Are we with e-cigarette as a friend or against it as a foe?

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Background and aim Cigarette smoking is the most important cause of avoidable premature mortality in the world, and quitting is known to reduce the risk of fatal diseases. Electronic cigarettes (e-cigarettes) are becoming increasingly popular, especially among younger adults; they may be effective aids to smoking cessation. Despite the increasing prevalence of e-cigarette use, little is known about their real-world use. The major concerns include the nicotine content and the potential harm due to the high concentrations of propylene glycol, chemicals, and other compounds found in the e-cigarette vapor. To our knowledge, there are no data on the health effects of acute use of nicotine-free e-cigarettes. The aim of this study is to evaluate the immediate effect of e-cigarette vapors on airway mechanics.

Participants and methods Forty apparently healthy never-smokers or light smokers were divided into two groups. The first group was instructed to 'vape' e-cigarettes with a 12-mg nicotine-filled cartridge, and the second group was asked to 'vape' e-cigarettes with an empty cartridge. Pulmonary function tests were assessed before and after 'vaping'.

Results There was a significant increase in peripheral airway resistance of the first group, in which individuals vaped a nicotine-filled cartridge.

Conclusion There is potential for more permanent changes in lung function with long-term exposure to e-cigarettes, as with cigarette smoking.

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Introduction

Smoking is a major public health problem worldwide, and it is considered by the WHO to be one of the leading causes of preventable deaths [1]. Concerns regarding the morbidity and mortality associated with smoking led to the WHO Framework Convention on Tobacco Control (FCTC), which was implemented on 27 February 2005 and was ratified by 177 countries, including Egypt [2].

Studies of smokers have shown that many would not smoke if they had their time again, and that 60–70% wanted to quit smoking. However, without assistance, most of those who attempt to quit smoking relapse, and only 4% remain abstinent at 1 year [3].

One of the most important factors that make smoking cessation more difficult is nicotine dependence. In this context, the electronic cigarettes (e-cigarettes) have emerged as a form of nicotine replacement therapy. The e-cigarettes were developed by Chinese pharmacist Hon Lik and were patented in 2003. Although there is a lack of data on their efficacy and safety, e-cigarettes are widely available for purchase on the internet, as well as being sold directly to consumers in various countries [4]. Currently, more than 2500 brands of e-cigarettes are sold worldwide [5].

As tobacco leaves are not combusted in this process, manufacturers claim that e-cigarettes are not cigarettes, using them is not smoking, and that the resulting vapor is free of the 4000 toxic chemicals and carcinogens [6]. They called the process of using e-cigarettes 'vaping' and not smoking. Nicotine is delivered by most, but not all, e-cigarette products. Most e-liquids contain 24, 18, 12, or 6^0mg/ml nicotine and are qualified by the manufacturers as high, medium, or low nicotine strength. The overall total amount of nicotine in the e-liquid depends on the size of the refill vial; for example, a 10-ml bottle of 24^0mg/ml contains a total of 240^0mg of nicotine. Blood levels of nicotine are generally lower from e-cigarette use than from conventional cigarettes, but users of some e-cigarette tank systems with more powerful batteries that heat liquids to higher temperatures may achieve blood nicotine levels comparable to those of cigarette smokers [7].

Usually, chemical additives and flavors (such as various brands of tobacco, chocolate, coffee, mint, or fruit) are also introduced into the cartridge [8]. Propylene glycol is the chemical that is added to generate artificial 'smoke' to simulate the appearance of using a 'real' cigarette. Data on the harmful effects of inhaling e-cigarette vapors, notably propylene glycol, are scarce. Eye irritation, upper airway irritation, cough, and mild

airway obstruction have been reported to occur in individuals without asthma even after short-term exposure [9].

For the time being, there is much debate about the potential benefits and risks of e-cigarettes in various capacities [10]. On one hand, they may be a valuable smoking cessation aid and contribute to the momentum of existing tobacco control programs. On the other hand, there are concerns about their safety, health risks, and possibility to renormalize and reglamorize smoking to vulnerable youth and developing world populations, thereby undermining the success of tobacco control activities [11].

Unfortunately, spirometric assessment is not sensitive for early small airway dysfunction, and extensive small airway disease may exist before it is detectable with conventional spirometric indices [12]. An understanding of the acute and early adverse effects of e-cigarettes therefore requires a more comprehensive assessment of pulmonary function than spirometry alone, such as the additional measurement of lung volumes and small airway function [13]. Among all the lung function tests, impulse oscillometry system (IOS) measurements have one of the highest rates of reproducibility and sensitivity to detect even the earliest pathophysiological changes in the patient's pulmonary mechanics and require the minimal physician subjectivity to obtain the correct measurement that corresponds to the patient's true pulmonary mechanical status. In contrast to traditional spirometry, IOS is a noninvasive tool, it is rapid, relatively effort-independent, it requires only passive patient cooperation, and it involves spontaneous tidal breathing [14]. It has been used in clinical trials to diagnose obstructive lung disease, and it has been shown to be superior to spirometry measurements during pulmonary assessment [15]. It is able to assess both small and large airway reactance, as well as resistance and capacitance of the lung. It is also helpful in assessing asymptomatic individuals with early, mild, and even transient peripheral airway dysfunction when spirometric results are still unchanged [16]. When previous researchers used IOS to assess airway dynamics in tobacco smokers, they documented significantly higher lung resistances at 5 and 20^0Hz compared with nonsmokers [17].

Aim

The aim of the present study is to evaluate the immediate effect of e-cigarette vapors on airway mechanics.

Patients and methods

The study included 40 apparently healthy individuals, who had either tried smoking before but were not smokers or were light smokers (38 male and two female), with a mean age of 29.9 years (range: 21–55 years). There were seven nonsmokers and 33 light smokers in this study. Light smoking is defined as smoking index less than 5 pack-years [18]. All the studied individuals have normal pulmonary function test (either spirometric, plethysmographic, or impulse oscillometric) before vaping the e-cigarettes. Exclusion criteria included any lung disease, including history of asthma, bronchial hyper-reactivity, acute illness during the previous 8 weeks, current use of any medications, or abnormal baseline pulmonary function before vaping e-cigarettes. The study was approved by Faculty of Medicine, Fayoum University Ethical Committee. All enrolled patients provided written informed consent before the study procedures. All smokers were instructed not to smoke at least 6^0h before the examination.

We divided them randomly (random selection from the studied group and in a different session) into two equal groups: individuals in group A, or the studied group ($n=20$), were asked to vape e-cigarettes with a 12-mg nicotine-filled cartridge for 15^0min as they would usually smoke. The second group was group B or the control group ($n=20$), in which the individuals were asked to vape e-cigarettes with an empty cartridge (without inclusion of the e-cigarette cartridge) for 15^0min as they would usually smoke. Therefore, e-cigarette vapor was neither created nor inhaled. The e-cigarette brands were (NOBACCO e-cigarettes, black line; NOBACCO) with the same nicotine concentration (12^0mg) as reported by the manufacturer. Pulmonary function tests were assessed before and after (30^0min before and after) e-cigarette vaping.

Pulmonary function tests

Spirometric and plethysmographic indices were assessed by constant volume plethysmography (Vmax 6200; Sensormedics, Bilthoven, The Netherlands). The following indices were recorded: forced vital capacity (FVC) (l), forced expiratory volume in the first second (FEV1) (l), FEV1/FVC ratio (FEV1%), peak expiratory flow (PEF) (l/s), forced expiratory flow at 25–75% (FEF25–75) (l/s), total lung capacity (TLC) (l), residual volume (RV) (l), specific airway conductance [1/(kPs × s)] (sGaw), and airway resistance (kPs/l/s) (Raw) [18]. The procedure was performed according to the recommendation of the

American Thoracic Society/European Respiratory Society Task Force guidelines [19].

The IOS apparatus generates pressure oscillations at the mouth that propagate through movement of the air column in the conducting airways, which is followed by distension and recoil of the elastic components of lung tissues and creation of backpressure [20]. Low-frequency signals (5^0Hz) penetrate out to the lung periphery, whereas high-frequency signals (20^0Hz) only reach the proximal airways paper [21]. IOS measures pulmonary impedance (Zrs), which comprises pulmonary resistance (energy required to propagate the pressure wave through the airways) and reactance (amount of recoil generated against that pressure wave) [22].

The explanation is because of the fact that lower-frequency oscillations, such as 5^0Hz, travel farther to the lung periphery and provide indices of the entire pulmonary system. Therefore, when either proximal or distal airway obstruction occurs, R5^0Hz (airway resistance at 5^0Hz, in kPa/l/s) and X5^0Hz (airway reactance at 5^0Hz, in kPa/l/s) are increased. Higher-frequency oscillations, such as 20^0Hz, transmit signals only proximally and provide information concerning the central airways. Thus, central airways obstruction will be reflected by an increased R20^0Hz (airway resistance at 20^0Hz, in kPa/l/s). Therefore, disease isolated to the distal airways will increase R5^0Hz to a greater extent than the R20^0Hz. Conversely, disease isolated to the proximal system will be reflected as an equivalent increase in R5 and R20^0Hz [20].

The measurements were carried out according to the instructions provided by the manufacturer (Masterscreen IOS; Erich Jaeger, Hochberg, Germany) [20]. The most relevant measurements of IOS include R5^0Hz (airway resistance at 5^0Hz, in kPa/l/s), which is the resistance in small and large airways, and R20^0Hz (airway resistance at 20^0Hz, in kPa/l/s) (resistance at 15^0Hz) or higher, which is the resistance in larger airways [18]. The whole maneuver lasted for 9 AQ7 we usually start with ISO followed by spirometric and polythesmography tests.

Statistical analysis

Data are expressed as mean ± SD or as frequencies. Two-way ANOVA was applied to the differences observed between basal values and those after smoking a filled or an empty e-cigarette, considering smoking habit and the crossover design as factors. The effects estimated by ANOVA are reported together with their 95% confidence intervals. A P value less than 0.05 is considered statistically significant. All analyses were performed using SPSS for Windows (SPSS Inc., Chicago, Illinois, USA).

Results

The subjects' characteristics are reported in Table 1. All the participants completed the study protocol. Some individuals reported mild adverse events such as dry cough ($n=5$) and throat irritation ($n=3$) when using e-cigarettes. All baseline pulmonary function tests, either spirometric (FEV1, FVC, FEV1/FVC, PEF, and FEF25–75), polythesmographic (TLC, RV, sGaw, and Raw), or impulse oscillometric studies (Z5, R5, R10, X5, X10, X10, X20^0Hz, peripheral R, central R, Fres), showed no statistical difference between smokers and nonsmokers ($P \geq 0.157$).

Table 2 shows changes in pulmonary mechanics before and after vaping of an e-cigarette. Using spirometric measures (FVC, FEV1, FEV1/FVC, PEF, FEF25–75), there was no statistically significant differences between mean values before and after vaping in both group A and group B. Using plethysmographic measures as regards lung volumes (TLC and RV), there was no statistically significant differences between mean values before and after vaping in both groups. However, as regards peripheral airway resistance, there was a significant increase in Raw in group A (studied group) by 0.6^0kPa/l (range: 0.5–1.1; $P=0.04$), in contrast to the insignificant increase in group B (control group) ($P=0.21$). SGaw significantly decreased in group A by 0.5^0kP/l (range: 1.2–0.7, $P=0.02$), in contrast to the insignificant decrease in group B ($P=0.17$).

Using IOS as an indicator of pulmonary function among the participants, airway impedance at Z5^0Hz increased in group A by 0.058^0kPa/l/s ($P=0.01$), whereas no significant differences were noted among group B participants ($P=0.32$). Correspondingly, lung resistance in group A also significantly increased at R5 and R10^0Hz by 0.059 and 0.048^0kPa/l/s ($P=0.03$ and 0.04, respectively). Moreover, peripheral pulmonary resistance also significantly increased by 0.048^0kPa/l/s ($P=0.04$), in contrast to insignificant changes in group B.

Discussion

E-cigarettes have been rapidly gaining ground on conventional cigarettes because of their assumed efficiency in reducing tobacco consumption and the

Table 1 Characteristics of participants

	Overall	Smokers	Nonsmoker	*P* value
Sex (male/female)	38/2	33/0	5/2	0.37
Age (mean±SD) (years)	29.9±18.6	34.8±11.8	27.5±13.6	0.29
Weight (mean±SD) (kg)	71.9±11.4	68.7±11.1	71.3±10.7	0.11
Height (mean±SD) (m)	169±10.0	163±7.4	176±8.3	0.09
BMI (mean±SD) (kg/m^2)	24.5±2.5	24.7±3.1	24.3±1.9	0.70
Spirometry				
FVC	4.45	4.41	4.53	0.47
FEV1	3.71	3.45	3.61	0.21
FEV1/FVC	0.83	0.81	0.82	0.31
PEF	8.3	8.2	8.5	0.63
FEF25–75	3.8	3.6	3.9	0.15
Plethysmography				
TLC	5.5	5.7	5.3	0.18
RV	1.1	1.3	1.1	0.32
sGaw	1.2	1.1	1.3	0.42
Raw	0.5	0.6	0.5	0.81
ISO (Hz)				
Z5	0.371	0.366	0.375	0.37
R5	0.341	0.342	0.339	0.62
R10	0.324	0.314	0.332	0.51
R20	0.315	0.316	3.10	0.22
X5	−0.921	−0.952	−0.910	0.42
X10	−0.029	−0.027	−0.029	0.11
X20	0.069	−0.072	0.061	0.32
Peripheral R	0.214	0.220	0.211	0.71
Central R	0.183	0.175	0.191	0.47
Fres	13.510	13.217	13.720	0.21

central R, central resistance (kPa/l/s); FEF25–75, forced expiratory flow at 25–75% (l/s); FEV1, forced expiratory volume in the first second (l); Fres, resonant frequency (Hz); FVC, forced vital capacity (l); PEF, peak expiratory flow (l/s); peripheral R, peripheral resistance (kPa/l/s); R, resistance; R10, airway resistance at 10^{0}Hz (kPa/l/s); R20, airway resistance at 20^{0}Hz (kPa/l/s); R5^{0}Hz, airway resistance at 5^{0}Hz (kPa/l/s); Raw, airway resistance (kPa/l/s); RV, residual volume (l); sGaw, specific airway conductance [1/(kPa×s)]; TLC, total lung capacity (l); X, impedance; X, reactance; X10, airway reactance at 10^{0}Hz (kPa/l/s); X20, airway reactance at 20^{0}Hz (kPa/l/s); X5, airway reactance at 5^{0}Hz (kPa/l/s); Z5, airway impedance at 5^{0}Hz (kPa/l/s).

perception of them being less harmful smoking alternatives [23]. Direct confirmation of a reduction in smoking-related diseases from e-cigarette use is not available [24]. Nonetheless, it is feasible to detect early changes in airway function in individuals using e-cigarettes [24].

In the present study, we studied 40 apparently healthy subjects who either tried smoking before but were not smokers or were light smokers (<5 pack-years). All participants had baseline normal pulmonary function tests. We divided them into two equal groups. Group A (the studied group) comprised 20 participants, who were instructed to vape the e-cigarettes with 12-mg nicotine-filled cartridge for 15^{0}min. Group B (the control group) comprised 20 participants who were asked to vape the e-cigarettes with similar frequency, but with empty cartridge included; therefore, vapor was neither created nor inhaled.

The following pulmonary function tests were assessed and compared in both groups before and after vaping the e-cigarettes: dynamic and static lung volumes, expiratory flow rates, airway resistance, and specific conductance. They were assessed by spirometric and plethysmographic examination. Total respiratory resistances were also assessed by IOS.

We did not detect immediate significant changes in the previous tests by the less sensitive respiratory function parameters [including FEV1, FVC, FEV1/FVC (FEV %), PEF, and FEF25–75]. However, by using more

Table 2 Changes in pulmonary mechanics before and after vaping of an e-cigarette

Characteristics	Group A Pre-mean	Group A Post-mean	*P* value	Group B Pre-mean	Group B Post-mean	*P* value
Spirometry						
FVC	4.41	4.39	0.32	4.50	4.49	0.17
FEV1	3.61	3.60	0.52	3.45	3.61	0.31
FEV1/FVC	0.82	0.82	0.61	0.77	0.80	0.51
PEF	8.2	8.3	0.37	3.7	3.7	0.41
FEF25–75	3.6	3.5	0.19	4.6	4.5	0.61
Plethysmography						
TLC	5.6	5.8	0.31	5.7	5.4	0.51
RV	1.3	1.5	0.55	1.2	1.1	0.31
sGaw	1.2	0.7	0.02*	1.3	1.2	0.17
Raw	0.5	1.1	0.04*	0.6	0.7	0.22
ISO (Hz)						
Z5	0.369	0.427	0.01*	0.375	0.381	0.32
R5	0.338	0.397	0.03*	0.340	0.342	0.55
R10	0.325	0.373	0.04*	0.331	0.337	0.21
R20	0.310	0.313	0.11	0.316	0.311	0.32
X5	–0.093	–0.098	0.31	–0.091	–0.093	0.22
X10	–0.027	–0.29	0.41	–0.029	- 0.031	0.25
X20	0.061	0.066	0.33	0.071	0.069	0.31
Peripheral R	0.215	0.263	0.04*	0.211	0.217	0.51
Central R	0.187	0.192	0.35	0.191	0.188	0.71
Fres	12.57	12.67	0.21	13.11	13.19	0.35

central R, central resistance (kPa/l/s); FEF25–75, forced expiratory flow at 25–75% (l/s); FEV1, forced expiratory volume in the first second (l); Fres, resonant frequency (Hz); FVC, forced vital capacity (l); PEF, peak expiratory flow (l/s); peripheral R, peripheral resistance (kPa/l/s); R, resistance; R10^{0}Hz, airway resistance at 10^{0}Hz (kPa/l/s); R20^{0}Hz, airway resistance at 20^{0}Hz (kPa/l/s); R5^{0}Hz, airway resistance at 5^{0}Hz (kPa/l/s); Raw, airway resistance (kPa/l/s); RV, residual volume (l); sGaw, specific airway conductance [1/(kPa×s)]; TLC, total lung capacity (l); X, impedance; X, reactance; X10^{0}Hz, airway reactance at 10^{0}Hz (kPa/l/s); X20^{0}Hz, airway reactance at 20^{0}Hz (kPa/l/s); X5^{0}Hz, airway reactance at 5^{0}Hz (kPa/l/s); Z5^{0}Hz, airway impedance at 5^{0}Hz (kPa/l/s).

sensitive tests, either plethysmography (i.e. sGaw and Raw) or oscillometry (i.e. Z5, R5, R10, R20, X5, X10, and X20^{0}Hz,), we find a minimal, but statistically significant, increase in peripheral airway resistance in group A (studied group), whereas in group B (the control group) in which individuals inhaled vaporless control e-cigarettes did not have any significant changes in airway resistance. As regards central airways (as reflected by R20 and X20^{0}Hz), there was a tendency for an increase; however, this was borderline and not statistically significant.

Lack of a significant effect on airflow obstruction when measured by FEV1, FVC, FEV%, and PEF after short-term e-cigarette use has been also confirmed in a more recent study by Flouris *et al.*[25]. Flouris and colleagues examined the acute impact of active and passive e-cigarette vapor exposure on lung function in 15 smokers and 15 never-smokers. They included spirometric measurements before, immediately after, and 1^{0}h after three exposures: room air, conventional cigarette smoke, and e-cigarette vapor. A 7-day washout period occurred between visits. No change was detected in FEV1 or FEV1/FVC with active or passive e-cigarette exposure. Active conventional cigarette smoke exposure was associated with an acute 7.2% reduction in FEV1/FVC (P=0.001); however, the previous results were contradictory to a study created by Chorti *et al.*[26], who found that short-term passive, but not active, vaping of one e-cigarette resulted in short-term lung obstruction, as assessed by FEV1, FEV1/FVC, and FEF25–75, indicating insufficient inhalation by e-cigarette-naive smokers. They found that short-term (1^{0}h) vaping of e-cigarettes generated a nonsignificant decrease in lung functions.

In the present study, when we used the more sensitive plethysmographic and oscillometric indices, we found a minimal, but statistically significant, increase in peripheral airway resistance in group A (studied group), whereas in group B (the control group), in

which individuals inhaled vaporless control e-cigarettes, we did not find any significant changes in airway resistance. These results were in accordance with other results – for example, Vardavas *et al.*[27], Palamidas *et al.*[28], and Gennimata *et al.*[29].

In the study of Vardavas *et al.*[27], the acute pulmonary effects of using an e-cigarette for 5^0min on pulmonary function tests and exhaled nitric oxide (FENO) among healthy adult smokers was investigated in 30 participants. The authors compared the exposure of e-cigarette smoking (experimental group) with that of using the e-cigarettes without a cartridge (sham exposure group) in a crossover setting. Spirometry was used for lung function measurements to determine FEV1 and FVC, whereas the IOS was applied to measure total respiratory resistance. Although spirometric parameters were not significantly affected, both FENO and IOS detect statistically significant changes. The authors showed that there was a sudden decrease in the FENO level together with an increase in impedance and peripheral airway flow resistance in the experimental group compared with the control group, with no change in values obtained with spirometry. The authors concluded that even short-term e-cigarette smoking causes immediate adverse physiological effects in the lungs.

Palamidas *et al.*[28] studied 60 participants before and after smoking an e-cigarette containing 11^0mg of nicotine (group A), and 10 nonsmoker subjects used e-cigarette cartridges containing nicotine-free vaporizing liquid (group B). Lung functions were assessed before and after vaping of e-cigarette, including lung volumes, Raw, sGaw, and the slope of phase III. As regards group A, they found a significant increase in Raw with a significant decrease in sGaw. A significant increased slope in phase III was shown only in some asthmatic patients of this group. As regards group B, they found a significant increase in Raw and a decrease in sGaw. These changes might be because of the vaporizing liquid but not because of the inhaled nicotine per second.

Gennimata *et al.*[29] studied spirometry, static lung volumes, Raw, sGaw, and the slope of phase III, before and after the use of an e-cigarette for 10^0min. They found an immediate significant increase in Raw, decrease in sGaw, and a significant increase in the slope of phase III.

Our recorded results in the present study about pattern of changes in airway mechanics experienced by subjects using e-cigarettes is very similar to that seen shortly after inhalation of tobacco smoke [30]. The implication is that with long-term exposure to e-cigarettes it is reasonable that, as with cigarette smoking, there is the potential for more permanent changes in lung function.

According to the results of the present study, we hypothesize that the increase in peripheral flow resistance may be attributable to the acute narrowing of the diameter of the peripheral airways, which could be because of either localized mucosal edema, smooth muscle contraction, or secretions [27]. As regards central airway resistance, there was a tendency for an increase; however, this was borderline and nonstatistically significant. It is possible that using an e-cigarette may have a greater impact on peripheral rather than central airways [27].

Conclusion

Smoking an e-cigarette for 15 minutes causes a significant effect on pulmonary mechanics. These data have great importance both from physiological and public health aspects. It clearly demonstrates that the advertisement strategy surrounding e-cigarettes suggesting that this method is associated with no harmful effects is misleading and points out a great need for further studies, strict regulations, and careful assessment of the use of these products.

Uncited references

[31–35]

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Conflicts of interest

There are no conflicts of interest.

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