CHEST

Original Research

TOBACCO CESSATION AND PREVENTION

Short-term Pulmonary Effects of Using an Electronic Cigarette

Impact on Respiratory Flow Resistance, Impedance, and Exhaled Nitric Oxide

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Background: **Debate exists over the scientific evidence for claims that electronic cigarettes (e-cigarettes) have no health-related ramifications. This study aimed to assess whether using an e-cigarette for 5 min has an impact on the pulmonary function tests and fraction of exhaled nitric oxide (FENO) of healthy adult smokers.**

Methods: **Thirty healthy smokers (aged 19-56 years, 14 men) participated in this laboratory-based experimental vs control group study. Ab lib use of an e-cigarette for 5 min with the cartridge included (experimental group, n = 30) or removed from the device (control group, n = 10) was assessed.**

Results: **Using an e-cigarette for 5 min led to an immediate decrease in FENO within the experimental group by 2.14 ppb (*P* = .005) but not in the control group (*P* = .859). Total respiratory impedance at 5 Hz in the experimental group was found to also increase by 0.033 kPa/(L/s) (*P* < .001), and flow respiratory resistance at 5 Hz, 10 Hz, and 20 Hz also statistically increased. Regression analyses controlling for baseline measurements indicated a statistically significant decrease in FENO and an increase in impedance by 0.04 kPa/(L/s) (*P* = .003), respiratory resistance at 5 Hz by 0.04 kPa/(L/s) (*P* = .003), at 10 Hz by 0.034 kPa/(L/s) (*P* = .008), at 20 Hz by 0.043 kPa/(L/s) (*P* = .007), and overall peripheral airway resistance (β, 0.042 kPa/[L/s]; *P* = .024), after using an e-cigarette.**

Conclusions: **e-Cigarettes assessed in the context of this study were found to have immediate adverse physiologic effects after short-term use that are similar to some of the effects seen with tobacco smoking; however, the long-term health effects of e-cigarette use are unknown but potentially adverse and worthy of further investigation.** ***CHEST 2012; 141(6):1400–1406***

Abbreviations: e-cigarette = electronic cigarette; FDA = US Food and Drug Administration; FENO = fraction of exhaled nitric oxide; IOS = impulse oscillometry system; MEF = maximal expiratory flow; PEF = peak expiratory flow; ppb = parts per billion; R5Hz = airway resistance at 5 Hz; R10Hz = airway resistance at 10 Hz; R20Hz = airway resistance at 20 Hz; Z5Hz = airway impedance at 5 Hz

Electronic cigarettes (e-cigarettes) are marketed as potentially reduced tobacco exposure products. The product resembles, but is not, a cigarette in design or function and is marketed as "safer" than a conventional cigarette. However, debate exists over the scientific evidence for the claims that the products have no health-related ramifications. Because e-cigarettes do not contain or burn tobacco, they do not appear to deliver the known toxins found in conventional cigarette smoke.[1-4] Conversely, US Food and Drug Administration (FDA) analyses have indicated that e-cigarettes contain a number of toxins and carcinogens, including tobacco-specific nitrosamines, diethylene glycol, and other components suspected of being harmful to humans.[5]

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Because of the increase in interest regarding e-cigarettes and they claims that they are potentially reduced-exposure product, a nicotine-delivery device,

or a smoking-cessation tool, it is imperative to assess the risks related to alternative nicotine delivery systems to protect public and consumer health.[6-10] Previous research has indicated that smokers have significantly higher lung resistances at 5 Hz and 20 Hz and lower concentrations of fraction of exhaled nitric oxide (FENO)—a noninvasive marker of bronchial inflammation—compared with nonsmokers.[11,12] To date, there is no published evidence of any direct health-related effect of acute physiologic response to using an e-cigarette; thus, the aim of the current study was to investigate whether using an e-cigarette ab lib for 5 min could affect respiratory mechanics and FENO within the context of an experimental vs control group study design.

MATERIALS AND METHODS

Subjects

Our study sample was composed of 30 adults (14 men, 16 women) of a mean age of 34.8 years (range 19-56 years) recruited from a community setting in Athens, Greece. All subjects were smokers with a minimum pack-year index of 5. Exclusion criteria included any chronic and/or lung disease (including history of bronchial asthma or bronchial hyperreactivity), acute illness during the previous 2 weeks, current pregnancy or lactation, or current use of any medication. All subjects were instructed not to eat or drink any kind of beverages for at least 2 h prior to the examination and to avoid smoking during the prior 4 h.

Study Design

A laboratory-based intervention study design was applied, within which two groups were created: the experimental group (n = 30) and the control group (n = 10). The 10 participants of the control group were randomly selected from the experimental group and, in a different session, participated in the experimental group. The role of using an e-cigarette was assessed through (1) comparing the changes noted among control group participants with changes noted among experimental group participants after the intervention (intragroup comparison), and (2) comparing pre vs post respiratory function among experimental group participants (intergroup comparison). The subjects enrolled in the experimental group were instructed to use the e-cigarette ad lib for 5 min as they would usually smoke. The control group subjects were asked to use the e-cigarette with similar frequency, but without the e-cigarette cartridge included; therefore, e-cigarette vapor was not created nor inhaled. As vapor was not formed in the control setting, blinding was not possible.

The ethics committee of the Hellenic Anti-Cancer Society, Athens, Greece, provided ethics approval (protocol number: 67-7/10/10). Each subject read and signed a written and an informed consent form prior to study enrollment.

e-Cigarette Usage and Chemical Composition

The e-cigarettes provided to the subjects were of the same brand (NOBACCO e-cigarettes, black line) and of the same nicotine concentration. The e-cigarette itself was composed of a steel shell, a microprocessor powered by a lithium battery, a filter, and a removable (and renewable) cartridge. Three types of cartridges were available in the market for this e-cigarette, and we chose the medium one (NOBACCO MLB-MED filter), for which the manufacturer reports a measured dose of 11 mg of nicotine. Further information on the e-cigarette used in the current study can be found on the manufacturer's website.[13] Moreover, the e-cigarette cartridge selected for use in the experimental group has been analyzed for its chemical composition by the National Center for Scientific Research, Demokritos, in Greece.[14] According to their analysis, the cartridge contained propylene glycol (α-propylene glycol or 1,2-propanediol) in a concentration > 60%, linalool (3,7-dimethylocta-1,6-dien-3-ol) in a concentration < 5%, nicotine (< 10%), tobacco essence (< 5%), and methyl vanillin (4-hydroxy-3-methoxybenzaldehyde) at < 1%; no polyaromatic hydrocarbons were detected.[14]

Lung Function Assessment

Exhaled Nitric Oxide: Measurements were made in a sitting position with a nose clip using an Eco Medics AG CLD 88 Series chemiluminescence analyzer equipped with a Spiroware 3.0 software program. The patient was instructed to inhale as deeply as possible to total lung capacity through a filter mouthpiece and consecutively exhale at a mouth flow rate of 50 mL/s for 10 s. The exhalation rate was held steady by applying a constant positive pressure (10 cm H_2O) through a resistance factor while coaching the patient to exhale steadily using visual stimulation on the system screen. Three consecutive trials were performed with a 30-s interval. Results were measured in parts per billion (ppb).

Dynamic Lung Volumes: Flows and lung volumes were measured in the sitting position, using a Jaeger MasterScreen spirometry system (heated pneumotach, resistance < 0.05 kPa/[L/s] at 10 L/s), with the highest FEV_1 recorded in line with pulmonary guidelines. Spirometry was measured according to the recommendations of the American Thoracic Society/European Respiratory Society task force guidelines.[15] FEV_1, FVC, FEV_1%, peak expiratory flow (PEF), and maximal expiratory flow (MEF) at 25%, 50%, and 75% of vital capacity were measured. Each maneuver was repeated for at least three technically acceptable forced expiratory flow curves. In order to attain the best results (the ones that represent the true status of the patient's respiratory system) from the basic pulmonary measurements (spirometry and dynamic lung volumes), the following criteria were established: (1) each measurement was repeated at least three times to confirm the proper collaboration of the patient and give the patient the chance to familiarize themselves with each process, and (2) the results of

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each measurement were reproducible (within 10% of the SD after three maneuvers).

Total Respiratory Resistances: The actual values of magnitude of respiratory impedance at 5 Hz (Z5Hz); respiratory resistance at 5, 10, and 20 Hz (R5Hz, R10Hz, and R20Hz, respectively); reactance at 5, 10, and 20 Hz; and resonant frequency were assessed with the use of an impulse oscillometry system (IOS). IOS is a noninvasive, easy examination that requires minimum, if any, compliance from the subject. During IOS measurements, a small loudspeaker creates a pulse-shaped pressure wave in front of the mouth, with alternate pulses (at different cycles per second [ie, 5 Hz, 10 Hz, 25 Hz]). The measurements were carried out according to the operating instructions provided by the manufacturer (Viasys Jaeger Masterscreen IOS system). After occluding the nose of the subject, he/she was instructed to breathe normally through a mouthpiece attached to the IOS system while seated. Among all the lung function tests, IOS measurements have one of the highest rates of reproducibility and sensitivity (as to detect even the earliest of pathophysiologic 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.[16,17] Patients followed the instructions, and no discomfort or failure to comply was noticed. The whole maneuver lasted for 90 s and was repeated for verification. Results were measured in kPa /(L/s).

Statistical Analysis

The Kolmogorov-Smirnov tests were applied to assess the normality of the data; all measurements were found to be normally distributed, with the exception of FENO. Pre vs post measurements, sex differences, and experimental vs control conditions were assessed through bivariate analyses. The paired Student *t* test was performed among parametric data, whereas nonparametric data were compared with the Wilcoxon signed rank test. Pearson correlations were applied to assess the correlations between the pre and post respiratory tests. Results are presented as means and 95% CIs. To control simultaneously for intervention group (experimental vs control) and baseline respiratory characteristics, additional linear regression analyses were performed; R^2 values, β coefficients, and 95% CI of the β are provided. The statistical analysis was performed with the statistical package PASW 18.0 (SPSS, Inc).

RESULTS

The descriptive characteristics and baseline pulmonary functional status of participating subjects are depicted in Table 1. Differences in baseline respiratory function, IOS, or FENO were not identified when stratified by group (experimental vs control), whereas when stratified by sex, female participants were found to have a lower FEV_1, FVC, PEF, MEF at 50% of vital capacity, and MEF at 75% of vital capacity; however, baseline FENO concentrations and IOS measurements were not found to differ.

Table 2 depicts the changes in FENO and respiratory mechanics before and after the use of an e-cigarette (experimental group) or a sham e-cigarette (control group). In all cases, the internal pre and post measurements per participant were highly correlated, whereas no differences between basic pulmonary measurements (data not shown) were identified between the two groups. In regard to pulmonary oxidative stress, our findings indicated that FENO within the experimental group decreased by 16% (by 2.14 ppb from 13.02 ppb to 10.89 ppb, $P = .005$) after the use of an e-cigarette, whereas FENO concentrations were not found to change within the control group (from 8.76 ppb to 8.75 ppb, $P = .859$). An additional sensitivity analysis among the 10 pairs of experimental group participants who also participated in the control group was performed and indicated a statistically significant decrease in FENO, by 1.69 ppb (from 8.76 ppb to 7.07 ppb, $P = .002$), after using an e-cigarette. Using IOS as an indicator of pulmonary function among the study participants, airway impedance at Z5Hz increased in the experimental group by 0.033 kPa/(L/s) (95% CI, 0.016-0.050 kPa/[L/s], $P < .001$), whereas no differences were noted among control group participants (mean difference of −0.002 kPa/[L/s]; 95% CI, −0.010 to 0.006 kPa/[L/s]; $P = .591$). Correspondingly, lung resistance in the

Table 1—*Baseline Characteristics and Respiratory Function of Study Participants by Sex*

Characteristic	Female	Male	*P* Value[a]
No.	16	14	
Age, y, mean ± SD	36 ± 11	33 ± 11	.473
Spirometry			
FVC, L	3.64	5.45	.001
FEV_1, L	3.02	4.33	.001
PEF, L/s	1.50	1.84	.001
MEF_{25}, L/s	3.93	5.08	.293
MEF_{50}, L/s	6.04	8.35	.050
MEF_{75}, L/s	3.64	5.45	.001
MMEF, L/s	3.16	4.10	.056
FENO, ppb	12.3	13.8	.689
IOS			
Z5Hz, kPa/(L/s)	0.409	0.339	.088
R5Hz, kPa/(L/s)	0.399	0.329	.072
R10Hz, kPa/(L/s)	0.349	0.296	.102
R20Hz, kPa/(L/s)	0.318	0.278	.176
X5Hz, kPa/(L/s)	−0.101	−0.079	.314
X10Hz, kPa/(L/s)	−0.034	−0.015	.214
X20Hz, kPa/(L/s)	0.052	0.076	.071
Peripheral R, kPa/(L/s)	0.253	0.189	.069
Central R, kPa/(L/s)	0.224	0.168	.094
Fres, Hz	14.116	11.587	.098

FENO = fraction of exhaled nitric oxide; Fres = resonant frequency; IOS = impulse oscillometry system; MEF = maximal expiratory flow; MEF_{25} = maximal expiratory flow at 25% of vital capacity; MEF_{50} = maximal expiratory flow at 50% of vital capacity; MEF_{75} = maximal expiratory flow at 75% of vital capacity; MMEF = maximal midexpiratory flow; PEF = peak expiratory flow; ppb = parts per billion; R = resistance; R5Hz = airway resistance at 5 Hz; R10Hz = airway resistance at 10 Hz; R20Hz = airway resistance at 20 Hz; X5Hz = airway reactance at 5 Hz; X10Hz = airway reactance at 10 Hz; X20Hz = airway reactance at 20 Hz; Z5Hz = airway impedance at 5 Hz.

[a]*P* values based on paired Student *t* tests for all other than FENO performed with Wilcoxon signed rank test. $P < .05$ classified as statistically significant.

Table 2—*Baseline Characteristics by Group and Subsequent Intersubject and Intergroup Changes (Pre vs Post) in FENO and Flow Resistance (IOS) Following Use of an e-Cigarette*

Characteristic	Group	No.	Pre-Mean	Post-Mean	Mean Difference	95% CI of the Mean Difference, Lower − Upper	Pre vs Post *P* Value[a]	Experimental vs Control *P* Value[b]
FENO, ppb	Experimental	29	13.02	10.89	−2.14	−3.53 to -0.74	.005[c]	.040[c]
	Control	10	8.76	8.75	−0.01	−0.13 to 0.11	.859	
Flow resistance								
IOS Z5Hz, kPa/(L/s)	Experimental	30	0.376	0.409	0.033	0.016 to 0.050	< .001[c]	.003[c]
	Control	10	0.418	0.416	−0.002	−0.010 to 0.006	.591	
IOS R5Hz, kPa/(L/s)	Experimental	30	0.367	0.397	0.031	0.014 to 0.048	.001[c]	.008[c]
	Control	10	0.405	0.402	−0.003	−0.012 to 0.006	.468	
IOS R10Hz, kPa/(L/s)	Experimental	30	0.325	0.353	0.029	0.013 to 0.045	.001[c]	.020[c]
	Control	10	0.353	0.354	0.001	−0.008 to 0.010	.811	
IOS R20Hz, kPa/(L/s)	Experimental	30	0.299	0.329	0.030	0.010 to 0.050	.005[c]	.054
	Control	10	0.323	0.322	−0.001	−0.010 to 0.008	.811	
IOS X5Hz, kPa/(L/s)	Experimental	30	−0.091	−0.101	−0.010	−0.023 to 0.003	.122	.187
	Control	10	−0.095	−0.092	0.003	−0.006 to 0.011	.468	
IOS X10Hz, kPa/(L/s)	Experimental	30	−0.025	−0.027	−0.002	−0.010 to 0.006	.559	.432
	Control	10	−0.036	−0.033	0.003	−0.004 to -0.011	.394	
IOS X20Hz, kPa/(L/s)	Experimental	30	0.063	0.066	0.003	−0.008 to 0.015	.556	.450
	Control	10	0.055	0.053	−0.002	−0.009 to 0.005	.555	
IOS peripheral R, kPa/(L/s)	Experimental	30	0.223	0.248	0.025	0.001 to 0.050	.050[c]	.043[c]
	Control	10	0.230	0.229	−0.001	−0.009 to 0.007	.780	
IOS central R, kPa/(L/s)	Experimental	30	0.198	0.218	0.020	−0.006 to 0.047	.130	.221
	Control	10	0.211	0.215	0.004	−0.005 to 0.013	.343	
IOS Fres, Hz	Experimental	30	12.94	12.48	−0.457	−1.720 to 0.806	.466	.513
	Control	10	13.75	14.02	0.270	−0.541 to 1.079	.472	

e-cigarette = electronic cigarette. See Table 1 legend for expansion of other abbreviations.

[a]*P* values assessed within groups (pre vs post usage).

[b]*P* values assessed between groups (experimental vs control).

[c]Significant.

experimental group also increased at R5Hz, R10Hz, and R20Hz by an average of 0.031 kPa/(L/s) (95% CI, 0.014-0.048 kPa/[L/s]), 0.029 kPa/(L/s), (95% CI, 0.013-0.045 kPa/[L/s]), and 0.030 kPa/(L/s), (95% CI, 0.010-0.051 kPa/[L/s]), respectively. Moreover, peripheral pulmonary resistance also increased from 0.22 kPa/(L/s) to 0.25 kPa/(L/s) ($P = .05$). Similar statistical results to those previously mentioned were identified through the intergroup comparison (mean change in control vs mean change in experimental group) as seen in Table 2. Stratifying the experimental vs control group analysis by sex did not alter the direction or statistical association of the above findings. Pulmonary function assessed via spirometry did not change in either group (data not shown).

Subsequently, a linear regression analysis was performed to assess the role of using an e-cigarette on the assessed respiratory outcomes, taking into account the baseline measurement of each participant and

Table 3—*Regression Analysis on the Effect of Using an e-Cigarette on FENO and Airway Flow Resistance (IOS), Controlling for the Participants' Baseline Measurements*

Variable	R^2	β	95% CI	*P* Value[a]
FENO, ppb	0.950	−2.194	−4.038 to −0.350	.021[b]
IOS Z5Hz, kPa/(L/s)	0.991	0.040	0.015 to 0.065	.003[b]
IOS R5Hz, kPa/(L/s)	0.991	0.040	0.015 to 0.065	.003[b]
IOS R10Hz, kPa/(L/s)	0.990	0.034	0.009 to 0.058	.008[b]
IOS R20Hz, kPa/(L/s)	0.981	0.043	0.012 to 0.074	.007[b]
IOS peripheral R, kPa/(L/s)	0.952	0.042	0.006 to 0.078	.024[b]
IOS central R, kPa/(L/s)	0.934	0.034	−0.003 to 0.071	.069

See Table 1 and 2 legends for expansion of abbreviations.

[a]Each value represents a separate linear regression model adjusting for the group (control vs experimental) and the relative baseline measurement (pre vs post).

[b]Significant.

the group to which they were allocated. The key findings are depicted in Table 3, strengthening the results identified through the bivariate associations, as the changes noted in respiratory function were even greater once we controlled for the participants' baseline responses. It is noteworthy that peripheral flow resistance was found to increase approximately 18% after use of the e-cigarette (by 0.042 kPa/[L/s]), whereas flow resistance at R5Hz, R10Hz, and R20Hz increased by 0.040 kPa/(L/s), 0.034 kPa/(L/s), and 0.043 kPa/(L/s), respectively. Peripheral resistance overall increased by 0.042 kPa/(L/s) ($P = .024$), whereas a tendency for overall central airway resistance was noted; however, this difference was borderline nonstatistically significant (β, 0.034 kPa/[L/s]; 95% CI, −0.003 to 0.071; $P = .069$).

Discussion

To our knowledge, this is the first study to find a physiologic response after inhaling from an e-cigarette. According to our findings, 5 min of use was sufficient to lead to an increase in lung flow resistance over a range of frequencies and was related to a decrease in FENO concentrations.

Impulse oscillometry as a methodologic approach has been used previously in clinical trials, can be used to diagnose obstructive lung disease, and has been shown to be superior to spirometry measurements during pulmonary assessment.[18-21] This is verified by the fact that e-cigarette usage was associated with increased flow resistance even though spirometry-assessed lung function was deemed normal, a finding corroborated by the fact that IOS can detect oncoming pathophysiologic changes of the respiratory system before spirometry.[20] Indeed, it has been demonstrated that changes in flow resistance precede changes in PEF and FEV_1 in experimentally induced airway obstruction, and it is possible that the changes we note in this study may indicate a similar preliminarily health effect.[21] We must state, however, that while the differences within our study are of statistical significance, the clinical changes may be too small to be of major clinical importance (ie, to induce dyspnea or breathing difficulties). However, these measurements were performed after only 5 min of ad lib e-cigarette use. A normal consumer would use the product likely several times a day; thus, the clinical impact might be greater. We hypothesize that the increase in peripheral flow resistance is attributable to the acute narrowing of the diameter of the peripheral airways, which could be due to either localized mucosal edema, smooth muscle contraction (and bronchospasm), or secretions. In the regression analysis, there was a tendency for central airway resistance to increase; however, this was borderline nonstatistically significant. It is possible that increasing the study's sample size might have increased the statistical significance, or we might hypothesize that using an e-cigarette may have a greater impact on peripheral rather than central airways.

A strong point of our findings was that e-cigarette use was associated with an immediate decrease in FENO concentrations. Nitric oxide is a gaseous mediator that has an important role in several physiologic processes in the respiratory tract, including vascular regulation, neurotransmission, host defense, and cytotoxicity.[22] Nitric oxide is an additional marker that has been implicated in the pathophysiology of airway diseases associated with smoking, is strongly correlated with eosinophilic inflammation and bronchial hyperreactivity, and has become an established marker for assessing oxidative stress, indicating the immediate effect e-cigarette usage might have on pulmonary homeostasis.[23-26]

As no standard definition of electronic nicotine delivery system exists, and as different manufacturers use different designs and incorporate a range of ingredients, there is limited evidence on the actual constituents of each brand. Although we identified the clinical changes in lung function due to electronic nicotine delivery system use, we can only hypothesize on the actual substances (or combination of substances) that could have caused the measured effect. One of the substances that was reported to be included in the e-cigarette we used was propylene glycol (other constituents included linalool, nicotine, tobacco essence, and methyl vanillin), and this could have played a role in the measured respiratory changes. Research has indicated that exposure to propylene glycol can induce respiratory irritation and increase the likelihood of developing asthma.[27,28] However, we cannot rule out the possibility that other constituents could be responsible or act in synergy with propylene glycol to induce the respiratory and oxidative responses that we noted.

This study has significant implications for product regulation and use and indicates a direction for further research. Our results were replicable and differed significantly in the bivariate analysis following exposure both within the experimental group (thus controlling for intersubject differences) and between groups (experimental vs control) and also in the regression analysis while controlling baseline characteristics. Controlling for baseline measurements allowed us to focus on the changes due to using the e-cigarette and not take into account underlying damage due to previous cigarette smoking or lung condition. The performed linear regression analysis furthermore allowed us to estimate the quantitative effects of using a single e-cigarette on mechanical and inflammatory measurable parameters. Moreover, the chemical composition of the cartridges used in e-cigarette

be disclosed; knowledge of the contents enabled this study. However, despite these novel findings, our sample size remains relatively small, and further research is needed to investigate the mechanistic and toxicologic effects of long-term usage, which are potentially adverse and worthy of further investigation.

In conclusion, use of an e-cigarette for 5 min was found to cause an increase in impedance, peripheral airway flow resistance, and oxidative stress among healthy smokers. We must state, however, that although the differences within our study are of statistical significance, the clinical changes may be too small to be of major clinical importance. Notably, because these short-term effects were present even after only very limited usage, and a normal consumer would use the product most likely many times a day, it is possible that if e-cigarette use were a short-term bridge to smoking cessation, the long-term health benefits associated with their use might outweigh the short-term risks; however, this would need to be clarified. The FDA, as well as other international regulatory bodies, should pursue the regulation of the e-cigarette until manufacturers provide scientific evidence to support their claims. Additional research is warranted to obtain concrete evidence of an adverse health outcome.

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Dr Vardavas: contributed to conception of the idea, data analysis, and manuscript preparation.
Dr Anagnostopoulos: contributed to performing laboratory measurements and helping draft the manuscript.
Dr Kougias: contributed to performing laboratory measurements and helping draft the manuscript.
Dr Evangelopoulou: contributed to performing laboratory measurements and helping draft the manuscript.
Dr Connolly: contributed to study design, data interpretation, and manuscript preparation.
Dr Behrakis: contributed to study supervision, study design, data interpretation, and manuscript preparation
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