Passive exposure to e-cigarette emissions: Immediate respiratory effects

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ABSTRACT

INTRODUCTION The present work examined the effect of passive exposure to electronic-cigarette (e-cigarette) emissions on respiratory mechanics and exhaled inflammatory biomarkers.

METHODS A cross-over experimental study was conducted with 40 healthy non-smokers, 18–35 years old with normal physical examination and spirometry, with body mass index <30 kg/m², who were exposed to e-cigarette emissions produced by a smoker, according to a standardized protocol based on two resistance settings, 0.5 ohm and 1.5 ohm, for e-cigarette use. All participants underwent a 30-minute control (no emissions) and two experimental sessions (0.5 and 1.5 ohm exposure) in a 35 m³ room. The following Impulse Oscillometry (IOS) parameters were measured at pre and post sessions: impedance, resistance, reactance, resonant frequency (*fres*), frequency dependence of resistance (*fdr*=R5–R20), reactance area (AX), and fractional exhaled nitric oxide (FeNO). Differences between pre and post measurements were compared using t-tests and Wilcoxon signed rank tests, while analysis of variance (ANOVA) was used for comparisons between experimental sessions (registered under ClinicalTrials.gov ID: NCT03102684).

RESULTS IOS and FeNO parameters showed no significant changes during the control session. For IOS during the 1.5 ohm exposure session, *fres* increased significantly from 11.38 Hz at baseline to 12.16 Hz post exposure (p=0.047). FeNO decreased significantly from 24.16 ppb at baseline to 22.35 ppb post exposure in the 0.5 ohm session (p=0.006).

CONCLUSIONS A 30-minute passive exposure to e-cigarette emissions revealed immediate alterations in respiratory mechanics and exhaled biomarkers, expressed as increased *fres* and reduced FeNO.

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INTRODUCTION

The adverse health effects of passive exposure to conventional cigarette smoke have been extensively studied and are well documented[1]. After 10 years of experience with electronic cigarettes (e-cigarettes)[2] it is known that its active use is associated with immediate adverse health effects[3-9]. However, limited studies have evaluated the potential impact on indoor air quality, as well as the health effects of exposure to second-hand aerosols from e-cigarettes[6,9-16]. Most studies that have examined passive exposure to e-cigarette emissions have several limitations, such as small sample sizes, use of smoking machines instead of humans, use of cell cultures or animal

European Respiratory Society [ATS/ERS] Task Force 2005) and body mass index (BMI) <30 kg/m², were included in the current study. Exclusion criteria included current (daily or occasional) smokers, former smokers (having quit smoking less than 1 year prior to the study), age under 18 or over 35 year, BMI >30 kg/m², pregnancy or lactation, any ongoing or recent illness or infection (<4 weeks prior to study), acute or chronic conditions, and any use of medication (<2 weeks prior to study). All participants were instructed to fast for two hours prior to each session[27].

Ethical and legal aspects

Volunteer participants were informed of the scope of the study and their right to access and withdraw at any time. Each participant gave their written informed consent prior to beginning the study. Ethics approval was granted from the Ethics Committee of the School of Medicine, National Kapodistrian University of Athens (protocol: 1617006410), and the study was registered in clinicaltrials.gov (ID NCT03102684).

Measurement of respiratory parameters

Flow-volume loop and exhaled carbon monoxide (eCO)

Baseline flow volume was performed prior to study sessions as a prerequisite for inclusion. The maneuver was performed in a sitting position with a nose-clip applied using a Jaeger MasterScreen Spirometry system (Franklin Lake, NJ, USA). Forced vital capacity (FVC), forced expiratory volume in the first second (FEV_1), Tiffeneau Index (FEV_1/FVC%), peak expiratory flow (PEF) and mid-expiratory flows (FEF at 25%, 50% and 75% of exhaled FVC) were measured along with their predictive values calculated by computer software.

Using a Bedfont® Scientific Ltd. Micro+™ Smokerlyzer® (Harrietsham, Maidstone, Kent) calibrated according to manufacturer's guidelines, eCO was measured prior to each session with inclusion <7 ppm[28] to ensure non-smoking status and absence of exposure prior to beginning each session. With a nose-clip applied, participants were instructed to inhale and hold their breath for approximately 15 seconds and then exhale into the mouthpiece for approximately 10 seconds[28].

Impulse oscillometry

Impedance at 5 Hz (Z5), resistance at 5, 10 and 20 Hz (R5, R10 and R20), reactance at 5 Hz (X5), resonant frequency (*fres*), frequency dependence of resistance (*fdr*) and reactance area (AX) were measured using a Viasys Jaeger Masterscreen IOS system (Franklin Lake, NJ, USA). In an upright sitting position with a nose-clip applied and cheeks lightly supported by the participant's hands, the participant was instructed to breathe normally and performed three reproducible trials with intra-assay coefficient of variation (CV) <10%[29].

Fractional exhaled nitric oxide (FeNO)

Using Eco Medics AG CLD 88 Series chemiluminescence analyzer (Durnten, Switzerland) equipped with a Spiroware 3.0 software program, three reproducible measurements (with intra-assay CV<10%) were performed in a sitting position with a nose-clip applied. Participants were instructed to deeply inhale through a filtered mouthpiece and consecutively exhale at a mouth flow rate of approximately 50 mL/s for 10 seconds.

All procedures were performed according to ATS/ERS guidelines[27,29,30].

Statistical analysis

Demographics and inclusion criteria for the whole sample of 40 young non-smokers were presented as mean and standard deviation (SD). IOS and FeNO measurements were also presented as mean and SD. The differences between pre and post IOS and FeNO measurements were evaluated for significance using Wilcoxon signed-rank test and student t-tests for paired data. Analysis of variance (ANOVA) for repeated measurements was used to assess differences between exposures accounting for differences between pre and post values. To account for multiple comparisons, a Tukey correction was used. All tests were two-tailed and statistical significance was set at 5% ($p < 0.05$). Data were analysed using Stata™ (Version 15.0 SE, Stata Corporation, College Station, TX 77845, USA).

RESULTS

Demographics and flow–volume loop

Participants had a mean age of 24.6 years, weight of 71.4 kg, height of 174.1cm and BMI of 23.4 kg/

m² (Table 1). Baseline flow-volume loops were within normal limits (Table 1). All exhaled CO measurements were <7 ppm prior to starting each session with an average of 2.1 ppm in all sessions ranging from 1 to 5 ppm. Five of the forty participants were former smokers, with three of them reporting having smoked for under 5 years and the other two for 7–8 years.

IOS and FeNO

As shown in Table 2, there was a significant increase in *fres* in the 1.5 ohm session and a significant decrease in FeNO in the 0.5 ohm session, pre to post exposure to SHA from e-cigarettes. Mean value for Z5 in the control session was 0.40 kPa/L/s pre and 0.41 kPa/L/s post exposure, indicating no significant change. In both experimental sessions, Z5 did not change significantly from pre to post exposure.

In the control session, R5 did not change significantly from pre to post exposure (p=0.472). In the 0.5 ohm session, mean pre and post measurements did not change from 0.39 kPa/L/s. In the 1.5 ohm session, R5 showed a post exposure decrease trend that was not significant, with mean values of 0.39 pre to 0.38 kPa/L/s post exposure (Table 2).

Table 1. Demographics, exhaled carbon monoxide (eCO) prior to sessions and baseline Spirometry among the 40 participants (20 men and 20 women), Athens 2017.

	Mean (SD)	
Age (years)	24.6 (4.3)	
Weight (kg)	71.4 (15.4)	
Height (cm)	174.1 (10.5)	
BMI (kg/m2)	23.4 (3.8)	
eCO (ppm)		
control	2.1 (1.0)	
0.5 ohm	2.2 (0.7)	
1.5 ohm	2.0 (0.6)	
Flow volume		% Predicted (SD)
FVC(L)	4.65 (1.18)	100.5 (10.3)
FEV$_1$(L)	3.86 (0.91)	97.8 (10.3)
FEV$_1$/FVC(%)	na	83.7 (6.2)
FEF$_{25/75}$ (L/s)	4.09 (1.20)	89.1 (21.1)
FEF$_{25\%}$(L/s)	7.74 (1.94)	104.1 (14.7)
FEF$_{50\%}$(L/s)	5.15 (1.50)	99.7 (24.7)
FEF$_{75\%}$(L/s)	2.21 (0.76)	89.7 (25.7)
PEF(L/s)	8.29 (2.01)	95.6 (12.3)

BMI: Body mass index; SD: standard deviation; FVC: forced vital capacity; FEV1: forced expiratory volume in the first second; Tiffeneau Index: FEV1/FVC%; Mid-expiratory flows: FEF at 25%, 50% and 75% of exhaled FVC; PEF: peak expiratory flow; na: not applicable.

In both control and 1.5 ohm sessions, R10 and R20 did not change from pre to post (mean 0.34 kPa/L/s). During the 0.5 ohm session, R10 remained

Table 2. Results of Impulse Oscillometry (IOS) and fractional exhaled nitric oxide (FeNO) pre and post all exposure sessions in 40 participants, Athens 2017.

	Session	Pre	SD	Post	SD	Diff.	p
Z5 (kPa/L/s)	control	0.40	0.11	0.41	0.11	0.01	0.302[t]
	0.5 ohm	0.41	0.12	0.41	0.12	0.00	0.661
	1.5 ohm	0.41	0.13	0.40	0.12	-0.01	0.930
R5 (kPa/L/s)	control	0.38	0.10	0.38	0.11	0.00	0.472[t]
	0.5 ohm	0.39	0.11	0.39	0.12	0.00	0.638
	1.5 ohm	0.39	0.13	0.38	0.12	-0.01	0.721
R10 (kPa/L/s)	control	0.34	0.09	0.34	0.09	0.00	0.291[t]
	0.5 ohm	0.35	0.10	0.35	0.10	0.00	0.540
	1.5 ohm	0.34	0.11	0.34	0.10	0.00	0.377
R20 (kPa/L/s)	control	0.34	0.08	0.34	0.09	0.00	0.580[t]
	0.5 ohm	0.34	0.09	0.35	0.09	0.01	0.373[t]
	1.5 ohm	0.34	0.09	0.34	0.09	0.00	0.571
Mean R5–R20 (kPa/L/s)	control	0.36	0.09	0.36	0.09	0.00	0.495[t]
	0.5 ohm	0.36	0.10	0.37	0.11	0.01	0.340
	1.5 ohm	0.36	0.11	0.36	0.10	0.00	0.584
X5 (kPa/L/s)	control	-0.11	0.04	-0.11	0.04	0.00	0.819[t]
	0.5 ohm	-0.12	0.04	-0.14	0.13	-0.02	0.906
	1.5 ohm	-0.12	0.04	-0.11	0.03	0.01	0.286

Table 2. Continued

	Session	Pre	SD	Post	SD	Diff.	p
fres (Hz)	control	11.15	3.24	11.33	3.30	0.18	0.141
	0.5 ohm	11.70	3.27	11.23	2.82	-0.47	0.066
	1.5 ohm	11.38	3.66	12.16	4.07	0.78	0.047
AX (kPa/L)	control	0.33	0.26	0.34	0.28	0.01	0.440
	0.5 ohm	0.36	0.26	0.34	0.25	-0.02	0.224
	1.5 ohm	0.38	0.46	0.36	0.26	-0.02	0.247
FeNO (ppb)	control	26.45	0.11	25.00	0.11	-1.45	0.070
	0.5 ohm	24.16	0.12	22.35	0.12	-1.81	0.006
	1.5 ohm	24.35	0.13	23.44	0.12	-0.91	0.368

SD: standard deviation; p-values result of Wilcoxon signed rank test unless indicated by t-results of t-test; Diff.: Difference between post and pre exposure.

at 0.35 kPa/L/s pre and post exposure, while R20 increased non-significantly from 0.34 to 0.35 kPa/L/s (Table 2). In both control and 1.5 ohm session, mean R5–R20 did not change from 0.36 kPa/L/s. In the 0.5 ohm session, mean R5–R20 exhibited a non-significant increase from 0.36 pre to 0.37 kPa/L/s post exposure (Table 2). As shown in Table 2, X5 did not change in the control session with mean -0.11 kPa/L/s. In the 0.5 ohm session, X5 decreased from -0.12 pre to -0.14 kPa/L/s post exposure, while in the 1.5 ohm session it increased from -0.12 to -0.11 kPa/L/s.

In the control and 0.5 ohm sessions, *fres* did not change significantly (p=0.141 and p=0.066, respectively). In the 1.5 ohm session, *fres* showed a significant increase of 6.9% (mean 11.38 Hz pre and 12.16 Hz post exposure, p=0.047) (Table 2). Pre and post changes differed significantly between the experimental sessions (p=0.030).

AX did not change significantly from pre to post exposure for all three sessions with mean measurements 0.33 pre to 0.34 kPa/L/s post exposure in the control session (p=0.440), 0.36 to 0.34 kPa/L/s in the 0.5 ohm session (p=0.224), and 0.38 to 0.36 kPa/L/s in the 1.5 ohm session (p=0.247) (Table 2).

In the 0.5 ohm session, FeNO exhibited a significant decrease of 7.5% (mean 24.16 ppb pre and 22.35 ppb post exposure, p=0.006), whereas in the control and 1.5 ohm sessions it did not change significantly (Table 2).

DISCUSSION

The current study found that passive exposure to SHA produced by e-cigarette users showed minor alterations in respiratory mechanics and exhaled NO of the exposed participants, while the role of the resistance/power settings was found to be inconclusive.

Respiratory mechanics were evaluated by IOS, as it only requires quiet breathing and captures subtle alterations of lung mechanics even when spirometry is still normal[31,32]. IOS captures the non-uniformities in airflow distribution, considered an early manifestation of small-airways disease and so represents an ideal screening tool[33]. The current study found a significant increase in *fres* after the 1.5 ohm session. It is known that *fres* decreases with age and increases for both restrictive and obstructive disorders[33,34]. The obstructive airway pattern, expressed with increased *fres*, AX, R5 and R20, is evident in asthma where *fres*, R5 and R20 increase with broncho-provocation and decrease with broncho-dilation[34]. The same combination of changes (increased *fres*, R5 and R20) are observed in the case of peripheral-airways obstructive pattern, as in the study of Lappas et al.[4], where IOS measurements pre and post active e-cigarette use revealed a peripheral-airways obstruction pattern. The alteration of *fres* found in the present study was isolated and did not fall into a specific diagnostic (restrictive or obstructive) pattern. However, it expresses the inhomogeneous airflow distribution[33], and hence the increased *fres* that was found could be interpreted as the footprint of the immediate likely irritative effect that SHA from e-cigarettes exerted on the airways.

The trend of FeNO reduction found post exposure was significant in the 0.5 ohm session. This finding is similar to previous studies that found FeNO

reduction after exposure to active smoking of combustible cigarettes, cigars and e-cigarettes[3,4,35,36], as well as after passive exposure to second-hand smoke[37]. Furthermore, the only study[15] that examined FeNO post SHA exposure, although having several methodological differences and limitations (including small sample size, no reported number of efforts or coefficient of variation in FeNO measurements), and most notably the use of a smoking machine, also found a similar trend in FeNO reduction immediately post exposure, however non-significant. It is known that cigarette smoke results in FeNO reduction by activating the down-regulation of NO synthases (inducible and endothelial isoenzymes)[38] through the nitric oxide it contains[39]. It is also known that the e-cigarette functions by heating the e-cigarette liquid to over >300 degrees Celsius[19] and that nicotine, when heated to >247 degrees Celsius, decomposes into nitric oxides and carbon monoxide[40]. Therefore, it is possible that FeNO reduction observed in the current study resulted from the activation of the down-regulation mechanism due to the NO produced from the thermal decomposition of nicotine during e-cigarette use.

Following the recommendations of the e-cigarette manufacturer, a higher power setting was combined with the lower resistance of the 0.5 ohm session. Kosmider et al.[41] found that setting the e-cigarette to higher power (watts) released significantly higher levels of carbonyls, such as formaldehyde, acetaldehyde and acetone than lower power settings. In addition, this effect was more pronounced in propylene glycol based e-cigarette liquids[41]. Sosnowski et al.[19] showed that the aerodynamic resistance of e-cigarettes is 10 times higher than for dry-powder inhalers and requires a significantly higher physical effort for inhalation than conventional cigarettes. Therefore, it is possible that regardless of the standardized breathing pattern of the e-cigarette user, due to the different resistance/power combinations, the SHA produced in each experimental session was slightly different, resulting in the different effects observed in FeNO.

Building on previous research on the health effects of active e-cigarette use, the current findings provide evidence that 30 minutes of passive exposure to e-cigarette emissions result in indications of small-airways irritation, reflected by increased *fres* and a mild inflammatory reaction of the airways expressed by reduced FeNO.

The current study examined short-term exposure and so conclusions on the potential long-term effects of SHA cannot be made. In terms of developing a scientific research base for evidence-based policy, further studies are needed to examine the possible impact of longer exposure duration and the potential additive effect of repeated exposure.

Strengths and limitations

The current study had several strengths, including use of a novel e-cigarette device, a cross-over trial study design, a statistically representative sample size of young healthy adults and standardized topography for e-cigarette use by an experienced smoker. In addition, all measurements were performed according to ATS/ERS guidelines.

As the aim of the current study was to explore the passive exposure among young healthy adults, it did not examine the possible effect on patients with respiratory or other medical conditions. Blind control was not possible since participants were able to visually detect the difference in exposure conditions (presence of aerosol cloud), therefore the possible psychological effect of this knowledge was not accounted for.

CONCLUSIONS

The current study provides evidence that exposure to SHA from e-cigarettes has immediate effects on respiratory mechanics and exhaled inflammatory biomarkers. These findings add to the growing amount of evidence on the immediate health effects of e-cigarettes. Whereas the clinical implications need further assessment, these findings should be taken into account in global policies regarding the regulation of e-cigarette use in public places and in assessments of the effects of SHA on the health of bystanders.

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