Short-term effects of electronic cigarette smoking on cardiorespiratory parameters, volatile organic compounds and inflammatory markers

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Shareable abstract (@ERSpublications)
This study aimed to evaluate the acute effect of a 30-min session of e-cigarette smoking; significant changes in cardiorespiratory parameters, exhaled VOCs and markers of inflammation were found https://bit.ly/3UQVHct

Cite this article as: Rizik S, Bar-Yoseph R, Hanna M, *et al*. Short-term effects of electronic cigarette smoking on cardiorespiratory parameters, volatile organic compounds and inflammatory markers. *ERJ Open Res* 2025; 11: 01096-2024 [DOI: 10.1183/23120541.01096-2024].

Received: 23 Oct 2024
Accepted: 5 Nov 2024

Abstract

Background Electronic cigarettes (e-cigarettes) have gained popularity in recent years. While initially introduced as a safe alternative for tobacco and a bridge for smoking cessation, subsequent studies found that they contain toxic substances. We aimed to assess the acute effect of a single session of e-cigarette smoking on cardiorespiratory parameters, exhaled volatile organic compounds (VOCs) and markers of inflammation.

Methods A prospective single-centre study was carried out. Participants (healthy volunteers, former e-cigarette users) were assessed before and after a 30-min session of e-cigarette smoking. Evaluations included vital signs, pulmonary functions – spirometry and fractional exhaled nitric oxide (FeNO) – blood and exhaled breath condensate (EBC) cytokines and electronic nose (e-nose) for analysis of exhaled VOCs profile.

Results 30 participants aged 27.9±4.4 years were enrolled in the study. Post-smoking observations revealed a significant increase in heart rate (77.5±10.9 to 85.5±12.1 beats·min^{-1}, p=0.002), respiratory rate (15.4±2.2 to 17.1±1.8 breaths·min^{-1}, p=0.002) and blood pressure (systolic 118±8.1 to 123.5±11.9, p=0.017; diastolic 73.9±8.4 to 78.5±6.3 mmHg, p=0.011). FeNO decreased significantly (median of 11 (7.5–15.5) to 9.7 (7.3–17.3) ppb, p=0.024). Analysis of e-nose found a significant change of exhaled VOC pattern after e-cigarette smoking. No significant changes were found in spirometry and cytokine levels in blood or EBC.

Conclusions A single session of 30 min of e-cigarette smoking caused significant cardiorespiratory effects, decreased FeNO and altered exhaled VOC pattern, similar to the effect seen with cigarette and water-pipe smoking. The observed acute effects, together with the well-known chronic risks, highlight the importance of effective regulation of e-cigarettes.

Introduction

Electronic cigarettes (e-cigarettes) were first introduced to the market in 2004. They were presented by the tobacco industry as a "harm reduction" tool for smokers [1, 2], and quickly gained popularity among both current smokers and nonsmokers [3, 4].

E-cigarettes represent a modern, technological alternative to traditional tobacco cigarettes. They contain e-liquids, primarily nicotine dissolved in propylene glycol (PG) or vegetable glycerin (VG). When heated, these e-liquids produce a vapour that is inhaled into the lungs [5, 6].

Recent evidence suggests that e-cigarettes may not be as safe as initially suggested [7]. An updated European Respiratory Society (ERS) position statement on novel nicotine and tobacco products states that much of the evidence around "harm reduction" comes from the tobacco industry; thus, it cannot approve the use of these products as safe alternatives in a population-based strategy [2].

The heating of additives and solvents (PG or VG) can generate carcinogenic compounds [8–10]. Moreover, some flavourings (such as coffee) have been found to produce higher levels of toxic chemicals compared to others [11–13]. Additionally, e-cigarette vapour has been shown to contain cytotoxic metal and silicate particles at levels comparable to, or exceeding, those in traditional cigarette smoke [14, 15]. Since 2019, a growing number of severe and potentially life-threatening cases of EVALI (e-cigarette or vaping product use associated lung injury) have been described [16].

In response to these concerns, the World Health Organization (WHO) and the US Food and Drug Administration (FDA) have prioritised efforts to prevent the uptake of e-cigarettes, particularly among youth, due to what has been described as an "epidemic" of youth use [17, 18].

Beyond the effect on the respiratory system, e-cigarettes have been found to have additional effects, leading to sympathetic nervous system predominance, endothelial cells dysfunction, elevated markers of oxidative stress and suppressed levels of the antioxidant vitamin E [19, 20].

A study by Rubinstein *et al.* [21] reported the presence of volatile organic compound (VOC) toxicants in adolescent e-cigarette smokers. VOCs are compounds with high vapour pressure at ambient conditions; they show distinct and immediate changes in pathological conditions that alter biochemical processes in the body, such as oxidative stress, cytochrome p450, liver enzymes, carbohydrate and lipid metabolism [22, 23]. Gas chromatography–mass spectrometry (GC–MS) is the gold standard for measuring exhaled breath VOCs [24–26]. However, it is a cumbersome and expensive instrument that requires well-trained personnel; thus, its application in breath analysis is limited [27]. Our study employed an electronic nose (e-nose), a quick and noninvasive tool, to detect VOC profiles [28].

The objective of our study was to evaluate the short-term effects of a single, 30-min session of e-cigarette smoking on cardiorespiratory parameters, VOCs and airway inflammation in healthy volunteers. Our hypothesis was that similarly to cigarette and water-pipe smoking, even a single session of e-cigarette smoking might adversely affect these parameters.

Methods

This was a single-centre prospective study, performed in indoor setting, at our paediatric pulmonology institute. The study was approved by the Institutional Review Board (0556–19), and participants signed an informed consent prior to enrolment.

Participants and setting

Eligible volunteers were older than 18 years and had previously smoked e-cigarettes. Exclusion criteria included any chronic lung disease, pregnancy or lactation in women, acute illness during the previous 2 weeks, corticosteroid treatment, smoking cigarettes or e-cigarettes in the previous 6 h or water-pipe smoking in the previous 24 h. The e-cigarettes used in the study contained 7 mL (1200 puffs). The e-liquid contained PG and VG with 2% nicotine and mango ice flavouring.

The participants were asked to smoke an e-cigarette for 30 min and to report any side-effects. Evaluations were performed before and after smoking, and included the following:

- Vital signs: Temperature, heart rate (HR), respiratory rate (RR), oxygen saturation (S_{pO_2}), blood pressure (BP). Vital signs were measured using a Datascope Duo Patient Monitor (Mindray, USA).
- Spirometry: Spirometry was performed in accordance with the American Thoracic Society (ATS)/ERS Task Force using a KoKo spirometer (nSpire Health, Inc, Louisville, CO, USA) [29]. Results are expressed as absolute values and % predicted (mean±SD).
- Fractional exhaled nitric oxide (FeNO): FeNO was measured using an ECO-medics AG device (Eco Medics, Switzerland) according to ATS recommendations. The measurement procedure included a deep inhalation to total lung capacity followed by an exhalation for 10 s, at a mouth flow rate of 50 $mL \cdot s^{-1}$ and a pressure of 10 cmH_2O [30]. Results are expressed in parts per billion (ppb) and presented as median (IQR).

- Electronic nose (e-nose) for the measurement of exhaled VOCs: In this study, we used a previously developed e-nose (sniffphone); details can be found in the paper by SHAN *et al*. [28]. Briefly, following baseline measurement of the ambient air, breath samples were collected by breathing directly into the aperture of the instrument for 10 s. The device consists of an array of eight gold nanoparticles, which are attached to chemical ligands sensitive to diverse VOCs. The sensors operate in a cross-reactive concept, by providing a cumulative response to whole breath composition rather than binding selectively to the VOCs. The change in electrical resistance of the sensors to the breath sample is recorded. Then, after using statistical methods and/or machine learning algorithm, the sensor array can be trained to identify the specific "fingerprint" response.
- Serum and exhaled breath condensate (EBC) cytokines*:* EBC (a noninvasive sampling of the lower airways) was collected in dedicated test tubes (Respiratory Research, Charlottesville, VA, USA) according to the manufacturer's instructions and ERS recommendations [31, 32]. Blood was also drawn for cytokine analysis; the collected EBC and serum samples were stored at −80°C until analysis. The levels of human interleukin (IL)-10, IL-1β, IL-4, IL-6 and tumour necrosis factor-α (TNF-α) were measured with the ProcartaPlex™ Multiplex Immunoassay (PPX-05, Invitrogen), using the Bio-Plex200 (Bio-Rad Laboratories, Hercules, CA, USA) according to the manufacturer's instructions.

Statistical methods

The statistical analysis was performed using SPSS version 28.

Descriptive statistics in terms of mean, standard deviation, median, percentages and ranges are presented for all the variables in the study. Normal distribution of continuous parameters was tested by Kolmogorov–Smirnov test. As a result, Wilcoxon signed rank test or paired t-test were used for the changes between before and after e-cigarette smoking.

For the e-nose, all raw data were evaluated; samples that were technically faulty (electronic noise, no response) were excluded. The area under the curve of the change in electrical resistance before and after smoking was calculated. The first and second samplings from the same volunteer (*i.e.*, correlated variables, paired data) were compared with a one-way platform using matching model analysis (paired analysis). The grouping effect (before and after smoking) was calculated using *F* tests.

$p<0.05$ was considered as significant.

Results

30 volunteers (21 females) participated in the study. Their baseline characteristics are presented in table 1. Participants had high-level education and most of them were dual users (cigarettes and e-cigarettes). During smoking, three participants had mild symptoms, which did not necessitate cessation of the smoking session; two patients complained of dizziness and one of palpitations.

Table 2 presents the vital signs and pulmonary functions before and after e-cigarette smoking. After smoking, there was a significant increase in mean±SD HR and RR (77.5±10.9 to 85.5±12.1 beats·min^{-1}, p=0.002; and 15.4±2.2 to 17.1±1.8 breaths·min^{-1}, p=0.002, respectively); BP also increased significantly (systolic 118±8.1 to 123.5±11.9 mmHg, p=0.017; diastolic 73.9±8.4 to 78.5±6.3 mmHg, p=0.011). FeNO decreased significantly, from a median of 11 (7.5–15.5) to 9.7 (7.3–17.3) ppb (p=0.024). There were no significant changes in fever, S_{pO_2} and spirometry values.

TABLE 1 Characteristics of participants (n=30)

Age years	27.9±4.4
Female	21 (70)
BMI kg·m^{-2}	24.6±4.6
Education years	16.2±2.2
Alcohol consumption	25 (83)
Cigarette smoking	22 (73)
Use of drugs	9 (30)
Medical cannabis (out of 9 using drugs)	5 (56)
Comorbidities	5 (17)

Values are presented as n (%) or mean±SD. BMI: body mass index.

TABLE 2 Vital signs and pulmonary functions: before and after e-cigarette smoking

	Before	After	p-value
Temperature °C	36.7±0.10	36.7±0.23	0.49
Heart rate beats·min^{-1}	77.5±10.9	85.5±12.1	0.002
Oxygen saturation %	98.8±1.2	99.1±1.06	0.35
Systolic blood pressure mmHg	118±8.1	123.5±11.9	0.017
Diastolic blood pressure mmHg	73.9±8.4	78.5±6.3	0.011
Respiratory rate breaths·min^{-1}	15.4±2.2	17.1±1.8	0.002
FeNO ppb	11 (7.5–15.5)	9.7 (7.3–17.3)	0.024
FVC L	3.97±0.97	3.87±0.96	0.052
FVC %	94.6±10.9	94.8±10.4	0.68
FEV_1 L	3.4±0.72	3.4±0.69	0.087
FEV_1 %	96.6±10.4	96.3±9.7	0.34
$FEF_{25–75\%}$ L	4.06±0.89	4.11±0.91	0.55
$FEF_{25–75\%}$ %	94.3±18.4	95.1±18.7	0.65

Values are presented as mean±SD or median (IQR). e-cigarette: electronic cigarette; FeNO: fractional exhaled nitric oxide; ppb: parts per billion; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of FVC.

In the cytokine analysis, no significant differences were found in EBC before and after smoking (table 3). Blood levels of the cytokines were below the threshold of detection; therefore, changes after smoking could not be detected.

Figure 1 presents the breath VOC analysis by e-nose, which was available for 20 participants (10 samples were technically unacceptable and were excluded). Four sensors were analysed; in three of them, significant differences in the VOC patterns were found before and after smoking ($p<0.0003$, $p<0.0008$ and $p<0.0008$), implying an increase in the sensor resistance after smoking.

Supplementary figure 1S presents a representative example of the raw data of the four sensors analysed. The response of the sensors to the breath samples of the same volunteer at two time points (before and after smoking) is presented.

Discussion

In this single-centre study, we evaluated the short-term effects of a 30-min *ad libitum* e-cigarette smoking session on cardiorespiratory parameters, exhaled VOCs and markers of inflammation. Our findings indicate that a single session led to significant changes in vital signs, including increased HR, RR and BP; a decrease in FeNO; and notable alterations in the VOC pattern. However, no significant changes were observed in spirometry values or cytokine levels in blood and EBC.

Evidence has been rising regarding the effects of long-term use of e-cigarettes. A population-based study found significant health hazards associated with e-cigarette smoking; the effect was more pronounced in dual users [7]. Knowledge on the initial response to e-cigarette smoking might further enhance the understanding of changes due to chronic use [33].

TABLE 3 EBC cytokine levels : before and after e-cigarette smoking

	Before (pg · mL^{-1})	After (pg · mL^{-1})	p-value
IL-1	2.43 (2.33–2.58)	2.43 (2.18–2.82)	0.48
IL-4	12.0 (11.5–17.4)	12.0 (11.5–17.4)	0.73
IL-5	10.4 (5.6–17.9)	10.4 (9.2–15.6)	0.47
IL-10	1.09 (0.89–2.6)	1.3 (0.89–2.71)	0.18
TNF-α	13.7 (13.5–15.7)	13.7 (13.04–17.7)	0.44

Values are presented as median (IQR). EBC: exhaled breath condensate; e-cigarette: electronic cigarette; IL: interleukin; TNF-α: tumour necrosis factor-α.

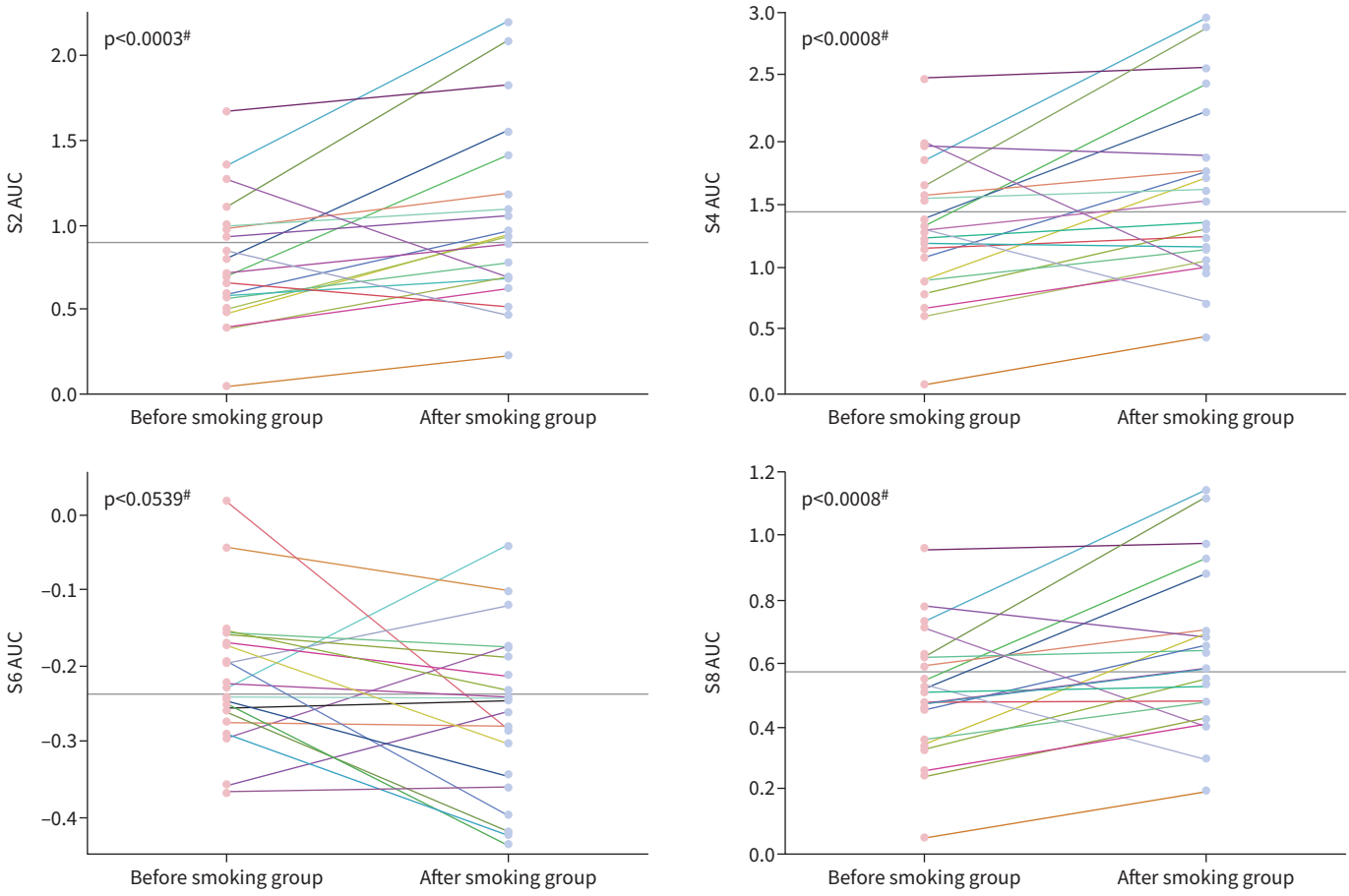

FIGURE 1 Paired analysis for the response of four sensors to breath VOCs before and after smoking. VOCs: volatile organic compounds; S: sensor; AUC: area under the curve. #: statistically significant.

In recent years, there had been increased awareness of the risks of e-cigarettes. *In vitro* and *in vivo* animal studies have shown that the aerosols produced by e-cigarettes, especially those containing nicotine and flavourings, can induce detrimental cellular changes [6, 34, 35]. Several pathophysiological mechanisms have been suggested, including oxidative stress [36, 37], disruption in metabolic pathways [38], exposure to toxic compounds formed during heating of e-liquids [39], decreased NO production [40, 41], and increased pro-inflammatory markers – lactate dehydrogenase (LDH), IL-6 and IL-8, and cytoplasmic Ca^{2+} [42–44]. Lung inflammation is central in the pathogenesis of most chronic lung diseases. In a prospective study of individuals requiring surgery to repair a primary spontaneous pneumothorax, e-cigarette smoking was associated with a significant reduction in mRNA related to the extracellular matrix, and increased genes related to ciliary function [45]. Thus, cellular processes caused by e-cigarette smoking have the potential to exacerbate associated clinical conditions, including COPD, asthma, interstitial lung disease and neoplasms [46].

In a study in mice, even a short-term exposure to e-cigarette vapour, particularly the combination of PG/VG and nicotine, promoted tumour cell migration and more aggressive metastases [34]. In human buccal epithelial cells, hypermethylation of cytosine-phosphate-guanine sites was found in cigarette and e-cigarette smokers; these changes were predictive of lung cancer development [47]. Review of the literature found strong scientific evidence for the oncogenesis of e-cigarettes [48, 49]. Recently, a case–control study found that dual users had a four-fold higher risk of lung cancer compared to cigarette smoking only [50]. In another study, switching to e-cigarettes after cigarette smoking cessation was associated with a higher risk of lung cancer [51]. These studies (*in vitro*, ex-cigarette smokers and dual smokers) suggest that e-cigarettes may increase the risk of lung cancer. However, it would likely take years of longitudinal epidemiological studies to reliably assess the risk of isolated e-cigarette smoking [46].

Each of the parameters evaluated is discussed in the following sections.

Symptoms

Out of 30 participants in the study, three experienced mild, transient symptoms – two reported dizziness and one reported palpitations. A previous study with 64 subjects found that symptoms such as cough, sore throat and palpitations were more common after smoking e-cigarettes containing 11 mg of nicotine, whereas dizziness was more frequent in nonsmokers using nicotine-free e-cigarettes [52]. The relatively low nicotine intake in our study might explain the fewer reported symptoms, although inter-subject variability could also play a role.

Vital signs

We found significant cardiorespiratory changes after smoking. Similarly, in a previous study from our group, a single session of water-pipe smoking led to increases in systolic BP, diastolic BP and in HR, albeit in a larger magnitude (a mean rise of 12.5 mmHg, 8.1 mmHg and 15 beats·min^{-1} with water-pipe *versus* 5.5 mmHg, 4.5 mmHg and 8 beats·min^{-1} with e-cigarettes, respectively) [53]. In the study mentioned earlier, HR increased only with e-cigarettes containing nicotine [52]. In a systematic review of 13 trials, BP increased consistently immediately to several hours after smoking e-cigarettes containing nicotine; variable changes were found with nicotine-free e-cigarettes, and no changes with placebo [54]. The increased HR observed herein was more pronounced than reported with cigarette smoking. In a meta-analysis, cigarette smoking was associated with mildly increased HR (1.93 beats·min^{-1}, 95% CI: 0.97–2.89) [55].

These haemodynamic changes were attributed to nicotine, which activates the sympathetic nervous system, increasing HR, BP and myocardial contractility [53, 54]. Other suggested non-nicotine-mediated mechanisms include direct endothelial dysfunction and oxidative stress caused by ultrafine and fine particles in e-cigarette aerosol [54].

Pulmonary function tests

We did not observe significant changes in spirometry values after 30 min of *ad libitum* e-cigarette smoking. Meo *et al.* [40] found that chronic (>6 months) daily e-cigarette smokers had lower spirometry values compared to matched controls. Polosa *et al.* [56] followed past smokers, who switched to e-cigarettes 3 months after quitting smoking, and found decreased forced expiratory flow at 25–75% of FVC, indicating peripheral airway obstruction. Impulse spirometry system (IOS) is considered as a more sensitive measure to evaluate peripheral small airway obstruction. Several studies found increased airway resistance after e-cigarette smoking [57, 58]. In the short-term, Vardavas *et al.* [41] found that a short session (only 5 min) of e-cigarette smoking led to an increase in peripheral airway resistance and impedance, with no change in spirometry values. Lappas *et al.* [57] also assessed the acute effect of a 5-min session of e-cigarette smoking, and similar changes were found. As most e-cigarette smokers use it for a longer duration, we chose to assess spirometry parameters after 30 min. The lack of change in our study may reflect the single session, short duration of smoking, low intake of nicotine or the small sample size. Other measurements of peripheral airway resistance and impedance with IOS, different contents of nicotine and longer duration of smoking should be carried out.

FeNO

We found a decrease of 1.3 ppb in FeNO after e-cigarette smoking. Our results are in concordance with several previous studies. Water-pipe smoking led to a smaller decrease in FeNO (0.44 ppb) [53]. Marini *et al.* [59] found a decrease of 3.2, 2.7 and 2.8 ppb for e-cigarettes without nicotine, with nicotine and for conventional cigarettes, respectively. Even 5 min of e-cigarette smoking was sufficient to decrease FeNO [41]. In a group of 54 participants (27 healthy and 27 asthmatic participants) 5 min of e-cigarette smoking led to a significant decrease in FeNO; in healthy smokers, values returned to baseline within 15 min, while in mildly asthmatic participants only 30 min after smoking [57]. Similarly to cigarettes and water-pipe smoking, possible mechanisms for FeNO reduction include downregulation of endothelial and inducible nitric oxide (NO) synthase, as well as increased consumption of NO in the airways [53, 59].

VOCs

To the best of our knowledge, this is the first study evaluating the effect of e-cigarettes on VOCs using e-nose. We found a significant difference in the breath print of VOCs, with increased resistance after smoking (implying increased inflammation). An increasing number of studies have shown the potential of e-nose in various respiratory diseases, such as asthma, COPD, pneumonia, interstitial lung disease and lung cancer, as well as several non-respiratory conditions, such as breast and colon cancer, liver failure and diabetes [27, 60]. In a study evaluating 24 healthy smokers, VOC profile changed significantly after cigarette smoking and was more prominent at 30 and 60 min than 5 min after smoking. The change was attributed to post-cigarette inflammation [27].

Inflammatory cytokines

We did not find significant changes in EBC cytokines after e-cigarette smoking; blood levels of the cytokines analysed were below the detection level. As mentioned earlier, several *in vitro* and *in vivo* studies found that e-cigarette exposure led to increased inflammatory markers, including cytokines. In humans, the results are variable. KOTOULAS *et al*. [61] found that a short session (5 min) of e-cigarette smoking led to a significant increase in IL-10 and TNF-α in asthmatic smokers, with no changes in healthy smokers. CHAUMONT *et al*. [62] found that 5 days after cessation of vaping, increased levels of club cell protein-16 in bronchoalveolar lavage (BAL) were indicative of decreased lung inflammation. SINGH *et al*. [63] found elevated oxidative stress and inflammatory biomarkers in urine samples, and elevated inflammatory biomarker in saliva samples of e-cigarette smokers compared to controls. In contrast, SONG *et al*. [64] did not find significant differences between vaping for 4 weeks and controls in terms of BAL inflammatory cells or cytokines. In our study, cytokines in blood and EBC were evaluated shortly after smoking; a longer time may be needed for notable changes. We assessed a set of five cytokines; a set with different cytokines may have resulted in appreciable changes after smoking.

Limitations

The main limitation of our study is the small sample size. The absence of significant changes in some parameters may be due to Type II errors. We did not have a control group (non-users) to compare baseline values of the parameters evaluated (BP, RR, cytokines, FeNO and VOC signature). The participants were instructed to use the e-cigarette for 30 min, but we did not control for the number of puffs or the volume of smoking, and we did not measure nicotine levels. Owing to technical problems, VOCs were evaluated only for 20 participants. Blood cytokine levels were below the detection level, thus changes after smoking could not be evaluated. Other more sensitive parameters, such as airway resistance or impedance, were not measured.

Conclusion

In conclusion, our study found significant short-term effects of a single e-cigarette smoking session. The changes are in concordance with previous findings following cigarette and water-pipe smoking. The observed acute effects, together with the well-known chronic risks, highlight the importance of effective regulation of e-cigarettes Public health measures should focus on reducing e-cigarette smoking, particularly among adolescents.

Acknowledgements: The authors acknowledge Ronit Leiba from the Medical Statistics Unit, Rambam Health Care Campus for the statistical help, and Hilla Azulay-Debby from the Technion Rappaport's Faculty of Medicine, for the help with cytokine analysis.

Provenance: Submitted article, peer reviewed.

This study is registered at Digitrials@moh.gov.il as MOH_2024-09-19_013654

Ethics statement: The study was approved by the Institutional Review Board (RMB-0556-19).

Author contributions: S. Rizik and R. Bar-Yoseph: equal contribution; literature search, data collection and analysis, and manuscript preparation. M. Hanna: respiratory technician; responsible for study evaluations. F. Hakim: study design and data analysis. Y. Broza: analysis of electronic nose (e-nose) data and manuscript draft preparation. A. Sader: data collection and manuscript preparation. Y. Toukan: study design and data collection. H. Haick: analysis of e-nose data and review of manuscript. L. Bentur: data analysis and review of manuscript. M. Gur: responsible for study design, analysis of data, manuscript preparation and review.

Conflict of interest: The authors declare no conflicts of interests.

Support statement: The study was supported by the Israel Cancer Association. Funding information for this article has been deposited with the Crossref Funder Registry. This research received partial funding from the European Union's Horizon Europe research and innovation programme under grant agreement no. 101096473.

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