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Acute pulmonary effects of using an e-cigarette: impact on respiratory flow resistance, impedance and exhaled nitric oxide.

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RUNNING HEAD: Immediate Respiratory effects of e-cigarette use.

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ABSTRACT

Background: Debate exists as to the scientific evidence for their claims that e-cigarettes have no health related ramifications. Our aim was to assess whether using an e-cigarette for five minutes has an impact on pulmonary function tests and exhaled nitric oxide (FeNO) among healthy adult smokers.

Methods: 30 healthy non smokers (ages 19-56, 14 male) participated in this laboratory based experimental vs. control group study. Ab lib use of an e-cigarette for 5 minutes 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 minutes was found to lead to an immediate decrease in exhaled FeNO within the experimental group by 2.14_{ppb}, (p=0.005) while not in the control group (p=0.859). Total impedance (Z5Hz) in the experimental group was found to also increase by $0.033_{kPa/(L/s)}$ (p<0.001) while flow resistance at R5Hz, R10Hz and R20Hz also statistically increased.). Regression analyses controlling for baseline measurements indicated statistically significant decrease in FeNO and an increase in impedance by $0.04_{kPa/(L/s)}$, (p=0.003), resistance at R5Hz by $0.04_{kPa/(L/s)}$, (p=0.003),at R10Hz by $0.034_{kPa/(L/s)}$, (p=0.008), at R20Hz by $0.043_{kPa/(L/s)}$, (p=0.007), and overall peripheral airway resistance (beta: $0.042_{kPa/(L/s)}$), (p=0.024), 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.

Keywords: respiratory system, flow resistance, impedance, active smoking, health effects, e-cigarettes, harm reduction, electronic nicotine delivery device,

ABBREVIATIONS

FeNo: Exhaled Nitric Oxide

FDA: Food and Drug Administration

TLC: Total lung capacity

ATS/ERS: American Thoracic Society/European Respiratory Society

FEV: Forced expiratory volume

FVC: Forced vital capacity

PEF: Peak expiratory flow

MEF: Mean expiratory flow

IOS: Impulse osscilometry system

TEXT

Introduction

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 one. However, to date debate exists as to the scientific evidence for their claims of no health related ramifications. Due to the fact that 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 U.S. 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].

Due to the increase in interest around e-cigarettes and their claims as a potentially reduced exposure product, a nicotine delivery device or as a smoking cessation tool, it is imperative to assess the risks related to alternative nicotine delivery systems so as to protect public and consumer health[6-10].

Previous research has indicated that smokers have been identified to have significantly higher lung resistances at 5Hz, and 20Hz, while lower concentrations of exhaled nitric oxide (FeNO), -a noninvasive marker of bronchial inflammation- in comparison to non smokers[11-12] To date there is no published evidence of any direct health related effect or acute physiological response of using an e-cigarette, thus the aim of the current study was to investigate into whether using ab-lib an e-cigarette for 5 minutes could affect respiratory mechanics and exhaled FeNO, within the context of an experimental vs. control group study design.

METHODS

Subjects

Our study sample was comprised of 30 adults (14 male, 16 female) of a mean age of 34.8 years (range 19-56) 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 hyper reactivity), acute illness during the previous two weeks, current pregnancy or lactation, current use of any medication. All subjects were instructed not to eat and drink any kind of beverages for at least 2 hours prior to the exam, and to avoid smoking in the previous 4 hours.

Study design

A laboratory based intervention study design was applied, within which two groups were created, the experimental (n=30) and the control group (n=10). These 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 in comparison to changes noted among experimental group participants after the intervention (intra-group comparison), as also by 2) comparing pre vs. post respiratory function among experimental group participants (inter-group comparison). The subjects enrolled in the experimental group were instructed to use the e-cigarette at lib, for 5 minutes as they would usually smoke. The control group subjects were requested to use the e-cigarette with similar frequency, however without the e-cigarette cartridge included and 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 oral informed consent form prior to study enrollment.

E-cigarette usage and chemical composition

The e-cigarette provided to the subjects were of the same brand (Nobacco e-cigarettes black line) and the of the same nicotine concentration. The electronic cigarette itself was comprised of a steel shell, a microprocessor, powered by a lithium battery and a filter and a removable (and renewable cartridge). Three types of cartridges were available in the market for this e-cigarette and in our case the "medium" one was chosen (Nobacco MLB-MED filter), for which the manufacturer reports a measured dose of 11mg of nicotine. Further information on the e-cigarette used in the current study can be found online 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 (industry funded) by the National Center for Scientific Research, "Demokritos" in Greece[14] According to their analysis the cartridge was found to contain 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 Vanilyn (4-Hydroxy-3-methoxybenzaldehyde) at <1%, while no Poly-Aromatic Hydrocarbons were detected.[14]

Lung function assessment

Exhaled nitric oxide (FeNo): Measurements were made in a sitting position with a nose clip using an *Eco Medics® 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 (TLC) through a filter mouthpiece and consecutively exhale at a mouth flow rate of 50 ml/sec for 10 seconds. 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 a visual stimulation on the system screen. Three consecutive trials were performed with a 30 second 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 <0.05kPa/ (l/s) at 10l/s), with the highest FEV_1 recorded in line with pulmonary guidelines. Spirometry was measured according to the recommendations of the ATS/ERS (American Thoracic Society/European Respiratory Society) Task force guidelines[15] FEV_1, FVC, FEV_1%, PEF and $MEF_{25, 50, 75}$ were measured. Each maneuver was repeated for at least three technically acceptable FEFV curves. In order to attain the best results (the ones that actually represent the true status of the patients' respiratory system) from the basic pulmonary measurements (spirometry and dynamic lung volumes) the following criteria were established: 1) Each measurement would be repeated at least 3 times in order to confirm the proper collaboration of the patient and give the patient the chance to familiarize themselves with each process. 2) The results of each measurement must be reproducible (within 10% of the standard deviation after 3 maneuvers)

Total respiratory resistances: The actual values of magnitude of respiratory impedance at 5 Hz (Z5), respiratory resistance at 5, 10 and 20 Hz (R5, R10 and R20 respectively) reactance at 5, 10 and 20 Hz (X5, X10 and X20 respectively) and resonant frequency (Fres) were assessed with the use of an Impulse Oscillometry System (IOS). IOS is a non invasive easy examination which requires a minimum, if any, collaboration with 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, i.e 5Hz, 10Hz, 25Hz). 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 breath normally through a mouth piece 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 pathophysiological changes in the patients' pulmonary mechanics) while at the same time requires the smallest amount of the author's subjectivity as to obtain the correct measurement that corresponds with the patient's true pulmonary mechanical status.[16-17] Patients have been found to comply smoothly with the instructions and no discomforts or failures to collaborate were noticed. The whole maneuver lasted for 90 seconds and was repeated for verification. Results were measured in kPa /(l/sec).

Statistical analysis

The Kolmogorov-Smirnov tests were applied so as to assess the normality of the data with all measurements found to be normally distributed, with the exception of exhaled FeNo. Pre vs. post measurements, gender differences and experimental vs. control conditions were assessed through bivariate analyses. The paired student t-test was performed among parametric data, while non parametric 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% confidence Intervals. So as to control simultaneously for intervention group (experimental vs. control) and baseline respiratory characteristics, additional linear regression analyses were performed while R^2 values, beta coefficients and 95% C.I of the beta are provided. The statistical analysis was performed with the statistical package PASW 18.0 (Chicago, USA).

RESULTS

The descriptive characteristics and baseline pulmonary functional status of participating subjects is depicted in **Table 1**. Differences in baseline respiratory function, IOS or FeNo were not identified when stratified by group (experimental vs. control), while when stratified by gender, female participants were found to have a lower FEV_1, FVC, PEF and MEF_{50} and MEF_{75}, however baseline FeNo concentrations and IOS measurements were not found to differ.

Table 2 depicts the changes in exhaled FeNO and respiratory mechanics, before and after the use of an e-cigarette (experimental group) or an sham e-cigarette (control group). In all cases, the internal pre and post measurements per participant were highly correlated, while no differences between basic pulmonary measurements (data not shown) were identified between the two groups. In regards to pulmonary oxidative stress, our findings indicated that exhaled FeNO within the experimental group decreased by 16%, (by 2.14_{ppb} from 13.02_{ppb} to 10.89_{ppb}, p=0.005) after the use of an e-cigarette, while FeNO concentrations were not found to change within the control group (from 8.76_{ppb} to 8.75_{ppb}, p=0.859). An additional sensitivity analysis among the 10 pairs of experimental group participants that also participated in the control group was performed, which indicated a statistically significant decrease in exhaled FeNO, by 1.69ppb (from 8.76ppb to 7.07ppb, p=0.002), after using an e-cigarette.Using IOS as an indicator of pulmonary function among the study participants, airway impedance at Z5Hz was found to increase in the experimental group by $0.033_{kPa/(L/s)}$ 95%C.I: 0.016 to $0.050_{kPa/(L/s)}$, p<0.001, while no differences were noted among control group participants (mean difference of $-0.002_{kPa/(L/s)}$ 95%C.I: -0.010 to $0.006_{kPa/(L/s)}$,, p=0.591). Correspondingly lung resistance in the experimental group was found to also increase at R5Hz, R10Hz and R20Hz by an average of $0.031_{kPa/(L/s)}$ (95%C.I: 0.014 to $0.048_{kPa/(L/s)}$), $0.029_{kPa/(L/s)}$, (95%C.I: 0.013 to $0.045_{kPa/(L/s)}$), and $0.030_{kPa/(L/s)}$, (95%C.I: 0.010-$0.051_{kPa/(L/s)}$) respectively. Moreover peripheral pulmonary resistance was also noted to increase from $0.22_{kPa/(L/s)}$ to $0.25_{kPa/(L/s),}$ p=0.05. Similar statistical results to the above were identified also through the intergroup comparison (mean change in control vs. mean change in experimental group) as also seen in **Table 2**. Stratifying the experimental vs. control group analysis by gender was not found to alter the direction or statistical association of the above findings. Pulmonary function accessed via spirometry was not found to change in either group (data not shown).

Subsequently a linear regression analysis was performed so as to assess the role of using an e-cigarette on the assessed respiratory outcomes, taking into account the baseline measurement of each participant and the group they were allocated to. The key findings are depicted in **Table 3**, which strengthen 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 $0.042_{kPa/(L/s)}$), while 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*=0.024), while a tendency for overall central airway resistance was noted, however this difference was borderline non statistically significant (beta $0.034_{kPa/(L/s)}$, 95%C.I: -0.003 to 0.071), *p*=0.069.

DISCUSSION

To our knowledge this is the first study to find a physiological response after inhaling on an e-cigarette. According to our findings 5 minutes 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 methodological approach, has been previously used in clinical trials and can be used to sensitively 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 that e-cigarette usage was associated with increased flow resistance even though spirometry assessed lung function was deemed normal, a finding that is corroborated by the fact that IOS can detect oncoming pathophysiological changes of the respiratory system, before spirometry is able to[20]. Indeed, it has been demonstrated that changes in flow resistance precede changes in PEF and FEV_1 in experimentally induced airway obstruction, and our findings may indicate such a preliminarily possible health effect[21]. We must state though that while the differences within our study are of statistical significance, the clinical changes may be too small to be of major clinical importance (i.e. to induce dyspnea or breathing difficulties), however as these measurements were performed after only 5 minutes of ad lib e-cigarette use, a normal consumer would use the product most likely many 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 oedema, smooth muscle contraction (and brochospasm) or secretions. In the regression analysis there was a tendency for central airway resistance to increase however this was borderline non-statistically significant, it is possible that increasing the studies sample size might have increased the statistical significance; or we could 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 exhaled FeNO concentrations. Nitric oxide is a gaseous mediator which has an important role in several physiological 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 and is strongly correlated with eosinophilic inflammation and bronchial hyperreactivity and has become an established research tool for assessing oxidative stress, indicating the immediate effect e-cigarette usage might have on pulmonary homeostasis[2326].

As no standard definition of ENDS 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. While we identified the clinical changes in lung function due to ENDS use, we are only able to hypothesize on the actual substances (or combination of substances) that could have caused the measured effect. One of the substances that were reported to be included in the e-cigarette we used was propylene glycol (other constituents included, linalool, nicotine, tobacco essence and methyl vanilyn) 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.

To our knowledge this is the first study to assess the respiratory effects of using an e-cigarette and thus 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 inter subject 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 underlining damage due to previous cigarette smoking or lung condition. The performed linear regression analysis furthermore allows us to estimate the quantitative effects of using a single e-cigarette on mechanical and inflammatory measurable parameters. Moreover it is of value that the chemical composition of the cartridge used in the e-cigarette is known. However, despite these novel findings, our sample size remains relatively small, while further research is needed to investigate the mechanistic and toxicological effects of long term usage which are potentially adverse and worthy of further investigation.

In conclusion, using an e-cigarette for 5 minutes was found to cause an increase in impedance, peripheral airway flow resistance and oxidative stress among healthy smokers. We must state though that while the differences within our study are of statistical significance, the clinical changes may be too small to be of major clinical importance. Notably, due to the fact that these acute 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 US FDA as other international regulatory bodies should pursue the regulation of the e-cigarette until manufacturers provide scientific evidence to support their claims, while additional research is warranted so as to obtain concrete evidence of an adverse health outcome.

Competing interests: We declare that we have no conflict of interest to report.

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Author contributions: Authors NA, MK and VE performed the lab measurements and helped draft the manuscript, author CV conceived the idea and had the main role in data analysis and manuscript preparation, while authors PB had the main role in study supervision and with GNC participated in study design, data interpretation and manuscript preparation.

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TABLES

Table 1. Baseline characteristics and respiratory function of study participants by gender.

	female	male	p-value[1]
N	16	14	n/a
Age(mean years ±SD)	36±11	33±11	0.473
Spirometry			
FVC [L]	3.64	5.45	0.001
FEV_1 [L]	3.02	4.33	0.001
PEF [L/sec]	1.50	1.84	0.001
MEF_{25} [L/sec]	3.93	5.08	0.293
MEF_{50} [L/sec]	6.04	8.35	0.050
MEF_{75} [L/sec]	3.64	5.45	0.001
MMEF [L/sec]	3.16	4.10	0.056
Exhaled Nitric Oxide			
FeNo ppb	12.3	13.8	0.689
IOS			
IOS Z5Hz [kPa/(L/s)]	0.409	0.339	0.088
IOS R5Hz [kPa/(L/s)]	0.399	0.329	0.072
IOS R10Hz [kPa/(L/s)]	0.349	0.296	0.102
IOS R20Hz [kPa/(L/s)]	0.318	0.278	0.176
IOS X5Hz [kPa/(L/s)]	-0.101	-0.079	0.314
IOS X10Hz [kPa/(L/s)]	-0.034	-0.015	0.214
IOS X20Hz [kPa/(L/s)]	0.052	0.076	0.071
IOS peripheral [kPa/(L/s)]	0.253	0.189	0.069
IOS central [kPa/(L/s)]	0.224	0.168	0.094
IOS Fres [Hz]	14.116	11.587	0.098

1: p values based on paired student t-tests for all other than FeNo performed with Wilcoxon signed rank test, p<0.05 classified as statistically significant.

Table 2. Baseline characteristics by group and subsequent inter-subject an inter-group changes (pre vs. post) in exhaled nitric oxide (FeNo) and flow resistance (IOS) following use of an e-cigarette.

	Group	n	Pre mean	Post mean	Mean difference	95% C.I of the mean difference (Lower - Upper)	Pre vs. post p-value[1]	Experimental vs. control p-value[2]
Exhaled Nitric Oxide								
FeNO [ppb]	***Experimental***	29	13.02	10.89	-2.14	(-3.53 to -0.74)	0.005*	0.040*
	Control	10	8.76	8.75	-0.01	(-0.13 to 0.11)	0.859	
Flow resistance								
IOS Z5Hz [kPa/(L/s)]	***Experimental***	30	0.376	0.409	0.033	(0.016 to 0.050)	<0.001*	0.003*
	Control	10	0.418	0.416	-0.002	(-0.010 to 0.006)	0.591	
IOS R5Hz [kPa/(L/s)]	***Experimental***	30	0.367	0.397	0.031	(0.014 to 0.048)	0.001*	0.008*
	Control	10	0.405	0.402	-0.003	(-0.012 to 0.006)	0.468	
IOS R10Hz [kPa/(L/s)]	***Experimental***	30	0.325	0.353	0.029	(0.013 to 0.045)	0.001*	0.020*
	Control	10	0.353	0.354	0.001	(-0.008 to 0.010)	0.811	
IOS R20Hz [kPa/(L/s)]	***Experimental***	30	0.299	0.329	0.030	(0.010 to 0.050)	0.005*	0.054
	Control	10	0.323	0.322	-0.001	(-0.010 to 0.008)	0.811	
IOS X5Hz [kPa/(L/s)]	***Experimental***	30	-0.091	-0.101	-0.010	(-0.023 to 0.003)	0.122	0.187
	Control	10	-0.095	-0.092	0.003	(-0.006 to 0.011)	0.468	
IOS X10Hz [kPa/(L/s)]	***Experimental***	30	-0.025	-0.027	-0.002	(-0.010 to 0.006)	0.559	0.432
	Control	10	-0.036	-0.033	0.003	(-0.004 to -0.011)	0.394	
IOS X20Hz [kPa/(L/s)]	***Experimental***	30	0.063	0.066	0.003	(-0.008 to 0.015)	0.556	0.450
	Control	10	0.055	0.053	-0.002	(-0.009 to 0.005)	0.555	
IOS peripheral [kPa/(L/s)]	***Experimental***	30	0.223	0.248	0.025	(0.001 to 0.050)	0.050*	0.043*
	Control	10	0.230	0.229	-0.001	(-0.009 to 0.007)	0.780	
IOS central [kPa/(L/s)]	***Experimental***	30	0.198	0.218	0.020	(-0.006 to 0.047)	0.130	0.221
	Control	10	0.211	0.215	0.004	(-0.005 to 0.013)	0.343	
IOS Fres [Hz]	***Experimental***	30	12.94	12.48	-0.457	(-1.720 to 0.806)	0.466	0.513
	Control	10	13.75	14.02	0.270	(-0.541 to 1.079)	0.472	

1: p-values assessed within groups (pre vs. post usage). Significance flagged with an *
2: p-values assessed between groups (experimental vs. control). Significance flagged with an *

Table 3. Regression analysis on the effect of using an e-cigarette on exhaled nitric oxide (FeNO) and airway flow resistance (IOS), controlling for the participants' baseline measurements.

Variable	R^2	beta	95% C.I	p-value[1]
FeNO [ppb]	0.950	-2.194	-4.038 to -0.350	0.021*
IOS Z5Hz [kPa/(L/s)]	0.991	0.040	0.015 to 0.065	0.003*
IOS R5Hz [kPa/(L/s)]	0.991	0.040	0.015 to 0.065	0.003*
IOS R10Hz [kPa/(L/s)]	0.990	0.034	0.009 to 0.058	0.008*
IOS R20Hz [kPa/(L/s)]	0.981	0.043	0.012 to 0.074	0.007*
IOS peripheral [kPa/(L/s)]	0.952	0.042	0.006 to 0.078	0.024*
IOS central [kPa/(L/s)]	0.934	0.034	-0.003 to 0.071	0.069

1: Each line represents a separate linear regression model adjusting for the group (control vs. experimental) and the relative baseline measurement (pre vs. post). Significance flagged with an *

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