104.00	44.83	26.08	44.00	6.00	95.00	0.114
	(3.58)	(2.06)	(3.42)	(0.37)	(8.11)	(3.40)	(2.04)	(3.35)	(0.49)	(7.38)	(0.14)
FEF50%	48.36	31.22	45.00	6.20	110.00	46.96	30.72	43.00	5.80	106.00	0.573
FEF75%	47.41	31.63	47.00	9.00	134.00	51.99	40.75	41.00	6.90	160.00	0.484
MMEF25-75%	49.01	30.89	48.00	7.80	114.00	48.59	32.37	44.00	8.30	111.00	0.445
Exhaled CO-level ppm	9.83	4.41	9.00	5.00	22.00	32.83	16.73	27.00	15.00	74.00	<0.001*
SpO_2%	96.83	1.37	97.00	93.00	98.00	96.30	1.72	96.00	91.00	98.00	0.022*
HR	77.74	12.26	76.00	62.00	110.00	92.00	13.08	88.00	72.00	117.00	<0.001*
Group 2											
FEV1/FVC	76.28	8.84	79.57	53.84	84.74	75.11	10.93	76.83	47.49	88.89	0.224
FEV1 %	78.79	18.89	84.00	42.30	106.00	76.56	22.53	81.50	29.20	104.00	0.065
FVC%	84.23	15.73	86.00	46.90	118.00	82.83	19.47	87.10	43.00	119.00	0.175
PEF L/s	66.41	21.06	64.00	28.80	114.00	60.07	21.46	61.00	20.00	102.40	0.02*
FEF25% (L/sec)	65.38	26.06	63.00	20.70	116.00	59.28	25.55	61.00	14.00	109.40	0.055
	(4.81)	(1.99)	(4.55)	(1.54)	(8.51)	(4.36)	(1.93)	(4.17)	(0.96)	(8.37)	(0.045*)
FEF50%	71.40	31.06	77.00	21.10	119.00	70.10	36.86	69.00	12.00	133.00	0.503
FEF75%	61.41	25.23	64.00	18.50	97.00	60.37	31.24	62.00	11.90	129.00	0.281
MMEF25-75%	67.93	28.26	70.00	18.60	109.00	65.64	31.92	66.10	11.30	120.00	0.201
Exhaled CO-level ppm	10.74	5.70	10.00	3.00	22.00	10.30	5.23	9.00	3.00	21.00	0.101
SpO_2%	97.43	0.90	98.00	95.00	99.00	96.65	1.07	97.00	94.00	98.00	0.002*
HR	72.04	8.43	71.00	56.00	90.00	87.65	10.38	88.00	68.00	110.00	<0.001*

SD, standard deviation; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF25%, forced expiratory flow of 25%; FEF50%, forced expiratory flow of 50%; FEF 75%, forced expiratory flow of 75%; FEF25-75%, forced expiratory flow of 25-75%; MMEF, maximum mid expiratory flow; CO, carbon monoxide; HR, heart rate; ppm, parts per millio; SpO_2, oxygen saturation. This table shows that the measurements of spirometry decreased post-conventional cigarette smoking (group 1), without statistical significance, except for PEF that was decreased with statistical significance (p=0.021), and the exhaled CO level increased post conventional cigarette smoking with statistical significance (p<0.001) (pre-smoking mean 9.83±4.41 SD and post-smoking mean 32.83±32.83 SD); also it shows decreased SpO2, and increased HR post-smoking with statistical significance p<0.001. Regarding (group 2) the measurements of spirometry decreased post-heated tobacco product smoking without statistical significance except PEF and FEF25% that was decreased with statistical significance, and the exhaled CO level did not increase after heated tobacco product smoking (pre-smoking mean of 10.74±5.70 SD and post-smoking mean of 10.30±5.23 SD), also showing decreasing SpO2, and increasing HR after smoking with statistical significance of p<0.001.

Also, two more studies showed the same findings, Maloney *et al*. and Goldenson *et al*. [14,18]. The first one concluded that among smokers, IQOS provided lower nicotine levels compared to cigarettes, with Cmax values of 20.4 ng/mL and 12.7 ng/mL for cigarettes and HTP 1, respectively. The second study found that the delivery of nicotine was highest for combustible cigarettes, followed by IQOS 18 mg/g, with Cmax values of 24.83 ng/mL and 13.68 ng/mL for cigarettes and HTP 1, respectively.

Contrary to our findings, Brossard *et al.* found that Cmax and area under the curve from the beginning of product use to the last measurable concentration (AUC 0-last) were comparable between THS and CC, with Cmax ratios ranging from 88 to 104% and AUC 0-last ratios between 96 to 98% [19].

Regarding the spirometric measures post-cigarette smoking in our study (group 1), we found that measurements of spirometry decreased without statistical significance, except for PEF, which was decreased with a statistically significant p-value of 0.021, although PEF may not be considered a measure of response as it is highly dependent on the patient's effort and cooperation. Pre-smoking mean was 54.89±20.83 SD, and post-smoking, the mean was 50.90±22.38 SD (Table 2). These results are in line with previous studies, as in the one by Kougias *et al.* [20], which found that mid-to-small size pulmonary airways were firstly affected (FEF25%, FEF50%, FEF25-75%) in a dose-dependent manner, indicating significant subclinical inflammatory changes in the peripheral bronchial tree, not just in the larger airways.

Also, Unverdorben *et al.* studied the acute effects of traditional cigarette smoking on pulmonary function [21]. It was found that FEF25% was significantly lower in CC smoking than in electrically heated smoking systems and non-smoking, and concluded that there were acute and reversible effects of traditional cigarette smoke exposures on mid to small-sized airways in a concentration -dependent manner. Another two studies, Flouris *et al*. and Chorti et al. [22,23], showed a decline in forced expiratory volume in the first second (FEV1)/FVC just after smoking traditional cigarettes.

Regarding the spirometric measures in group 2 (Table 2), our finding is in line with Pataka *et al*. [2], which revealed that FEF25%, FEF50%, and PEF declined significantly after IQOS use; this study explained that the main conclusion was that pulmonary function was immediately decreased in all participants, both non-smokers and smokers, suggesting that IQOS may impact airways function even after just 5 minutes of use, potentially due to bronchospasm, mucosal edema, or even secretions. In contrast, the study by Majek *et al*. found no alterations in spirometric parameters between those smoking HTPs and traditional cigarettes [11].

IQOS was developed by Philip Morris International as a "reduced harm" substitute to traditional smoking, aiming to substitute nicotine intake from combustible cigarettes. Moazed *et al*. estimated industry data on the pulmonary and immunosuppressive effects of HTPs under near-real-world conditions and also compared the participants with those who continued smoking CC [24]. The industry data indicated no improvement in lung function after 3 months of switching to IQOS compared to those who continued smoking CC. A significant increase in FEV1/FVC was observed only in the group that abstained from smoking. This finding regarding improvement in lung function with smoking cessation is also found by Pezzuto and Carico, 2020 [25], who studied the benefit of smoking cessation over 3 months in terms of improvement of respiratory functional variables, and found improvement in oxygen desaturation index, FEV1, walking test, COPD assessment test score, PaO2, and SaO2. A recent study by Sohal *et al.* discovered that IQOS causes similar harmful effects on human airway epithelium and smooth muscle cells *in vitro* as the CC, due to changes in mitochondrial function, airway inflammation, and remodeling [26].

The findings shown in Table 2 were in line with Pataka *et al.* [2], who found that in the whole group of 50 participants, SaO2% decreased significantly after IQOS use. Also, Majek *et al.* found that after the HTP smoking, there was a statistically significant decline in peripheral oxygen saturation from 99% at baseline to 98% 30 minutes after exposure [11]. Also, a significant rise in HR

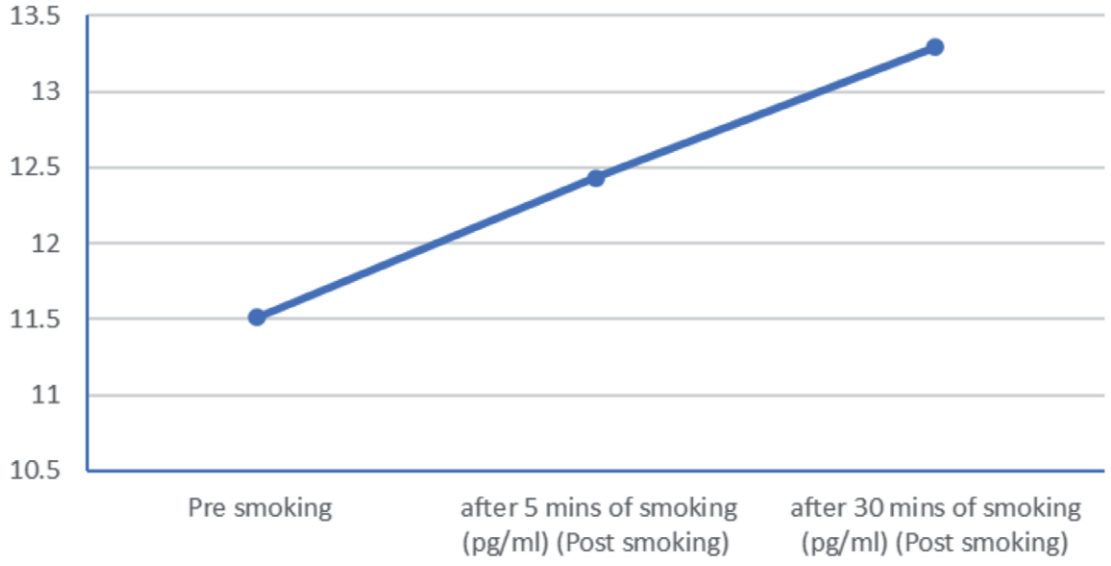

Figure 2. Serum cotinine level in group 2 (pg/mL). Serum cotinine level increased post-smoking heated tobacco products with statistical significance, and the rate of increase in the first 5 minutes is almost the same in the remaining 25 minutes.

and blood pressure was observed after the traditional cigarette smoking group, the group of HTPs, and the e-cigarette group, and concluded that using HTPs causes acute respiratory and cardiovascular health effects. The similar rise in HR and blood pressure after the use of HTPs and conventional tobacco may be attributed to the comparable nicotine levels in the two products. The increase in HR and blood pressure following HTP use aligns with former experimental research, such as the studies by Başaran *et al*. and Kopa and Pawliczak [27,28].

Our study showed a negative correlation between smoking index (pack/year) and spirometric measures, but with no statistical significance except with FVC (p=0.029), and a positive correlation with exhaled CO without statistical significance. This is in line with Barthwal and Singh [29], who studied the early detection of COPD in asymptomatic smokers using spirometry and found that pulmonary function parameters are significantly lower in smokers as compared to non-smokers. With a higher smoking index, heavy smokers showed a greater decrease in lung function, FVC, and FEV1 than with increasing age. Also, in Deveci *et al.* [12], there was a significant positive correlation between CO levels and both daily cigarette consumption and smoking duration in healthy individuals. The same finding was found by Gonzalez et al. [30], who found that CO in expiration significantly correlated with the number of cigarettes smoked.

In our study, the pre-smoking exhaled CO was elevated in the studied cases in comparison to the control group, with statistical significance p<0.001. Also, pre-smoking serum cotinine level was elevated in the studied cases but with no statistical significance in Table 3, but the maximum cotinine level in our control group was 13.5 pg/mL which may be due to passive smoking or environmental exposure which were under-reporting which is in line with Wall *et al.* [31], who measured cotinine in the saliva, serum and urine of passive smokers, non-smokers and active smokers and found that mean urine cotinine level was somewhat elevated in passive smoker than a non-smoker.

Also in our control group, the maximum level of exhaled CO was 7 ppm which also may be due to passive smoking or environmental exposure (which were under-reporting as shown in Table 3, which is in line with Deveci *et al*. [12], who used a portable CO monitor to compare the exhaled CO levels between established smokers and non-smokers, and found that passive smokers had higher mean exhaled CO levels than non-smokers, though the difference was not statistically significant (p>0.05). Similarly, Laranjeira *et al*. elicited that environmental tobacco smoke is the likely cause of higher CO levels observed among passive smokers [32].

In the current study, all the spirometric findings of the cases were significantly lower than those of the control group, with p<0.001, as shown in Table 3. This is in line with Dutt *et al.* [33], who showed that pulmonary function parameters are significantly reduced in smokers as compared to non-smokers.

Conclusions

HTPs have acute respiratory and cardiovascular effects like CCs, but with less exhaled CO than CCs. Although these changes were relatively minor and not likely to be of major clinical significance, they should be a matter of concern about the long-term safety of the product. The slope of the nicotine curves during the initial phase of consuming nicotine-containing products determines the addictive potential of these products. More research is required to evaluate both the short- and long-term effects of IQOS, mainly in patients with respiratory conditions.

This study offers a novel assessment of the acute respiratory and cardiovascular effects of HTPs compared to CCs. While previous research has predominantly focused on the chemical composition of emissions from HTPs, this study is among the first to directly compare exhaled CO levels post-smoking, revealing a significant reduction with HTPs. Despite this, both HTPs and CCs showed similar acute physiological effects, including increased serum cotinine levels and HR, along with decreased spirometry

Table 3. Comparison between the studied cases and the control group regarding the pre-smoking pulmonary function test, exhaled carbon monoxide, serum cotinine level, heart rate, and oxygen saturation.

Pre-smoking	Cases					Control					p
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
FEV1/FVC	74.17	11.18	77.45	43.43	88.97	84.33	5.93	83.73	72.80	99.54	<0.001*
FEV1 %	69.57	24.75	74.85	15.30	106.00	93.06	10.79	90.00	72.00	127.60	<0.001*
FVC%	75.37	22.04	77.00	28.40	118.00	92.76	12.85	89.90	75.00	138.30	<0.001*
PEF L/s	60.65	21.52	60.00	19.00	114.00	81.52	16.62	79.00	57.00	126.50	<0.001*
FEF25%	56.33	27.39	56.50	5.00	116.00	84.77	16.84	86.50	48.90	124.00	<0.001*
FEF50%	59.88	32.92	61.00	6.20	119.00	93.08	17.55	93.00	56.00	131.40	<0.001*
FEF75%	54.41	29.16	53.50	9.00	134.00	84.01	19.49	78.80	57.00	135.00	<0.001*
MMEF25-75%	58.47	30.80	60.00	7.80	114.00	88.86	13.89	91.00	59.00	117.00	<0.001*
Exhaled CO-level ppm	10.28	5.06	9.00	3.00	22.00	2.87	1.36	3.00	1.00	7.00	<0.001*
serum cotinine level (pg/mL)	9.50	10.54	6.90	1.50	55.40	5.99	2.65	5.60	1.40	13.50	0.120
SpO_2%	97.13	1.19	97.50	93.00	99.00	97.53	1.01	98.00	96.00	99.00	0.130
HR	74.89	10.80	75.00	56.00	110.00	79.98	8.78	80.00	64.00	94.00	0.005*

FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF 25%, forced expiratory flow of 25%; FEF 50%, forced expiratory flow of 50%; FEF 75%, forced expiratory flow of 75%; FEF 25-75%, forced expiratory flow of 25-75%; MMEF, maximum mid expiratory flow; CO, carbon monoxide; HR, heart rate; SpO_2, oxygen saturation. This table shows that all the measurements of the spirometry were low in comparison to the control group, with a statistical significance p<0.001, and the pre-smoking exhaled CO was elevated in the studied cases in comparison to the control group, with a statistical significance p<0.001. Also, pre-smoking serum cotinine level was elevated in the studied cases, but with no statistical significance. *significant p<0.05.

and oxygen saturation. These findings highlight the need to evaluate both chemical emissions and physiological outcomes to better understand the health implications of HTPs. Despite the valuable insights provided by this study, several limitations should be acknowledged; the study focused only on acute effects within a 30-minute timeframe post-smoking. Long-term studies are necessary to evaluate the chronic impact of HTPs on respiratory and cardiovascular health. Also, participants were limited to current smokers and healthy non-smokers; including ex-smokers and individuals with pre-existing respiratory or cardiovascular conditions could provide a more comprehensive understanding of the effects of HTPs.

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Informed consent: written informed consents were obtained from all participants before the enrollment to participate in the study.

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