12-18-2020

Short term effects of electronic cigarettes on pulmonary function in healthy adult smokers when compared to conventional cigarette use

Kayleen Lynch
James Madison University

Rachel Bastianelli
James Madison University

Short Term Effects of Electronic Cigarettes on Pulmonary Function in Healthy Adult Smokers When Compared to Conventional Cigarette Use

Kayleen Lynch, PA-S
James Madison University

Rachel Bastianelli, PA-S
James Madison University

Short Term Effects of Electronic Cigarettes on Pulmonary Function in Healthy Adult Smokers When Compared to Conventional Cigarette Use

Kayleen Lynch and Rachel Bastianelli

Abstract

Background: *Electronic cigarettes (e-cigarettes) first appeared on the U.S. market in 2007[1], but to date, little is known about their safety. Concern about long term adverse effects on overall health continues to increase as we explore the potential of e-cigarettes to aid in smoking cessation practices. E-cigarettes have gained popularity and support through this idea that by using them to help patients quit smoking, the benefits of ultimately abstaining from tobacco use will outweigh the harms associated with e-cigarette use[1]. While the idea of reducing tobacco usage by any means possible remains the goal for most providers, without clear-cut recommendations from the Food and Drug Administration (FDA) and Centers for Disease Control (CDC) and supportive long term research and data analysis, providers are being forced to decide between the lesser of two evils.* ***Objective:*** *The purpose of this review is to explore current research that quantifiably measures the effect of e-cigarettes on pulmonary function.* ***Methods:*** *A PubMed search was performed using the MeSH terms "electronic nicotine delivery systems" or "vaping," and "respiratory function tests," and a Scopus search was performed using the terms "respiratory function test," "electronic cigarette," and "short-term." Search results were then further stratified to exclude articles with non-human species (3 articles), non-healthy subjects (4 articles), review articles (2 articles), and non-smokers (5 articles). Of the articles remaining, one article was excluded for being a single subject case study, and the rest were used for quantitative meta-analysis.* ***Conclusion:*** *The results of the 3 studies included in the meta-analysis revealed a lack of statistically significant changes in pulmonary function as demonstrated by FEV1 and FVC with the use of e-cigarettes vs. conventional cigarettes. Further well-designed long-term RCT's are needed in order to elicit more conclusive evidence on the safety of e-cigarettes before formal recommendations can be made to patients regarding their use.*

Keywords: *Electronic cigarette (e-cigarette), electronic nicotine delivery devices (ENDS), The Food and Drug Administration (FDA), The Centers for Disease Control (CDC), pulmonary function tests (PFTs), chronic obstructive pulmonary disease (COPD), forced vital capacity (FVC), peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV1), Tiffeneau-Pinelli index (FEV1/FVC), blood pressure (BP), heart rate (HR), carbon monoxide (CO), nitrous oxide (NO), dynamic inhalation scintigraphy (DIS)*

Introduction

To date, little is known about the safety of e-cigarettes, and with a recent nationwide outbreak of severe respiratory illness associated with use of e-cigarettes or vaping products, there is increasing concern for public safety. The general public is under the invalid assumption that e-cigarettes are harmless or that they impose a lower overall health risk compared to that brought on by conventional cigarette use[1]. Appealing to the public through this idea of "harm reduction" masks the lack of credible research surrounding this topic[1].

A typical e-cigarette is composed of three main components including a rechargeable or disposable battery, a heating element that generates an inhalable aerosol, and either a switch or puff-activated circuitry[2]. The typical commercial e-cigarette also has a liquid solution containing aerosol-forming excipients such as glycerol and/or propylene glycol, flavoring materials and optionally, nicotine[2]. According to the surgeon general, e-cigarettes can contain other potentially harmful chemicals including flavorants such as diacetyl, a chemical linked to serious lung disease, volatile organic compounds, and heavy metals such as nickel, tin, and lead[3].

The liquid solution within the e-cigarette is usually delivered from a small reservoir by capillary wicking to the heating zone, which generates an aerosol resembling cigarette smoke[2]. The devices have many different names such as vape pens, pod mods, tanks, ENDS, e-hookahs and e-cigarettes[4]. The liquid contained within may be called e-juice, e-liquid, cartridges, pods, or oil[4]. A large variety of e-cigarette sizes, configurations, formulations, and designs are emerging on a continual basis in response to an expanding worldwide marketplace and evolving personal preferences[2].

Concern about long term adverse effects of e-cigarettes on overall health continues to grow as we explore their potential to aid in smoking cessation practices. E-cigarette use first appeared on the U.S. market in 2007[1]. Since then both experimental and regular use has become increasingly popular amongst various age groups within the population. The rationale behind choosing an e-cigarette over a conventional cigarette varies amongst users. A global survey of e-cigarette users revealed that the majority of middle-aged and older adults who currently smoke or previously smoked conventional cigarettes reported using e-cigarette as a means to quit smoking conventional cigarettes and improve their overall health[1].

Over the last ten years, the association between increased e-cigarette use and overall smoking cessation rates has become apparent and is commonly brought up in conversations with healthcare providers in a primary care setting[1]. Clinical research has shown a correlation between smoking and poor health outcomes. Cessation is considered one of the most beneficial lifestyle modifications for conditions seen frequently by primary care providers such as hypertension, diabetes mellitus, cerebrovascular disease, coronary artery disease, acute coronary syndrome, and more. Abstaining from using tobacco products is universally recommended.

A major concern about the potential risks associated with e-cigarette usage is whether the FDA is able to adequately monitor the production of these products. While the FDA has recently extended its tobacco regulatory power to include e-cigarettes as of 2016, the research to guide these policies is currently limited[1]. A detailed description of the FDA's current regulations can be viewed below in Table 1. Due to the current nationwide outbreak of respiratory disease

associated with e-cigarette usage, the CDC has advised the public to avoid e-cigarettes while under investigation by federal and state officials[4]. As part of their investigations, state health officials have sent samples of products to the FDA for analysis for THC and other cannabinoids, nicotine, vitamin E acetate, along with cutting agents/diluents and other additives, pesticides, opioids, poisons, heavy metals, and toxins[4,6]. According to the FDA, many of the recent cases have involved a gradual start of symptoms including dyspnea on exertion, shortness of breath, and/or chest pain before hospitalization. However, it is not clear if they have a common cause or if they involve different diseases with similar presentations, and more information is needed to determine what is causing the respiratory illness[6]. The ramifications that this research has for society are quite substantial considering that more than 3.6 million middle and high school students currently use e-cigarettes,[4] and 15% of U.S. adults in 2014 reporting trying an e-cigarette[8].

Table 1. FDA Regulation of Electronic Nicotine Delivery Systems (ENDS)[7]

FDA regulates the following in terms of ENDS[a,b]
Manufacturing Importation Packaging Labeling Advertising Promotion Sales Distribution
[a]Information adapted from www.fda.gov[7]. [b]Regulations apply to components and parts of ENDS including e-liquid, a glass or plastic vial container of e-liquid, cartridges, atomizers, certain batteries, cartomizers and clearomizer, digital display or lights to adjust settings, tank systems, drip tips, flavoring for ENDS, and programmable software. ENDS accessories are excluded from FDA regulations.

The CDC recommendations state that "adults who used e-cigarettes containing nicotine to quit cigarette smoking" should not return to smoking conventional cigarettes, but they provide no specific recommendations about refraining from e-cigarette use for these patients[5]. The FDA only recommends seeking medical attention with suspected e-cigarette induced lung disease, along with provider reporting of these incidences[6]. Without clear-cut recommendations from the FDA and CDC, providers are forced to decide between the lesser of two evils. With the

lack of long term research and data analysis, do you recommend staying away from e-cigarettes, or does the overall benefit of reducing conventional cigarette use outweigh the unknown, potentially detrimental effects of e-cigarette usage? While the idea of reducing tobacco usage by any means possible remains the goal for most providers, supporters of e-cigarette use as a healthier alternative to conventional cigarette smoking are promoting the benefits of this cessation technique without evidence to support their claims and inadvertently putting the lives of their patients at risk.

The purpose of this paper is to explore current research that quantifiably measures the effect of e-cigarettes on pulmonary function. The major type of PFTs include spirometry, spirometry before and after a bronchodilator, lung volumes, and quantitation of diffusing capacity for carbon monoxide[9]. Spirometry is the most useful and readily available pulmonary function test, only takes 10 to 15 minutes to complete, and carries minimal risk[9]. It is important in the evaluation of chronic cough and airflow obstruction and used to diagnose and monitor a broad spectrum of respiratory diseases including asthma, COPD, interstitial lung disease, and neuromuscular diseases affecting respiratory muscles[9].

Spirometry is performed by measuring the volume of air exhaled at specific time points during a forceful and complete exhalation after a maximal inhalation[9]. The most important variables gained from PFTs are the total exhaled volume (FVC), the volume forcibly exhaled in one second (FEV1), and the ratio of these values (FEV1/FVC)[9]. An obstructive disease pattern is indicated by a low FEV1/FVC ratio, which is defined as less than 70% of expected or below the fifth percentile in adults, and less than 85% in patients between 5 and 18 years of age[10]. A

restrictive disease pattern is indicated by an FVC below the fifth percentile in adults, or less than 80% in patients between 5 to 18 years of age[10].

Case

S.C. is a 65 year old male with a 40 pack year smoking history who recently was advised by his primary care provider on the health benefits of smoking cessation. He is worried about his health, but no matter what method he tries, he is unable to quit smoking. He is interested in the possibility of replacing his conventional cigarettes with e-cigarettes because he hears he can control the amount of nicotine he is getting. However, he has seen a lot of negative media on e-cigarettes lately and is wondering if they would actually be safer for him to use than traditional cigarettes. Should the recommendation be made for him to switch to e-cigarettes?

Clinical Question

Among healthy adult smokers, does e-cigarette smoking as compared to traditional cigarette smoking improve pulmonary function tests?

Table 2. PICO Framework Table

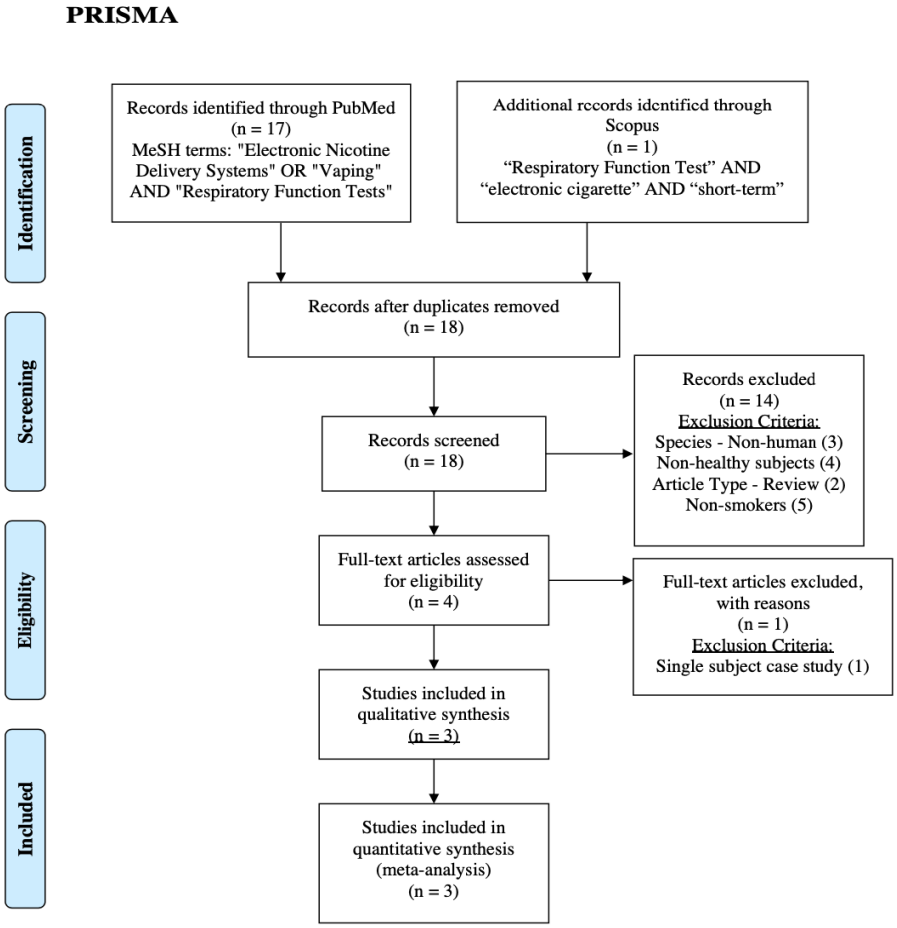
PICO Framework Table		
P	Population	Healthy Adult Smokers
I	Intervention	E-cigarette smoking
C	Comparison	Conventional cigarette smoking
O	Outcome	Improvement in Pulmonary Function Tests (FEVI, FVC)

Methods

Initially, in September of 2019, a PubMed search was performed using the MeSH terms “electronic nicotine delivery systems” or “vaping,” and “respiratory function tests,” and a Scopus

search was performed using the terms “respiratory function test,” “electronic cigarette,” and “short-term.” Search results yielded a total of 18 articles, which were then further stratified to exclude articles with non-human species (3 articles), non-healthy subjects (4 articles), review articles (2 articles), and non-smokers (5 articles). Of the 4 articles remaining, one article was excluded for being a single subject case study, leaving a total of 3 articles to be used for quantitative meta-analysis. The PRISMA flow chart used is located in Figure 1.

Figure 1. PRISMA Flow Diagram.



Results

Study #1

Measurement of Cardiovascular and Pulmonary Function Endpoints and other Physiological Effects Following Partial or Complete Substitution of Cigarettes with Electronic Cigarettes in Adult Smokers. D'Ruiz et al.

Study Objective

To evaluate acute changes in select physiological parameters associated with cardiovascular physiology (systolic and diastolic BP and HR), pulmonary function (FVC, FEV1, and exhaled CO and NO), and adverse events among groups that either completely or partially switched from conventional cigarettes to e-cigarettes or completely discontinued using tobacco and nicotine products altogether[11].

Study Design

One hundred and five (105) subjects meeting the eligibility criteria were enrolled into the study and randomized into one of six study groups described below in Table 3. The main criteria for inclusion and exclusion in the study are described below in Table 4. This was a randomized, open-label, forced-switch parallel arm study conducted at a single independent research center (Celerion, Lincoln, NE)[11]. Baseline assessments occurred on the morning of day one prior to the start of randomized product use and post-baseline assessments were performed in the morning on days one through six[11].

Table 3. Study #1 Study Groups[11].

Exclusive E-Cigarette Use Groups	
Group A1	Tobacco flavor rechargeable blu™ e-cigarette
Group A2	Cherry flavor rechargeable blu™ e-cigarette
Group A3	Cherry flavor disposable blu™ e-cigarette
Dual Use Groups	
Group B1	Tobacco flavor rechargeable blu™ e-cigarette + usual brand combustible tobacco cigarette
Group B2	Cherry flavor disposable blu™ e-cigarette + usual brand combustible tobacco cigarette
Group B3	Cherry flavor disposable blu™ e-cigarette + usual brand combustible tobacco cigarette
Cessation Group	
Group C	Complete tobacco and nicotine product cessation

Table 4. Study #1 - Inclusion and Exclusion Criteria[11].

Inclusion Criteria	Exclusion Criteria
● Healthy adult male and female smokers ● 21-65 years of age ● A smoker for at least 12 months ● Currently smoked an average of 10 or more conventional manufactured tobacco cigarettes per day (any brand, any style) ● Consistent use of their current usual brand style for 14 days prior to check in ● Positive urine cotinine at screening (≤ 500 ng/mL) ● Exhaled carbon monoxide >12 ppm at screening.	● History or presence of clinically significant mental or physical health conditions ● Females who were pregnant or breast-feeding ● High blood pressure ● Body mass index < 18 kg/m^2 or > 40 kg/m^2 ● Acute respiratory illnesses requiring treatment within 2 weeks prior to check-in ● Use of prescription smoking cessation treatments ● Anti-diabetic or insulin drugs or medications ● Positive urine screen for alcohol or drugs of abuse ● Self-reported mouth-hold smokers

Use of tobacco or nicotine-containing e-cigarette products was only permitted per the study protocol and randomization during the entire duration of the study, and was documented daily by clinic staff[11]. Subjects in the cessation group were housed in an area of the clinic separate from other groups to minimize the chance for illicit product use and cross-contamination[11]. With few exceptions, all product use was *ad libitum* from 07:30 to 23:00 on days 2-5[11]. The exceptions were meals and questionnaire administration, 15 minutes prior to blood sampling and vital sign measurements, and 30 minutes prior to and during spirometry and exhaled CO and NO measurements[11].

Subjects randomized to receive the e-cigarette products were trained on how to use the e-cigarettes upon check-in and then again on day 1[11]. New e-cigarettes were supplied to the subjects each morning and throughout the day if the e-liquid solution was fully consumed, and all e-cigarettes were weighed before and after use. Subjects in the dual use group were required to reduce their daily cigarette consumption on days 1-5 by ~50% of that reported at baseline[11]. To assess how much nicotine was being delivered to the subjects, a rough estimate of the maximum amount of nicotine possibly delivered from each e-cigarette was calculated using the following simple mass-balance calculation: Estimated Nicotine Delivery (mg) = Pre-weight - Post-weight difference (mg) nicotine strength (%)[11]. Product use data was listed by subject and day and was summarized by subject, product use group, and day using descriptive statistics (arithmetic mean, standard deviation, coefficient of variation, sample size, minimum, maximum, and median)[11]. A paired t-test was used to make within-group cohort comparisons of the daily estimated amount of nicotine delivered by the e-cigarettes and the number of cigarettes smoked per day[11].

Spirometry measures of the volume of air exhaled during a forced breath in one second (FEV1) and total volume of air exhaled (FVC) were measured by the study physician or appropriate clinical staff in subjects to assess any impacts of product use on lung function[11]. Both baseline (day 1) and post-baseline (day 5) changes in FVC and FEV1 spirometry endpoints were performed in the afternoon using a KoKo® Spirometer and methods consistent with American Thoracic Society guidelines[11]. FVC and FEV1 values were documented and descriptive statistics, including a measured value summary and measured value percentage change from baseline was provided for all data[11]. A paired t-test was used to make within-group comparisons and a linear mixed model was used to compare between-group differences in FVC and FEV1[11].

Statistical analyses were performed using SAS procedures in SAS® Version 9.3[11]. A paired t-test was used to make within-group comparisons between study days and a linear mixed model was used to assess between-group differences[11]. Baseline values were included in the statistical models for the between-group comparisons as a covariate[11]. Differences were considered statistically significant at an alpha level of 5% ($p < 0.05$).

Study Results

The measured FVC summary and statistical comparisons can be viewed in Tables 5 and 6 below. The only statistically significant data occurred in the exclusive e-cigarette use groups in those using the Tobacco Rechargeable (p-value of 0.0207) and Cherry Rechargeable e-cigarettes (p-value of 0.0113), meaning the difference from the day 1 baseline measurement and the day 5 measurement in terms of FVC was significant in these groups[11]. The measured FEV1 summary and statistical comparisons can be viewed in Tables 7 and 8 below. The only statistically

significant data occurred in the Tobacco Rechargeable (p-value 0.0148) and Cherry Rechargeable users (p-value 0.0276) within the exclusive e-cigarette use group, as well as the Cherry Rechargeable users within the Dual Use Group (p-value 0.0191); meaning the difference in FEV1 between the day 1 baseline and day 5 measurements, was statistically significant in these groups[11].

In summary, the use of e-cigarettes for five days under the various study conditions did not lead to negative respiratory health outcomes[11]. The pulmonary function test results showed small, but non-statistically significant improvements in FEV1 and FVC is most user groups[11]. The most consistent statistically significant results occurred within the exclusive e-cigarette use group in those using either of the two rechargeable e-cigarettes.

Figure 2. Summary of FVC and FEV1 Changes from Baseline by Use Group from Baseline to Day 5[11].

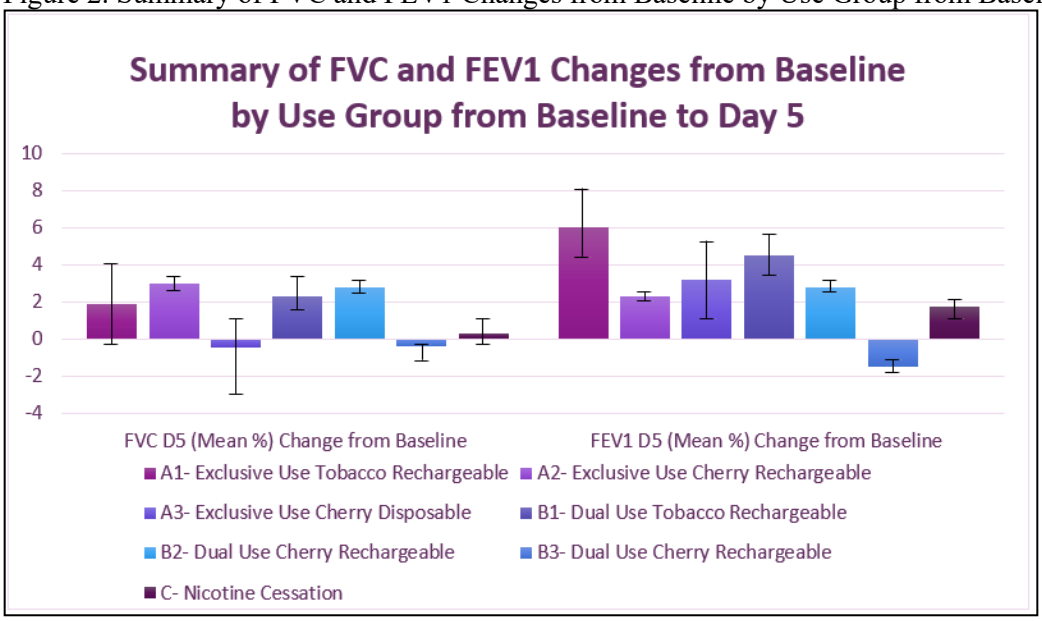


Table 5. Measured FVC Summary and Day 5 vs. Baseline Statistical Comparisons[11].

Day	Exclusive E-Cigarette Use Groups			Dual Use Groups			Nicotine Cessation
	Tobacco Rechargeable	Cherry Rechargeable	Cherry Disposable	Tobacco Rechargeable	Cherry Rechargeable	Cherry Disposable	
−1	4.5 ± 1.1	4.4 ± 1.1	4.6 ± 0.9	4.5 ± 0.8	5.0 ± 1.0	4.4 ± 1.1	4.7 ± 0.8
5	4.6 ± 1.1	4.5 ± 1.1	4.4 ± 0.9	4.6 ± 0.9	5.1 ± 1.0	4.4 ± 1.1	4.8 ± 0.8
Day 5 Change from Day -1 (baseline)							
N	15	15	14	15	15	14	14
Absolute Change	0.1 ± 0.1	0.1 ± 0.2	−0.1 ± 0.3	0.1 ± 0.2	0.1 ± 0.3	−0.0 ± 0.1	0.0 ± 0.1
p-Value	***0.0207***[a]	***0.0113***[a]	0.4017	0.0615	0.1288	0.2440	0.4266
% Change	1.9 ± 2.3	3.1 ± 4.1	−0.9 ± 5.4	2.6 ± 4.7	3.0 ± 7.9	−0.8 ± 2.8	0.5 ± 2.3

Day −1 and 5 and absolute change values are presented as arithmetic mean ± SD in L.
% change presented as arithmetic mean ± SD.
[a] Statistically significant.

Table 6. Measured FEV1 Summary and Day 5 vs. Baseline Statistical Comparisons[11].

Day	Exclusive E-Cigarette Use Groups			Dual Use Groups			Nicotine Cessation
	Tobacco Rechargeable	Cherry Rechargeable	Cherry Disposable	Tobacco Rechargeable	Cherry Rechargeable	Cherry Disposable	
−1	3.4 ± 0.8	3.3 ± 1.0	3.4 ± 0.7	3.2 ± 0.5	3.8 ± 0.8	3.3 ± 0.9	3.5 ± 0.7
5	3.6 ± 0.9	3.4 ± 1.0	3.4 ± 0.8	3.3 ± 0.7	3.9 ± 0.8	3.2 ± 0.9	3.7 ± 0.7
Day 5 Change from Day -1							
N	15	15	14	15	15	14	14
Absolute Change	0.2 ± 0.3	0.1 ± 0.1	0.1 ± 0.2	0.1 ± 0.3	0.1 ± 0.1	−0.0 ± 0.1	0.1 ± 0.2
p-Value	***0.0148***[a]	***0.0276***[a]	0.0986	0.1040	***0.0191***[a]	0.1735	0.2143
% Change	6.0 ± 8.6	2.8 ± 4.6	3.2 ± 6.8	4.6 ± 9.6	2.7 ± 4.2	−1.5 ± 3.5	1.6 ± 5.0

Day −1 and 5 and absolute change values are presented as arithmetic mean ± SD in L.
% change presented as arithmetic mean ± SD.
[a] Statistically significant.

Study Critique

The main limitation of this study is that it was only a short-term 5-day trial, and therefore the results gained from it are difficult to translate into long term recommendations for patients looking for another option besides conventional cigarettes. Therefore, longer-term studies may be more appropriate for measuring the outcomes and physiological parameters associated with e-cigarette product use. This study also only used one product type, namely the closed system e-cigarettes[11], making it difficult to make broad conclusions on all e-cigarettes as a whole. Lastly, because the participants were housed at the research center throughout the duration of the study, this may have motivated them to behave differently than they would in their regular daily lives, which could have potentially affected the results of the study. However, this may be offset by the fact that closer monitoring of patients allowed for better control of study variables that would not have otherwise been possible.

Study #2

Short-term Pulmonary Effects of Using an Electronic Cigarette - Impact on Respiratory Flow Resistance, Impedance, and Exhaled Nitric Oxide. Vardavas et al.

Objective

To assess whether or not smoking an e-cigarette for 5 minutes has an effect on the pulmonary function tests (FEV_1, FVC, FEV_1%, PEF, maximal expiratory flow at 25%, 50%, and 75%, and maximal mid-expiratory flow) in healthy smokers[12].

Study Design

Thirty (30) adults, both male and female (14 men, 16 women), from Athens, Greece were enrolled in this study based on whether or not they met the inclusion and exclusion criteria provided in Table 5 below[12]. The e-cigarettes used during this study were all NOBACCO e-cigarettes, black line, and all contained the same amount of nicotine, 11 mg, reported by the manufacturer[12].

Researchers implemented a laboratory-based intervention study design[12]. Participants were told to withhold from eating and drinking for at least 2 hours and avoid smoking for 4 hours prior to conduction of the study. All participants received baseline testing prior to the e-cigarette trials. Ten participants were randomly selected to act as the control group during the first session. During this session, both groups were asked to use an e-cigarette for 5 minutes as if normally smoking. E-cigarettes given to the control group had the cartridges removed[12]. Doing so prevented vapor production, therefore blinding was not possible. The experimental group was given the same instructions but were provided e-cigarettes with the cartridge intact. Researchers

then compared changes in pulmonary function between the experimental group (20 participants) and the control group (10 participants)[12]. In the second session the same procedure was repeated without a control group. Every subject participated as part of the experimental group (30 total participants), smoking e-cigarettes with an intact cartridge, and researchers compared spirometry findings of each individual to their own baseline pulmonary function.

Table 7. Study #2 - Inclusion and Exclusion Criteria[12].

Inclusion Criteria	Exclusion Criteria
● Age 19-56 years old (average age 34.8) ● Minimum pack-year index of 5 ● Current smokers at the time study was conducted	● Chronic disease ● Lung disease (including history of bronchial asthma or bronchial hyperreactivity) ● Acute illness in the 2 weeks prior to the study ● Currently pregnant or lactating ● Current use of any medications

Pulmonary function was measured via guidelines set by the American Thoracic Society/European Respiratory Society task force guidelines using a Jaeger MasterScreen spirometry system[12]. They measured FEV1, FVC, FEV1%, PEF, maximal expiratory flow at 25%, 50%, and 75% of vital capacity, and maximal mid-expiratory flow while the participants were in a seated position[12]. Each test was repeated at least three times and all measurements needed to be within 10% of the standard deviation after three attempts in order to meet the criteria set for the study[12]. These criteria were put in place to ensure that subjects had received proper instruction about how to use the equipment and allow them time to practice to feel comfortable using the spirometer, in hopes to obtain a more accurate reading[12].

The authors of this study implemented the Kolmogorov-Smirnov tests for statistical analysis of their data, and assessed the differences between pre- and post-measurements, response based on gender, and experimental and control conditions using bivariate analysis[12]. They report using the paired Student t test for parametric data and the Wilcoxon signed rank test for nonparametric data[12]. The correlation between respiratory function tests prior to and after intervention were analyzed by applying Pearson correlations[12].

Study Results

Baseline spirometry results are listed in Table 6 below. No change in PFTs measured using spirometry was noted after 5 minutes of e-cigarette use.

Table 8. Baseline Characteristics and Respiratory Function of Study Participants by Sex[12].

Characteristic	Female	Male	P Value[a]
Number	16	14	
Age, y, mean ±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/s	1.50	1.84	0.001
MEF_{25}, L/s	3.93	5.08	0.293
MEF_{50}, L/s	6.04	8.35	0.050
MEF_{75}, L/s	3.64	5.45	0.001
MMEF, L/s	3.16	4.10	0.056

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 mid-expiratory flow, PEF - peak expiratory flow, FVC - forced vital capacity, FEV1 - forced expiratory volume in 1 s

[a]"P Values based on Student t tests for all... performed with Wilcoxon signed rank test. $P < 0.05$ classified as statistically significant."

Overall, researchers concluded that using an e-cigarette for as little as 5 minutes resulted in physiologic responses, such as increased lung flow resistance, based on impulse oscillometry[12]. Since impulse oscillometry is known to "detect oncoming pathophysiologic changes of the respiratory system before spirometry," these changes were not reflected in spirometry results[12]. Although changes to pulmonary flow resistance noted during the study were too small to induce any clinically relevant symptoms in study participants, researchers claim that the general public is at a higher risk of becoming symptomatic with increased regular use given they smoke more than 5 minutes per day[12].

Study Critique

Although this study did a good job of excluding individuals with chronic and/or lung disease and other potential confounding, health-related variables, the authors of this study failed to report spirometry data other than baseline measurements. Data and statistical analysis from other measurements, such as impulse oscillometry, was performed and reported, but these findings were not of interest in this meta-analysis. Without explicit data from this study, we were unable to determine what the spirometry results showed and if they were statistically significant. This forced us to analyze the results of this study based off of what we could infer from their conclusion, deeming our analysis invalid due to insignificant data. Limitations, determined by the authors of this study, have convinced researchers to recommend that more research be done in order to support the claims they have made, determine more tangible evidence of adverse health effects, and look into if the long term benefits of smoking cessation outweigh the short term adverse effects of e-cigarette use[12].

Study #3

First Comparative Results About the Direct Effect of Traditional Cigarette and E-cigarette Smoking on Lung Alveolocapillary Membrane Using Dynamic Ventilation Scintigraphy. Barna, et al.

Objective

To compare Dynamic Inhalation Scintigraphy (DIS) results in healthy subjects with a history of conventional cigarette smoking, after using an e-cigarette and after returning to smoking conventional cigarettes for one week[13].

Study Design

Twenty-four (24) healthy male subjects, with an average age of 35 years old, volunteered to participate in this study. The inclusion and exclusion criteria set by researchers is present in Table 7 below[13]. Each participant received baseline pulmonary function testing while using e-cigarettes regularly[13]. Participants were then instructed to return to smoking conventional cigarettes for one week, requiring them to smoke at least 20-25 cigarettes per day[13]. After one week of conventional cigarette use, pulmonary function tests were performed for a second time in all patients except one who was examined after 8 days of conventional cigarette use[13]. Data from this individual was not included in their analysis. Respiration tests, measuring FVC, FEV_1, PEF, and FEV_1/FVC, were performed using EuTest Plus VT-17 spirometry[13].

Statistical analysis, using the paired t-test, was done to compare differences between the initial baseline pulmonary function with e-cigarette use and measurements after one week of conventional cigarette use[13].

Table 9. Study #3 - Inclusion and Exclusion Criteria[13].

Inclusion Criteria	Exclusion Criteria
● Age ranging from 20-64 years old ● Heavy smokers in the past ● Regular use of e-cigarettes containing ≥ 10 mg nicotine/mL at the time of the study	● Subjects with respiratory complaints ● Subjects with known pulmonary disease

Study Results

Data collected from individual test subjects is located in Table 8, and the results of statistical analysis are presented in Table 9. Data from this study showed statistically significant decreases in FVC and FEV1 ($p < 0.05$, paired t-test) after 1 week of traditional cigarette use, but no significant differences in PEF and FEV1/FVC were found between cigarette and e-cigarette use[13]. This study concluded that from their results, the harm associated with e-cigarette use is less significant than that of conventional cigarettes[13]. They recommended e-cigarettes be used as a tool to help patients who are heavy smokers quit smoking[13].

Table 10. Study #3 - Baseline with Regular E-cigarette Use vs. Conventional Cigarette Use 7 Days[13].

Pulmonary Function Tests	# of Study Participants			
	e-cigarette > cigarette	e-cigarette < cigarette	e-cigarette = cigarette	Total
FVC	16	5	3	24
FEV1	2	22	0	24

Cigarette - Spirometry results after 7 days of conventional cigarette use
E-cigarette - Baseline spirometry results with regular e-cigarette use
FVC - forced vital capacity, FEV1 - forced expiratory volume in 1 sec

Table 11. Study #3 - Results of Statistical Comparison of Pulmonary Test Parameters[13].

	Paired Differences						
Comparison: ec to c	Mean	SD	SEM	95% CI of the difference	*t*	*d.f.*	Significance (two tailed)
FVC	0.13750	0.28135	0.05743	0.01870 - 0.25630	2.394	23	0.025
FEV1	0.15833	0.36406	0.07431	0.00461 - 0.31206	2.131	23	0.044
PEF	0.77750	1.91179	0.39024	- 0.02978 to 1.58478	1.992	23	0.058
FEV1/FVC	0.01000	0.03683	0.00752	- 0.00555 to 0.02555	1.330	23	0.197

Shapiro-Wilk test (P > 0.1) and paired t-test.
c - conventional cigarette, ec - e-cigarette, d.f - degrees of freedom, FVC - forced vital capacity, FEV1 - forced expiratory volume in 1 s, PEF - peak expiratory flow rate

Study Critique

Limitations of this study include its size and researchers' ability to control smoking frequency, methods, and nicotine intake prior to and during the experiment. This study was too small with a very limited number of participants all of whom were male, and the study groups were not randomized or blinded.

All participants were considered to be "heavy smokers" requiring prior use of conventional cigarettes in order to meet inclusion criteria. Determinants of what was considered

to be heavy smoking, the frequency or duration of their conventional cigarette use, nor the amount of time passed since participants stopped using conventional cigarettes was explicitly stated by researchers. Considering the wide variety of ages, these parameters would have been important in determining the homogeneity or heterogeneity of the study population being studied.

Regular use of e-cigarettes containing at least 10 mg nicotine/mL at the time of the study was also required to participate. The frequency and duration of "regular" e-cigarette use was never defined. There was no maximum limit to the amount of nicotine allowed in e-cigarettes used by study participants. They did not report the amount of nicotine in each individual's e-cigarette cartridge prior to the study.

During the study, participants were asked to return to conventional cigarette use for 1 week and were informed to smoke at least 20-25 cigarettes/day, but there was no maximum limit to how many cigarettes they could smoke in a day, and the number of cigarettes smoked per day by participants was not explicitly stated.

All of the following has lead us to believe that there could have been large variations in pulmonary function between study participants. Researchers did not correct for these confounding variables, affecting the validity of their results.

Discussion

The first study was the largest and most well-designed study that was analyzed. It involved over one-hundred adult male and female participants who had to satisfy strict inclusion and exclusion criteria. Similarly, to much of the current literature on this topic, the main critique of the study was that it was short-term, lasting only 5 days. Based on the results within this study, there is a lack of statistically significant evidence to recommend that a patient make the switch from a conventional to a traditional cigarette. The data that was significant informs us that there might be a benefit to exclusive e-cigarette usage with either a rechargeable tobacco flavored or rechargeable cherry flavored e-cigarette, however further long term studies are needed in order to strengthen this data.

In the second study, researchers compared PFTs of experimental and control groups after 5 minutes of e-cigarette use, with the only difference between groups being the presence or absence of the e-cigarette cartridge (respectively). They also measured the difference between PFTs of current smokers before (baseline) and after 5 minutes of e-cigarette use. The results of spirometry, both baseline and post-exposure, were deemed within normal limits. This, along with other limitations of the study, is the reason data from this study cannot be applied to our patient or be used for making clinical decisions regarding e-cigarettes.

The third study was the only study from our analysis to actually give recommendations about the role of e-cigarettes as a smoking cessation technique. Researchers reported that “it can be recommended to heavy smokers who are unable to stop smoking” since their research was able to reveal statistically significant evidence of decreased FVC and FEV1 after smoking

conventional cigarettes for a total of 7 days[13]. Although this data is the most recent from the articles analyzed in the review the limitations of this study negate the validity of it's statistically significant data.

Out of all the studies reviewed, the third one had the least amount of criteria for participants entering into the study. The study only included subjects of male gender, had a very small sample size used in statistical analysis (23 subjects), did not account for confounding variables that could have affected lung function and adaptability prior to participation, and were unable to limit the amount of cigarettes smoked amongst study participants during the experiment which in turn impaired their ability to provide equivocal amounts of e-cigarette and conventional cigarette use for comparison. All of which could have led to the results they found.

Of importance was the lack of a maximum limit for cigarette and e-cigarette use present in any of the studies reviewed. All set minimum amounts for participants to comply with, but without a maximum limit it can be suspected, especially with the wide age ranges consistent between studies, that some participants with a history of increased duration/frequency of cigarette use were predisposed to alterations in lung function due to an inability of their lungs to adapt to physiologic changes caused by cigarette or e-cigarette use.

The differences between the chosen studies due to the lack of available literature on this topic currently, created a weakness in our meta-analysis itself as well. Most notably, while each of our studies included measurements of pulmonary function testing (FEV1, FVC) in healthy adult smokers, they each had very different study designs. The first study specifically tried to

look at the differences in physiologic parameters in those who either partly switched to e-cigarettes, fully switched to e-cigarettes, or gave up tobacco products entirely, while the second study looked at differences between those using e-cigarettes with and without a cartridge, and the third study observed changes seen after one week of conventional cigarette use in prior e-cigarette users. The lack of congruence seen in the current data reflects our need for further evaluation on this topic.

Conclusion

Two out of the three studies that were analyzed did not yield statistically significant results able to be utilized in formal recommendations for patients. The main obstacle that these studies faced was that they were short term, measuring physiologic changes either over a 5 day, or a 5 minute period. The third and final study was able to come to the conclusion that e-cigarette usage is safer than conventional cigarettes and should be offered to patients as a safer alternative. However, this study had the most flaws out of all three, making this conclusion a weak one at best. Specifically, this study had the smallest sample size, with only 23 subjects included in the data analysis, included only male subjects, and had very few parameters the amount of e-cigarette usage throughout the study.

Before a formal recommendation can be made to S.C. on whether he should switch from conventional cigarettes to e-cigarettes, more long-term, well designed studies need to be performed. At this time, we recommend that S.C be shown the current evidence in support of e-cigarettes, while also being warned about possible untoward side effects and making sure he is well informed on the current cases of vaping related deaths so that he can make an educated decision.

References

1. Sood AK, Kesic MJ, Hernandez ML. Electronic cigarettes: one size does not fit all. J Allergy Clin Immunol. 2018;141(6):1973-1982. doi:10.1016/j.jaci.2018.02.029
2. Misra M, Leverette RD, Cooper BT, Bennett MB, Brown SE. Comparative in vitro toxicity profile of electronic and tobacco cigarettes, smokeless tobacco and nicotine replacement therapy products: e-liquids, extracts and collected aerosols. *Int J Environ Res Public Health. 2014*;11(11):11325-11347. doi:10.3390/ijerph111111325
3. Know the risks: e-cigarettes & young people. U. S. Surgeon general's report. https://e-cigarettes.surgeongeneral.gov/. Accessed September 30, 2019.
4. Raven K. Teen vaping linked to more health risks. Yale Medicine. https://www.yalemedicine.org/stories/teen-vaping/. Accessed September 30, 2019.
5. Outbreak of Lung Injury Associated with E-cigarette Use, or Vaping. www.cdc.gov. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html. Published September 27, 2019. Accessed October 1.
6. Lung Illnesses Associated with Use of Vaping Products. www.fda.gov. https://www.fda.gov/news-events/public-health-focus/lung-illnesses-associated-use-vaping-products. Updated September 26, 2019. Accessed October 1.
7. Vaporizers, e-cigarettes, and other electronic nicotine delivery systems(Ends). U.S. Food & Drug Administration Website. September 2019. http://www.fda.gov/tobacco-products/products-ingredients-components/vaporizers-e-cigarettes-and-other-electronic-nicotine-delivery-systems-ends. Accessed September 30, 2019.
8. Ghosh S, Drummond MB. Electronic cigarettes as smoking cessation tool: are we there? *Curr Opin Pulm Med*. 2017;23(2):111-116. doi:10.1097/MCP.0000000000000348
9. Overview of Pulmonary Function Testing in Adults. Up to Date. https://www.uptodate.com/contents/overview-of-pulmonary-function-testing-in-adults?search=pulmonary%20function%20tests&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed September 30, 2019.
10. Johnson JD, Theurer WM. A stepwise approach to the interpretation of pulmonary function tests. *AFP*. 2014;89(5):359-366.
11. D'Ruiz C, O'Connell G, Graff D, Yan S. Measurement of cardiovascular and pulmonary function endpoints and other physiological effects following partial or complete substitution of cigarettes with electronic cigarettes in adult smokers. *Regul Toxicol Pharmacol*. 2017;87:36-53.
12. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN, Behrakis PK. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. Chest. 2012;141(6):1400-1406. doi:10.1378/chest.11-2443
13. Barna S, Rózsa D, Varga J, et al. First comparative results about the direct effect of traditional cigarette and e-cigarette smoking on lung alveolocapillary membrane using dynamic ventilation scintigraphy. Nucl Med Commun. 2019;40(2):153-158. doi:10.1097/MNM.0000000000000957