Original Paper

Immediate effects of second-hand smoke on the mechanics of tidal breathing

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- Respiratory Resistance,
- Respiratory mechanics,
- Impulse Oscillometry,
- Passive smoking,
- SHS

Abbreviations:
ATS/ERS: American Thoracic Society/European Respiratory Society
AX: Reactance Area
BMI: Body Mass Index
COPD: Chronic obstructive pulmonary disease
EBC: Exhaled Breath Condensate
FeNO: Exhaled Nitrogen Oxide
fdr: Frequency Dependence of Resistance
FRC: Functional Residual Capacity
fres: Resonant Frequency
IOS: Impulse Oscillometry
IQR: Inter-quartile range
R5: Resistance at 5 Hz
R10: Resistance at 10 Hz
R20: Resistance at 20 Hz
SD: Standard deviation
SHS: Second-Hand Smoke
10/250: exposure for 10 min. in a 250 μg/m^3 concentration of $PM_{2.5}$
20/250: exposure for 20 min. in a 250 μg/m^3 concentration of $PM_{2.5}$
10/500: exposure for 10 min. in a 500 μg/m^3 concentration of $PM_{2.5}$
20/500: exposure for 20 min. in a 500 μg/m^3 concentration of $PM_{2.5}$
X5: Distal Capacity Reactance at 5 Hz
X20: Reactance at 20 Hz
Z5: Total Impedance at 5 Hz

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ABSTRACT

BACKGROUND: Limited studies have examined the implications of Second-Hand Smoke (SHS) on lung function; majority used traditional diagnostic lung function tests requiring forced respiratory manoeuvres. Aim of our study was to assess the immediate effects of exposure to SHS on the respiratory mechanics during tidal breathing. **METHODS:** 20 healthy non-smokers 18-45-years-old participated in four exposure sessions; 10 minutes in 250 μg/m^3 $PM_{2.5}$ (10/250), 20 minutes in 250 μg/m^3 $PM_{2.5}$ (20/250), 10 minutes in 500 μg/m^3 $PM_{2.5}$ (10/500) and 20 minutes in 500 μg/m^3 $PM_{2.5}$ (20/500). A pre and an immediately post exposure IOS measurement were obtained. Differences in Impulse Oscillometry (IOS) parameters pre and post exposure for each session were assessed with paired t-tests or Wilcoxon tests. Differences between exposure sessions were assessed with mixed linear models. Analysis was performed in Stata 14. **RESULTS:** Statistically significant differences were observed in IOS parameters in all exposure sessions, with most changes observed in 10/500 and least in 20/500 session. Analysis between sessions showed significantly different results between 20/250 compared to 10/250 session in many IOS parameters, while 10/500 differed statistically significantly to 10/250 only in R10 inspiratory. **CONCLUSIONS:** Present study is the first to show that acute exposure of healthy non-smokers to SHS leads to alterations of resting breathing mechanics, successfully captured by IOS. Alterations were expressed by increased Resistance of peripheral and central airways, findings suggestive of a likely broncho-constrictive response to the irritative inhalant. A mild, linear effect of exposure duration was found, while no clear effect was observed for the level of exposure.
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INTRODUCTION

Second-Hand Smoke (SHS) is defined as the mixture of fine particles and gases emitted by the burning cigarette (sidestream) and through the

smoker's expiration (mainstream). It is composed of thousands of compounds known for their irritative, toxicant and carcinogenic properties[1,2].

The adverse health effects associated with exposure to second hand smoke were first published in 1981[3,4], showing that spouses of smokers were at increased risk for lung cancer; since then, scientific evidence and concerning epidemiological data have led to the development of protective legislation and educational campaigns.

Most previous studies on SHS exposure have been performed in animals, cell cultures, or in humans in laboratory settings, using traditionally burning cigarettes or smoking machines to simulate the SHS[5]. Majority of studies have examined epidemiological data, symptoms[6,7], association with cardiovascular and respiratory disorders[5], effects on pregnancy and foetus, as well as physical and cognitive development of children and adolescents[8]. To quantify the effects, other studies have simulated exposure to specific conditions such as inside the cars[9], bars and restaurants[10].

Limited studies have examined the implications on lung function; some have examined the chronic occupational effect on exercise testing[11], while others examined exhaled nitrogen oxide (FeNO) and biomarkers in the exhaled breath condensate (EBC)[12]. The majority of those examining respiratory mechanics have enabled the traditional diagnostic lung function tests that require forced respiratory manoeuvres, such as spirometry and body plethysmography, however with conflicting results[8,13]. Only Schivinski et al. have used both forced and resting breathing techniques, such as spirometry and Impulse Oscillometry (IOS), to study the respiratory mechanics in children and adolescents who were chronically exposed to SHS at home, in comparison with those non exposed[14].

To date, the gold standard test for diagnosis and lung function evaluation is considered spirometry and the flow-volume loop, which however mainly reflect the abnormalities (obstruction) of the conducting (large and medium size) airways; when the earlier FEV_1 reduction is captured by spirometry, a substantial area of small airways has already been affected by the disease process, thus the "silent lung zone"[15]. Furthermore, the forced spirometric manoeuvres greatly depend on the subjects' collaboration, a disadvantage by default; in contrast, IOS allows the evaluation of the respiratory mechanics by superimposing multiple frequencies over resting (tidal) breathing, a great advantage being the easy, effort independent technique in addition to the continuous measurement and the possibility for intra-breath analysis of the inspiratory and expiratory component respectively[15]. While of low specificity, not useful for diagnostic purposes, the method yields however a high sensitivity[16] making it an ideal test to detect mild disorders, evaluate the response to treatment and bronchoprovocation challenge, as well as for detecting the impact of exposure to various hazardous inhalants including cigarette smoke[17].

To the authors knowledge, there is currently a literature gap in studies that have examined the effect of exposure to SHS on respiratory mechanics during tidal breathing as well as the effect of duration and level of exposure. Therefore, the present study aimed to assess the immediate effects of exposure to SHS on the respiratory mechanics of healthy non-smokers, in a controlled environment, during tidal breathing and to examine the effect of duration and level of exposure, in addition to the intra-breath analysis of this effect.

METHODS

A total of 20 individuals, males and females were voluntarily recruited from Athens area. Eligibility to participate in the study was based on the following criteria: Non-smokers, aged 18–45 years, healthy (insignificant medical history, normal physical examination), BMI <30 kg/m^2, spirometry within normal limits according to the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force 2005, no current or recent illness or acute infection (< 4 weeks prior to enrolment), no recent surgery (<2 months prior to enrolment), no medication intake including contraceptives, no pregnancy or lactation.

Study design

A four-session experimental study was designed to measure the effect of exposure to SHS on healthy non-smokers, who were individually exposed one at a time. The sessions took place in four separate days and included a pre and an immediately post exposure IOS measurement:

- Session (10/250): exposure for 10 minutes in a 250 $\mu g/m^3$ concentration of $PM_{2.5}$
- Session (20/250): exposure for 20 minutes in a 250 $\mu g/m^3$ concentration of $PM_{2.5}$
- Session (10/500): exposure for 10 minutes in a 500 $\mu g/m^3$ concentration of $PM_{2.5}$
- Session (20/500): exposure for 20 minutes in a 500 $\mu g/m^3$ concentration of $PM_{2.5}$.

Ethics approval & informed consent

Participants were informed of the study's aim and their right to access and withdraw at any time. Their informed consent was given in writing prior to the study. Ethics approval was issued by the Ethics Committee of the National and Kapodistrian University of Athens School of Medicine (protocol number 5109/17.02.2012).

Exposure room & equipment

Participants were exposed one at a time in a 20 m^3 room. The room had an interior door to the rest of the office apartment and a window to the exterior, both closed during exposure to keep the levels of pollution stable and as designed per each session.

SHS pollution was created using a custom-made smoking machine. The levels of SHS pollution in terms of $PM_{2.5}$ concentrations were monitored using an AM 510 SIDEPAK calibrated according to the manufacturer's guidelines. The $PM_{2.5}$ concentration was created using one and two cigarettes for the 250 and 500 session respectively; in case an adjustment to a lower level was needed, the desired concentration was achieved by simple room ventilation.

For standardization purposes the same cigarette brand was used (nicotine: 0.8mg tar: 10mg) throughout all sessions and for all participants.

IOS measurement was performed using a Viasys Jaeger Masterscreen IOS system (Franklin Lake, NJ, USA), according to ATS/ERS guidelines[17].

Participants were asked to take an upright, neutral sitting position, with legs uncrossed, apply a nose clip and lightly support their cheeks by own hands and finally, they were instructed to breathe normally at the Functional Residual Capacity (FRC) level for 90 seconds, avoiding to swallow, cough, or sigh.

IOS parameters measured

Total Impedance at 5 Hz (Z5), Resistance at 5, 10 and 20 Hz (R5, R10 and R20), Distal Capacity Reactance at 5 Hz (X5), Reactance at 20 Hz (X20), Resonant Frequency (fres) and Reactance Area (AX) were measured, in addition to their inspiratory and expiratory components. Additionally, the parameters R5 and R20 were used to assess whether R5 >R20, to identify the presence of Frequency Dependence of Resistance.

Statistical analysis

Statistical analysis was performed for each exposure session, looking at differences of the IOS parameters within each session. Additionally, analysis was performed between exposure sessions to assess if the different exposure conditions affected the IOS parameters differently.

Normality of the data was assessed with the Shapiro-Wilk statistic. Descriptive characteristics are presented as mean and standard deviation for the normally distributed variables while median and interquartile range (IQR), defined as the 25^{th} and 75^{th} percentile, are presented for the non-normally distributed variables. Effect sizes have been calculated by implementing Cohen's d formula.

To look at differences in the IOS parameters within each exposure session, taking into account the measurement before each session (pre) and the measurement after each session (post), paired t-tests for the normally distributed variables and Wilcoxon tests for the non-normally distributed variables were performed.

To test for differences between exposure sessions, mixed linear models were introduced. Based on our study design, repeated measurements were on two levels; on the participant level (the same individuals participated in all exposure sessions) and on the IOS parameter level (two measurements per individual were obtained within each exposure session). To remove one level and make models less complicated, we calculated the difference of the measurements post - pre exposure of the IOS parameters for each individual. This difference for each IOS parameter was introduced as the dependent variable in each mixed model. The different exposure sessions were introduced as a single categorical variable in the models, with the lowest exposure session (10 minutes in 250 μg/m^3) as the reference category. Regression coefficients (β), their standard errors and their corresponding p-values are presented.

Statistical significance was set at $p < 0.05$, while all p-values presented are two-tailed. Analysis was performed in Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, Texas: StataCorp LP).

RESULTS

A total of 20 volunteers participated in the study, 9 males and 11 females. Median age of participants was 31 years old. Participants were of a normal weight (mean BMI 21.9) (Table 1).

Exposure of 10 minutes in 250 μg/m^3

Statistically significant differences were observed between pre vs post the 10/250 session in X20, X20 ex-

TABLE 1. Participants' characteristics

Variable	Total N=20
Sex, n (%)	
Male	9 (45%)
Female	11 (55%)
Age (years) (Mean, SD)	30,5 ± 4.4
Height (cm) (Mean, SD)	176.3 ± 11.6
Weight (kg) (Median, IQR)	65 (54.5-84)
Body mass index (BMI) (Mean, SD)	21.9 ± 2.8
Flow volume	
FEV1% (Mean, SD)	102.1 ± 11.2
PEF% (Mean, SD)	104.9 ± 14.0

SD: standard deviation, IQR: inter-quartile range

piratory and fres expiratory. Mean X20 was 0.09 kPa/(L/s) pre compared to 0.10 kPa/(L/s) post exposure (p=0.03) with a medium effect size of 0.53 and a mean percentage change of 18.5% among participants. Mean X20 expiratory was 0.085 kPa/(L/s) pre compared to 0.094 kPa/(L/s) post exposure (p=0.03) with a medium effect size of 0.54 and a mean percentage change of 7.1%. Finally, median fres expiratory was 10.45 (1/s) pre compared to 10.11 (1/s) post exposure (p=0.01) with a relatively large effect size of 0.70 and a mean percentage change of -5.8% among participants, showing a decrease after the exposure (Tables 2 and 4).

Exposure of 20 minutes in 250 μg/m^3

Statistically significant differences were observed between pre vs post the 20/250 session in X5 inspiratory,

TABLE 2. IOS parameters pre and post exposure, for the four different exposure sessions

IOS parameter		10/250		20/250		10/500		20/500	
		Mean±std/ Median (IQR)	p-value	Mean±std/ Median (IQR)	p-value	Mean±std/ Median (IQR)	p-value	Mean±std/ Median (IQR)	p-value
Z5 kPa/(L/s)	Pre	0.35±0.08	0.84	0.34 (0.30–0.39)	0.21	0.33 (0.31–0.42)	0.12	0.31 (0.29–0.4)	0.56
	Post	0.35±0.08		0.34 (0.30–0.43)		0.35 (0.31–0.41)		0.32 (0.30–0.43)	
R5 kPa/(L/s)	Pre	0.33±0.08	0.72	0.32 (0.26–0.38)	0.34	0.31 (0.28–0.39)	0.08	0.31 (0.28–0.39)	0.61
	Post	0.34±0.07		0.32 (0.29–0.40)		0.33 (0.30–0.39)		0.30 (0.28–0.41)	
R5 inspiratory kPa/(L/s)	Pre	0.29 (0.26–0.37)	0.87	0.30 (0.27–0.34)	0.45	0.30 (0.27–0.34)	0.13	0.30 (0.27–0.33)	0.75
	Post	0.32 (0.27–0.36)		0.30 (0.28–0.37)		0.31 (0.28–0.37)		0.30 (0.26–0.38)	
R5 expiratory kPa/(L/s)	Pre	0.35±0.09	0.86	0.34 (0.30–0.40)	0.28	0.33 (0.29–0.42)	0.09	0.32 (0.29–0.45)	0.93
	Post	0.35±0.08		0.34 (0.30–0.41)		0.35 (0.30–0.42)		0.31 (0.29–0.45)	
R10 kPa/(L/s)	Pre	0.28 (0.26-0.33)	0.999	0.29 (0.25–0.34)	0.08	0.29 (0.26–0.35)	0.06	0.3±0.07	0.3
	Post	0.30 (0.26–0.37)		0.30 (0.26–0.37)		0.30 (0.27–0.36)		0.31±0.09	
R10 inspiratory kPa/(L/s)	Pre	0.26 (0.23–0.30)	0.52	0.27 (0.23–0.30)	0.1	0.27±0.06	0.03	0.28±0.07	0.27
	Post	0.27 (0.24–0.31)		0.27 (0.25–0.34)		0.29±0.07		0.28±0.08	
R10 expiratory kPa/(L/s)	Pre	0.32±0.08	0.77	0.31 (0.26–0.38)	0.09	0.31 (0.28–0.39)	0.03	0.31 (0.27–0.44)	0.91
	Post	0.32±0.08		0.32 (0.28–0.40)		0.33 (0.29–0.40)		0.29 (0.27–0.42)	
R20 kPa/(L/s)	Pre	0.29 (0.25–0.33)	0.51	0.30 (0.24–0.34)	0.13	0.29 (0.27–0.36)	0.03	0.31±0.07	0.52
	Post	0.31 (0.27–0.36)		0.31 (0.25–0.35)		0.32 (0.28–0.36)		0.31±0.09	
R20 inspiratory kPa/(L/s)	Pre	0.29±0.07	0.95	0.28 (0.23–0.31)	0.08	0.29±0.06	0.0497	0.29±0.07	0.52
	Post	0.29±0.05		0.29 (0.24–0.34)		0.31±0.08		0.30±0.08	
R20 expiratory kPa/(L/s)	Pre	0.32±0.09	0.74	0.31 (0.25–0.37)	0.23	0.33±0.09	0.57	0.32 (0.26–0.38)	0.6
	Post	0.32±0.08		0.31 (0.26–0.37)		0.34±0.10		0.31 (0.26–0.36)	

TABLE 2. IOS parameters pre and post exposure, for the four different exposure sessions

IOS parameter		10/250		20/250		10/500		20/500	
		Mean±std/ Median (IQR)	p-value	Mean±std/ Median (IQR)	p-value	Mean±std/ Median (IQR)	p-value	Mean±std/ Median (IQR)	p-value
X5 kPa/(L/s)	Pre	-0.10±0.04	0.79	-0.09±0.03	0.13	-0.10±0.04	0.57	-0.10±0.04	0.69
	Post	-0.10±0.04		-0.10±0.03		-0.10±0.03		-0.10±0.04	
X5 inspiratory kPa/(L/s)	Pre	-0.11±0.04	0.999	-0.096±0.03	0.04	-0.10±0.04	0.58	-0.11±0.04	0.32
	Post	-0.11±0.04		-0.10±0.03		-0.10±0.03		-0.10±0.04	
X5 expiratory kPa/(L/s)	Pre	-0.10±0.04	0.27	-0.09±0.03	0.35	-0.10±0.04	0.2	-0.11±0.05	0.26
	Post	-0.09±0.04		-0.09±0.03		-0.10±0.04		-0.10±0.04	
X10 kPa/(L/s)	Pre	-0.004±0.03	0.27	0.01±0.03	0.999	-0.001±0.02	0.33	-0.01 (-0.02–0.02)	0.999
	Post	5.2E-19±0.03		0.01±0.03		0.003±0.03		0 (-0.02–0.02)	
X10 inspiratory kPa/(L/s)	Pre	-0.003±0.03	0.36	0.004±0.03	0.999	0.002±0.02	0.87	2.6E-19±0.02	0.999
	Post	0.001±0.03		0.004±0.03		0.003±0.03		0±0.02	
X10 expiratory kPa/(L/s)	Pre	-0.01±0.04	0.06	0.003±0.03	0.4	-0.003±0.03	0.58	0.01 (-0.03–0.02)	0.97
	Post	0.001±0.03		0.001±0.03		-0.001±0.03		-0.01 (-0.03–0.02)	
X20 kPa/(L/s)	Pre	0.09±0.04	0.03	0.10±0.03	0.38	0.10±0.03	0.94	0.09±0.03	0.9
	Post	0.10±0.04		0.09±0.04		0.10±0.03		0.09±0.03	
X20 inspiratory kPa/(L/s)	Pre	0.10 (0.07–0.11)	0.16	0.1±0.04	0.75	0.10±0.03	0.53	0.09±0.03	0.72
	Post	0.10 (0.08–0.12)		0.10±0.04		0.10±0.03		0.10±0.03	
X20 expiratory kPa/(L/s)	Pre	0.085±0.05	0.03	0.10±0.03	0.11	0.09±0.04	0.83	0.08 (0.06–0.11)	0.82
	Post	0.094±0.05		0.09±0.04		0.09±0.04		0.09 (0.06–0.10)	
fres [1/s]	Pre	9.77 (8.85–12.24)	0.41	9.41 (8.44–11.19)	0.63	9.83 (8.64–11.82)	0.999	10.05 (8.88–12.05)	0.91
	Post	9.89 (8.45–12.70)		9.50 (8.31–11.64)		9.67 (8.24–12.80)		10.6 (8.87–11.69)	
fres inspiratory [1/s]	Pre	10.51±2.10)	0.65	9.55 (8.67–11.00)	0.54	9.84 (8.45–10.95)	0.68	10.03 (9.06–11.38)	0.77
	Post	10.38±1.89		9.81 (8.66–11.20)		10.01 (8.79–11.78)		10.4 (8.95–10.89)	
fres expiratory [1/s]	Pre	10.45 (8.94–13.73)	0.01	9.14 (8.17–11.65)	0.48	10.95±2.87	0.9	9.28 (8.72–13.69)	0.68
	Post	10.11 (8.50–12.19)		9.09 (8.40–12.13)		11.01±3.36		11.23 (8.79–13.53)	
AX [kpa/L]	Pre	0.24 (0.16–0.34)	0.13	0.23 (0.11–0.28)	0.3	0.23 (0.15–0.32)	0.39	0.21 (0.12–0.34)	0.82
	Post	0.25 (0.14–0.31)		0.21 (0.11–0.28)		0.22 (0.13–0.33)		0.21 (0.15–0.35)	
AX inspiratory [kpa/L]	Pre	0.27±0.15	0.61	0.20 (0.13–0.32)	0.22	0.24±0.14	0.6	0.22 (0.16–0.29)	0.9
	Post	0.26±0.14		0.24 (0.15–0.27)		0.23±0.11		0.22 (0.13–0.36)	
AX expiratory [kpa/L]	Pre	0.23 (0.16–0.35)	0.12	0.19 (0.10–0.26)	0.11	0.21 (0.16–0.31)	0.58	0.19 (0.14–0.39)	0.81
	Post	0.21 (0.13 -0.34)		0.19 (0.11–0.33)		0.21 (0.12–0.33)		0.21 (0.15–0.35)	
R5-R20	Pre	0.027±0.04	0.24	0.028±0.04	0.21	0.021±0.04	0.36	0.026±0.01	0.56
	Post	0.023±0.04		0.022±0.04		0.017±0.04		0.029 ±0.01	

with a mean value of -0.096 pre compared to -0.10 kPa/(L/s) post exposure (p=0.04) and a medium effect size of 0.50. Mean percentage change of X5 inspiratory among participants was 7.5% (Tables 2 and 4).

Exposure of 10 minutes in 500 μg/m^3

Statistically significant differences were observed between pre vs post the 10/500 session in R10 inspiratory, R10 expiratory, R20 and R20 inspiratory. Mean R10 inspiratory pre was 0.27 kPa/(L/s) compared to 0.29 kPa/(L/s) post exposure (p=0.03), with a medium effect size of 0.51 and a mean percentage change of 7.7%. Median R10 expiratory pre was 0.31 kPa/(L/s) compared to 0.33 kPa/(L/s) post exposure (p=0.03), with a medium effect size of 0.52 and a mean percentage change of 6.5%. Median R20 pre was 0.29 kPa/(L/s) compared to 0.32 kPa/(L/s) post exposure (p=0.03), with a medium effect size of 0.45 and a mean percentage change of 6.8% among participants. Finally, mean R20 inspiratory was 0.29 kPa/(L/s) pre compared to 0.31 kPa/(L/s) post exposure (p=0.0497), with a medium effect size of 0.47 and a mean percentage change of 6.9% among participants (Tables 2 and 4).

Exposure of 20 minutes in 500 μg/m^3

There were no statistically significant differences observed between measurements pre and post this exposure session among participants (Table 2).

Thirteen additional individuals participated in this exposure session to assess if differences were to be observed with more participants. The 13 additional participants had similar characteristics with the rest of our sample; 8 (62%) were males and 5 (38%) females, with a mean age of 31 years old and a mean BMI of 24 (data not shown). After the addition of the 13 participants, statistically significant differences were observed between pre vs post the 20/500 session in X5 inspiratory, with a median of -0.1 kPa/(L/s) pre compared to -0.11 kPa/(L/s) post exposure (p=0.03) and a small effect size of 0.27. The mean percentage change of X5 inspiratory among participants was -15.9%, showing a decrease in X5 inspiratory post exposure (Table 3).

Statistically significant differences were observed between the exposure sessions of 20/250 and 10/250 and the IOS parameters R10 inspiratory, X20, X20 expiratory, fres expiratory, AX and AX expiratory. In particular R10

TABLE 3. IOS parameters pre and post exposure of 20 minutes in 500 μg/m^3 for the 33 participants

IOS parameter		Mean ± std / Median (IQR)	p-value	Mean change (mean % change)	Effect size (absolute)
Z5 kPa/(L/s)	Pre	0.33 (0.29 - 0.40)	0.28	0.01 (3.1%)	0.24
	Post	0.35 (0.30 - 0.42)			
R5 kPa/(L/s)	Pre	0.32 (0.28 - 0.38)	0.19	0.01 (3.8%)	0.30
	Post	0.33 (0.28 - 0.39)			
R5 inspiratory kPa/(L/s)	Pre	0.30 (0.26 - 0.33)	0.34	0.01 (3.2%)	0.22
	Post	0.30 (0.27 - 0.35)			
R5 expiratory kPa/(L/s)	Pre	0.35 (0.29 - 0.42)	0.51	0.01 (2.7%)	0.14
	Post	0.34 (0.29 - 0.43)			
R10 kPa/(L/s)	Pre	0.29 (0.25 - 0.34)	0.13	0.01 (3.6%)	0.29
	Post	0.29 (0.26 - 0.36)			
R10 inspiratory kPa/(L/s)	Pre	0.26 (0.22 - 0.30)	0.16	0.01 (4.3%)	0.31
	Post	0.27 (0.24 - 0.32)			
R10 expiratory kPa/(L/s)	Pre	0.31 (0.27 - 0.39)	0.49	0.01 (2.4%)	0.12
	Post	0.31 (0.27 - 0.41)			
R20 kPa/(L/s)	Pre	0.30 (0.25 - 0.34)	0.46	0.01 (2.5%)	0.16
	Post	0.31 (0.25 - 0.35)			

TABLE 3. IOS parameters pre and post exposure of 20 minutes in 500 μg/m³ for the 33 participants

IOS parameter		Mean ± std / Median (IQR)	p-value	Mean change (mean % change)	Effect size (absolute)
R20 inspiratory kPa/(L/s)	Pre	0.28 (0.24 - 0.32)	0.44	0.01 (3.5%)	0.18
	Post	0.28 (0.25 - 0.33)			
R20 expiratory kPa/(L/s)	Pre	0.32 (0.26 - 0.36)	0.79	-0.001 (0.3%)	0.03
	Post	0.32 (0.27 - 0.35)			
X5 kPa/(L/s)	Pre	-0.11 ± 0.05	0.45	0.002 (-0.8%)	0.13
	Post	-0.11 ± 0.04			
X5 inspiratory kPa/(L/s)	Pre	-0.10 (-0.12 - -0.09)	0.03	0.01 (-15.9%)	0.27
	Post	-0.11 (-0.12 - -0.07)			
X5 expiratory kPa/(L/s)	Pre	-0.11 ± 0.05	0.35	0.004 (-2%)	0.16
	Post	-0.10 ± 0.05			
X10 kPa/(L/s)	Pre	-0.01 (-0.02 - 0.01)	0.89	0 (-10.9%)	0
	Post	0 (-0.02 - 0.02)			
X10 inspiratory kPa/(L/s)	Pre	3.68E-19 ± 0.03	0.17	-0.004 (18.5%)	0.24
	Post	-0.004 ± 0.03			
X10 expiratory kPa/(L/s)	Pre	0 (-0.02 - 0.02)	0.88	-0.0003 (10.6%)	0.02
	Post	0 (-0.02 - 0.02)			
X20 kPa/(L/s)	Pre	0.09 ± 0.04	0.79	-0.001 (0.19%)	0.05
	Post	0.09 ± 0.04			
X20 inspiratory kPa/(L/s)	Pre	0.10 ± 0.03	0.93	0.0003 (0.6%)	0.02
	Post	0.10 ± 0.04			
X20 expiratory kPa/(L/s)	Pre	0.09 ± 0.04	0.84	-0.001 (-1.1%)	0.04
	Post	0.09 ± 0.05			
fres [1/s]	Pre	10.54 (8.88 - 12.61)	0.94	0.27 (3%)	0.17
	Post	10.63 (8.87 - 12.71)			
fres inspiratory [1/s]	Pre	10.24 (9.27 - 11.83)	0.79	0.14 (1.2%)	0.12
	Post	10.37 (9.13 - 11.42)			
fres expiratory [1/s]	Pre	9.48 (8.76 - 13.58)	0.82	0.4 (4.6%)	0.20
	Post	11.37 (8.72 - 13.21)			
AX [kpa/L]	Pre	0.22 (0.15 - 0.37)	0.82	0.01 (2.4%)	0.07
	Post	0.19 (0.15 - 0.38)			
AX inspiratory [kpa/L]	Pre	0.24 (0.17 - 0.30)	0.79	0.003 (0.3%)	0.04
	Post	0.23 (0.19 - 0.37)			
AX expiratory [kpa/L]	Pre	0.18 (0.14 - 0.39)	0.97	0.01 (6.4%)	0.04
	Post	0.21 (0.15 - 0.39)			
R5-R20	Pre	0.03 ±0.04	0.21		
	Post	0.03 ±0.04			

TABLE 4. Mean percentage change and effect size for IOS parameters in the four exposure sessions

IOS parameter	10/250		20/250		10/500		20/500	
	Mean change (mean % change)	Effect size (absolute)	Mean change (mean % change)	Effect size (absolute)	Mean change (mean % change)	Effect size (absolute)	Mean change (mean % change)	Effect size (absolute)
Z5 [kPa/(L/s)]	0.002 (1.5%)	0.05	0.02 (5.2%)	0.35	0.01 (4.4%)	0.34	0.01 (3.1%)	0.23
R5 [kPa/(L/s)]	0.004 (2.1%)	0.08	0.01 (4.9%)	0.31	0.02 (5.2%)	0.39	0.01 (3.2%)	0.24
R5 inspiratory [kPa/(L/s)]	-0.004 (0.5%)	0.10	0.01 (5.5%)	0.31	0.02 (5.9%)	0.40	0.01 (1.7%)	0.11
R5 expiratory [kPa/(L/s)]	-0.002 (0.5%)	0.04	0.02 (5.1%)	0.28	0.02 (5.1%)	0.46	0.01 (2.7%)	0.12
R10 [kPa/(L/s)]	0.003 (2.2%)	0.06	0.02 (6.6%)	0.41	0.02 (5.9%)	0.43	0.01 (3.1%)	0.24
R10 inspiratory [kPa/(L/s)]	-0.01 (-0.2%)	0.14	0.02 (6.8%)	0.41	0.02 (7.7%)	0.51	0.01 (3.6%)	0.26
R10 expiratory [kPa/(L/s)]	-0.004 (0.3%)	0.07	0.02 (7.1%)	0.37	0.02 (6.5%)	0.52	0.002 (1.1%)	0.03
R20 [kPa/(L/s)]	0.01 (3.9%)	0.17	0.02 (7.3%)	0.43	0.02 (6.8%)	0.45	0.01 (2.3%)	0.15
R20 inspiratory [kPa/(L/s)]	0.001 (1.8%)	0.01	0.02 (7.3%)	0.49	0.02 (6.9%)	0.47	0.01 (3%)	0.15
R20 expiratory [kPa/(L/s)]	0.004 (2.9%)	0.08	0.01 (5.9%)	0.30	0.01 (3.2%)	0.13	-0.003 (-0.5%)	0.05
X5 [kPa/(L/s)]	0.001 (0.3%)	0.06	-0.005 (5%)	0.35	0.002 (0.3%)	0.13	0.002 (0.3%)	0.09
X5 inspiratory [kPa/(L/s)]	0 (2.1%)	0	-0.01 (7.5%)	0.50	-0.002 (9.5%)	0.12	0.004 (-4.3%)	0.23
X5 expiratory [kPa/(L/s)]	0.01 (-5.1%)	0.25	-0.005 (5.6%)	0.21	0.01 (-4.9%)	0.29	0.01 (-2.5%)	0.26
X10 [kPa/(L/s)]	0.004 (9.8%)	0.25	0 (-22.1%)	0	0.004 (-0.1%)	0.22	0.001 (-27.5%)	0.04
X10 inspiratory [kPa/(L/s)]	0.004 (-13.3%)	0.21	0 (-11.7%)	0	0.0005 (-15.7%)	0.04	0 (-12.3%)	0
X10 expiratory [kPa/(L/s)]	0.01 (2.5%)	0.46	-0.003 (-19.7%)	0.19	0.003 (-9%)	0.13	0 (-24.1%)	0
X20 [kPa/(L/s)]	0.01 (18.5%)	0.53	-0.004 (-4.7%)	0.20	-0.0005 2.4%)	0.02	0.001 (2.1%)	0.03
X20 inspiratory [kPa/(L/s)]	0.01 (11.1%)	0.40	-0.002 (-1.3%)	0.07	0.004 (8%)	0.14	0.002 (2.8%)	0.08
X20 expiratory [kPa/(L/s)]	0.01 (7.1%)	0.54	-0.01 (-9.6%)	0.37	-0.002 (1.8%)	0.05	9.31323E-11 (3.3%)	0
fres [1/s]	-0.19 (-0.7%)	0.15	0.35 (3.3%)	0.26	0.002 (0.5%)	0	0.12 (2.3%)	0.08
fres inspiratory [1/s]	-0.13 (-0.3%)	0.10	0.24 (2.2%)	0.24	0.02 (0.9%)	0.02	0.04 (0.3%)	0.04
fres expiratory [1/s]	-0.79 (-5.8%)	0.70	0.5 (4.9%)	0.27	0.06 (0.8%)	0.03	0.22 (4%)	0.12
AX [kPa/L]	-0.03 (-4.1%)	0.33	0.02 (11.9%)	0.33	-0.02 (-1.4%)	0.17	-0.004 (1.2%)	0.06
AX inspiratory [kPa/L]	-0.01 (7.4%)	0.12	0.02 (11.4%)	0.24	-0.01 (8.1%)	0.12	0.002 (-2.7%)	0.03
AX expiratory [kPa/L]	-0.05 (-10.4%)	0.38	0.03 (11.7%)	0.39	-0.01 (-1.5%)	0.09	-0.02 (8.4%)	0.14

inspiratory had a higher increase in the exposure session of 20/250 (6.8% increase post vs pre exposure) compared to the exposure session of 10/250 (-0.2% decrease post vs pre exposure), a difference marginally statistically significant (p=0.05). A decrease in X20 was observed in the exposure session of 20/250 (-4.7% decrease post vs pre exposure) compared to an increase of 18.5% (post vs pre exposure) in 10/250, (p=0.04). Similarly, X20 expiratory decreased in 20/250 exposure session (-9.6% decrease post vs pre exposure) while it increased in 10/250 (7.1% increase post vs pre exposure), (p=0.02). On the contrary, fres expiratory increased by 4.9% (post vs pre exposure) in 20/250 while it decreased by -5.8% in 10/250 (post vs pre exposure) (p=0.02). Also, AX increased by 11.9% (post vs pre exposure) in 20/250 exposure session while it decreased by -4.1% (post vs pre exposure) in 10/250 (p=0.04). Similarly, AX expiratory increased by 11.7% in 20/250 (post vs pre exposure) while it decreased by -10.4% in 10/250 (p=0.03) (Tables 4 and 5).

A statistically significant difference was observed in

TABLE 5. Regression coefficients, standard errors and p-values from mixed linear models for IOS parameters

IOS parameter	20/250 vs 10/250		10/500 vs 10/250		20/500 vs 10/250	
	β (se)	p-value	β (se)	p-value	β (se)	p-value
Z5 kPa/(L/s)	0.014 (0.01)	0.25	0.011 (0.01)	0.36	0.008 (0.01)	0.51
R5 kPa/(L/s)	0.011 (0.01)	0.38	0.012 (0.01)	0.33	0.007 (0.01)	0.58
R5 inspiratory kPa/(L/s)	0.019 (0.01)	0.15	0.02 (0.01)	0.12	0.009 (0.01)	0.50
R5 expiratory kPa/(L/s)	0.017 (0.01)	0.24	0.018 (0.01)	0.21	0.009 (0.01)	0.55
R10 kPa/(L/s)	0.015 (0.01)	0.20	0.014 (0.01)	0.233	0.008 (0.01)	0.52
R10 inspiratory kPa/(L/s)	0.022 (0.01)	0.05	0.025 (0.01)	0.03	0.015 (0.01)	0.20
R10 expiratory kPa/(L/s)	0.023 (0.01)	0.11	0.023 (0.01)	0.12	0.005 (0.01)	0.73
R20 kPa/(L/s)	0.012 (0.01)	0.36	0.012 (0.01)	0.38	-0.001 (0.01)	0.97
R20 inspiratory kPa/(L/s)	0.020 (0.01)	0.13	0.019 (0.01)	0.14	0.007 (0.01)	0.61
R20 expiratory kPa/(L/s)	0.011 (0.02)	0.50	0.004 (0.02)	0.81	-0.007 (0.02)	0.69
X5 kPa/(L/s)	-0.006 (0.00)	0.25	0.001 (0.00)	0.83	0.001 (0.00)	0.92
X5 inspiratory kPa/(L/s)	-0.006 (0.00)	0.27	-0.002 (0.00)	0.69	0.004 (0.00)	0.48
X5 expiratory kPa/(L/s)	-0.011 (0.01)	0.14	0.001 (0.01)	0.94	0.001 (0.01)	0.94
X10 kPa/(L/s)	-0.004 (0.00)	0.42	-8.67e-19 (0.00)	1.00	-0.003 (0.00)	0.49
X10 inspiratory kPa/(L/s)	-0.004 (0.00)	0.40	-0.003 (0.00)	0.47	-0.004 (0.00)	0.40
X10 expiratory kPa/(L/s)	-0.009 (0.01)	0.09	-0.004 (0.01)	0.45	-0.007 (0.01)	0.21
X20 kPa/(L/s)	-0.012 (0.01)	0.04	-0.009 (0.01)	0.15	-0.008 (0.01)	0.20
X20 inspiratory kPa/(L/s)	-0.009 (0.01)	0.12	-0.004 (0.01)	0.55	-0.006 (0.01)	0.30
X20 expiratory kPa/(L/s)	-0.017 (0.01)	0.02	-0.01 (0.01)	0.15	-0.009 (0.01)	0.22
fres [1/s]	0.533 (0.4)	0.21	0.189 (0.4)	0.66	0.301 (0.4)	0.48
fres inspiratory [1/s]	0.372 (0.32)	0.24	0.148 (0.32)	0.64	0.170 (0.32)	0.59
fres expiratory [1/s]	1.288 (0.54)	0.02	0.843 (0.54)	0.12	1.012 (0.54)	0.06
AX [kpa/L]	0.05 (0.02)	0.04	0.015 (0.02)	0.55	0.026 (0.02)	0.29
AX inspiratory [kpa/L]	0.026 (0.02)	0.21	0.002 (0.02)	0.94	0.011 (0.02)	0.52
AX expiratory [kpa/L]	0.082 (0.04)	0.03	0.043 (0.04)	0.26	0.036 (0.04)	0.35

R10 inspiratory between the exposure sessions of 10/500 compared to 10/250. In particular, R10 inspiratory had a higher increase in the exposure session 10/500 (7.7% increase post vs pre exposure) compared to the exposure session 10/250 (-0.2% reduction post vs pre exposure) (p=0.03) (Tables 4 and 5).

DISCUSSION

The current study showed for the first time that a brief 10-20 minutes exposure of healthy non-smokers to SHS, resulted in measurable changes of respiratory mechanics during tidal breathing. Parameters of Impedance, Resistance and Reactance, showed changes post exposure in all sessions and for all individuals. Central airways alterations were observed mainly in inspiration, whereas peripheral airways alterations prevailed in expiration.

From the comparison between sessions, the 20/250 exposure was the session depicting significant alterations in several parameters; specifically, Resonant Frequency and AX area increased, while high frequency Reactance X20 decreased. Following the intra-breath analysis, alterations were also observed in the expiratory components of Resonant Frequency, AX and X20 as well as in the inspiratory component of Resistance R10. Keeping $PM_{2.5}$ concentration constant at 250 μg/m^3 and examining 10 and 20 minutes of exposure respectively, revealed significant changes in the 20/250 session in comparison to the 10/250, an indication it was likely the effect of prolonged duration that was associated with findings. Resonant Frequency represents the frequency where the sum of the two components of Reactance, Elastance and Inertance, equals 0, since their measures are equal and opposite in sign. In high frequencies (above fres) it is the inertive pressure of the large airways that predominates, while in the lower frequencies the elastic properties of the lung periphery prevail. The triangular area below the Resonant Frequency, AX area, expresses the Respiratory Elastance, the reciprocal of Compliance and is a marker of airway closure; increased AX, as was found in the 20/250 exposure session, expresses the increased Respiratory Elastance and consequently reduced Compliance[18]. Increased fres and AX indicate alteration of the elastic properties in the lung periphery and in association with a more negative, decreased X5 express the expiratory flow limitation of the small airways[18,19]. While R10 is not usually included in the IOS interpretation in the adult clinical settings, it is worth noting that Komarow et al found that R10 showed a better ability to differentiate between children with and without asthma[20]; thus it is suggested that the increased R10 taken together with the also increased fres, AX and AX expiratory post exposure in the present study, could reflect the likely broncho constrictive response to the irritative SHS compounds.

The 10/500 session showed increased central and medium airway Resistance (R20, R20 inspiratory, R10, R10 inspiratory, R10 expiratory) in addition to a higher increase in R10 inspiratory than the 10/250 session. The acute exposure to an irritative inhalant including SHS, induces chemesthesis, expressed by the sensory irritation of eyes, nose, and the large upper airways; sensory irritation is mediated by the trigeminal, glossopharyngeal and vagus nerves respectively; this response may explain the increased central airways Resistance found in the 10/500 session[21]. However, while in the 10/500 session increased central airway Resistance (R20) was observed, no changes were depicted in the 20/500 to verify the effect of duration. The addition of another 13 individuals in this session, led to a significantly more negative inspiratory component of Distal Capacitive Reactance (X5) post exposure; these findings indicate that the same $PM_{2.5}$ concentration, in the brief 10 minute exposure led to increased central airway Resistance, while the prolonged, double the duration, 20 minutes exposure, led to decreased Distal Capacitive Reactance, a marker of lung periphery. Distal Capacitive Reactance, X5, reflects the elastic properties of the lung periphery, and indirectly the dimension of peripheral airways[18]. X5 in reflecting the elastic recoil of the small airways, takes more negative values in disorders that lead to both reduced lung elasticity and hyperinflation[22]; the more negative X5 observed post exposure in the present study, points out to the small airways being the site of the immediate alterations induced by SHS.

It is worth noting that while not significant, the 20/500 session in addition to the significant X5 inspiratory reduction, also showed a trend for Z5, R5, fres and AX to increase, a combination that describes the peripheral airway obstruction pattern, characteristic of the Chronic Obstructive Pulmonary Disease (COPD)[18], known to be causally related to active[23] and passive smoking[24]. Furthermore, this trend, captured following a brief 20 min exposure to SHS, could be interpreted as the likely initial footprint of the long, insidious process that precedes the spirometric detection of the FEV_1 decline associated with smoking and chronic exposure to SHS[15].

In line with a previous study by Mangnussen[25], cur-

rent study did not show a consistent response to the SHS exposure, neither did document a clear association with $PM_{2.5}$ concentration; we did however observe that increased exposure duration led to changes of respiratory mechanics post exposure at 20 minutes, those changes being stronger in the 20/250 compared to the 20/500 session.

While these findings may appear conflicting and not consistent, it is worth noting that Shusterman et al in their review[21] suggest that there are three types of concentration/time relationships in regards to sensory irritation, i) the ($c \times t = k$) relationship described under Haber's law, that has only been experimentally documented in humans for certain compounds such as war gases, ii) a ($c^a \times t = k$) relationship valid for certain time intervals within the exposure duration and iii) a plateau reaching relationship, followed by waning or reversing of the time effects; the authors concluded that further studies using physiologically based pharmacokinetic models (PBPK) are needed. In the case of the present study it is likely that a plateauing (concentration/duration) relationship leading to waning of effects could explain why it was the 10/500 session that revealed significant changes in contrast to the longer 20/500 exposure. Furthermore, it is suggested that SHS aging and temporal effect (hygroscopic growth, particle coagulation, deposition on surfaces), could partly explain why contrary to what was anticipated, weaker changes were observed in the higher exposure (20/500)[2].

Our study has some limitations

As participants were able to detect the presence and smell of smoke, the possible psychological effect of this knowledge was not accounted for. To overcome the within individual confounding factors, we examined the same participants in all four sessions. We did not however measure the respiratory and heart rate of participants which could vary between and within individuals across sessions and could therefore lead to the inhalation of different SHS quantities. We did use the same exposure room with constant volume and ventilation conditions across all sessions[26] although the actual air flow and ventilation rate were not directly measured. Finally, the fact that we did not perform a control session meant that we could only test for differences between the exposure sessions having one of the sessions as our reference category.

CONCLUSION

Present study is the first to show that acute exposure of healthy non-smokers to SHS, equivalent to that produced by one and two cigarettes respectively, leads to alterations of resting breathing mechanics, successfully captured by IOS. Alterations were expressed by increased Resistance of peripheral and central airways; specifically, mainly the expiratory components of the peripheral airways and the inspiratory component of central airways Resistance increased, findings suggestive of a likely broncho-constrictive response to the irritative inhalant, bearing the potential for airflow limitation. A mild, linear, effect of exposure duration was found, while no clear effect was observed for the level of exposure. Further research is needed to establish the exact impact of exposure determinants in the pathophysiology of the SHS induced disease.

CONFLICTS OF INTEREST
None.

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ΠΕΡΙΛΗΨΗ

Άμεσες επιπτώσεις του παθητικού καπνίσματος στη μηχανική της ήρεμης αναπνοής

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Εισαγωγή: *Περιορισμένες έρευνες έχουν εξετάσει τις συνέπειες της έκθεσης σε παθητικό κάπνισμα (SHS) στην αναπνευστική λειτουργία· η πλειοψηφία έχει χρησιμοποιήσει τις κλασσικές τεχνικές λειτουργικού ελέγχου που απαιτούν βίαιες αναπνευστικές δοκιμασίες. Σκοπός της παρούσας μελέτης ήταν να εκτιμηθούν οι άμεσες επιπτώσεις της έκθεσης σε SHS στη μηχανική της ήρεμης αναπνοής.* ***Μεθοδολογία:*** *20 υγιείς, μη καπνιστές, 18-45 ετών συμμετείχαν σε 4 συνεδρίες έκθεσης σε SHS· 10 λεπτά σε 250 μg/m³ $PM_{2.5}$ (10/250), 20 λεπτά σε 250 μg/m³ $PM_{2.5}$ (20/250), 10 λεπτά σε 500 μg/m³ $PM_{2.5}$ (10/500) και 20 λεπτά σε 500 μg/m³ $PM_{2.5}$ (20/500). Παράμετροι Παλμικής Ταλαντωσιμετρίας (IOS) μετρήθηκαν προ και αμέσως μετά από κάθε συνεδρία. Οι διαφορές των παραμέτρων IOS για κάθε συνεδρία (προ/μετά) εκτιμήθηκαν με paired t-tests ή Wilcoxon tests. Οι διαφορές μεταξύ των συνεδριών εκτιμήθηκαν με mixed linear μοντέλα. Η ανάλυση πραγματοποιήθηκε στο Stata 14.* ***Αποτελέσματα:*** *Στατιστικά σημαντικές διαφορές παρατηρήθηκαν στις παραμέτρους IOS στις τέσσερις συνεδρίες, με τις περισσότερες διαφορές στην 10/500 και τις λιγότερες στην 20/500. Η ανάλυση μεταξύ των συνεδριών έδειξε στατιστικά σημαντικές διαφορές σε πολλές παραμέτρους IOS μεταξύ 20/250 και 10/250, ενώ η 10/500 διέφερε σημαντικά από την 10/250 ως προς την εισπνευστική συνιστώσα R10.* ***Συμπεράσματα:*** *Πρόκειται για την πρώτη μελέτη που διαπιστώνει ότι η οξεία έκθεση υγειών μη καπνιστών σε SHS, οδηγεί σε μεταβολές της μηχανικής της ήρεμης αναπνοής. Η μέθοδος IOS αποτυπώνει αυξημένη αντίσταση περιφερικών και κεντρικών αεραγωγών, ευρήματα ενδεικτικά βρογχοσύσπασης, πιθανώς ως απόκριση στον εισπνεόμενο ερεθιστικό παράγοντα. Το αποτέλεσμα της έκθεσης φαίνεται να συσχετίζεται κυρίως με τη διάρκειά της, ενώ δεν παρατηρήθηκε σαφής επίδραση του επιπέδου ρύπανσης.*

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