

Effect of e-Cigarette Use on Cough Reflex Sensitivity



Peter V. Dicpinigaitis, MD, FCCP; Alfredo Lee Chang, MD; Alis J. Dicpinigaitis; and Abdissa Negassa, PhD

BACKGROUND: E-cigarettes (e-cigs) have attained widespread popularity, yet knowledge of their physiologic effects remains minimal. The aim of this study was to evaluate the effect of a single exposure to e-cig vapor on cough reflex sensitivity.

METHODS: Thirty healthy nonsmokers underwent cough reflex sensitivity measurement using capsaicin cough challenge at baseline, 15 min, and 24 h after e-cig exposure (30 puffs 30 s apart). The end point of cough challenge is the concentration of capsaicin inducing five or more coughs (C_5). The number of coughs induced by each e-cig inhalation was counted. A subgroup of subjects ($n = 8$) subsequently underwent an identical protocol with a non-nicotine-containing e-cig.

RESULTS: Cough reflex sensitivity was significantly inhibited (C_5 increased) 15 min after e-cig use (-0.29 ; 95% CI, -0.43 to -0.15 ; $P < .0001$); 24 h later, C_5 returned to baseline (0.24 ; 95% CI, 0.10 - 0.38 ; $P = .0002$ vs post-15-min value). A subgroup of eight subjects demonstrating the largest degree of cough reflex inhibition had no suppression after exposure to a non-nicotine-containing e-cig ($P = .0078$ for comparison of ΔC_5 after nicotine vs non-nicotine device). Furthermore, more coughing was induced by the nicotine-containing vs non-nicotine-containing device ($P = .0156$).

CONCLUSIONS: A single session of e-cig use, approximating nicotine exposure of one tobacco cigarette, induces significant inhibition of cough reflex sensitivity. Exploratory analysis of a subgroup of subjects suggests that nicotine is responsible for this observation. Our data, consistent with previous studies of nicotine effect, suggest a dual action of nicotine: an immediate, peripheral protussive effect and a delayed central antitussive effect.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT02203162; URL: www.clinicaltrials.gov.

CHEST 2016; 149(1):161-165

KEY WORDS: capsaicin; cough; electronic cigarette; nicotine

ABBREVIATIONS: C_5 = concentration of capsaicin inducing five or more coughs; e-cig = e-cigarette

AFFILIATIONS: From the Department of Medicine (Drs P. Dicpinigaitis, Lee Chang, and A. J. Dicpinigaitis) and Department of Epidemiology and Population Health (Dr Negassa), Albert Einstein College of Medicine; and Department of Medicine (Drs P. Dicpinigaitis, Lee Chang, and A. J. Dicpinigaitis), Montefiore Medical Center, Bronx, NY.

Part of this article has been presented in abstract form at the American Thoracic Society International Conference, May 19, 2015, Denver, CO.

FUNDING/SUPPORT: The authors have reported to CHEST that no funding was received for this study.

CORRESPONDENCE TO: Peter V. Dicpinigaitis, MD, FCCP, Einstein Division/Montefiore Medical Center, 1825 Eastchester Rd, Bronx, NY 10461; e-mail: pdicpin@gmail.com

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DOI: <http://dx.doi.org/10.1378/chest.15-0817>

e-Cigarettes (e-cigs) have rapidly attained common usage worldwide, prompting significant discussion and speculation in the medical and lay media regarding potential harms and benefits of these devices,¹⁻⁶ their role as smoking cessation aids,⁷⁻¹⁰ and how their sale and distribution should be regulated, if at all.^{11,12} Despite the popularity of e-cigs, remarkably little scientific data have been generated exploring the physiologic effects of e-cig use or “vaping.” Few studies have evaluated the effect of e-cig use on the respiratory tract¹³⁻¹⁶ and on pulmonary function^{17,18} and none, to our knowledge, has evaluated its effect on cough reflex sensitivity. Indeed, there has been a call for increased medical research efforts in the field of health effects of e-cigs.^{1,19,20}

Previous studies have shown that otherwise healthy smokers of tobacco cigarettes have a diminished cough reflex sensitivity relative to nonsmokers,²¹ presumably on the basis of chronic, cigarette smoke-induced desensitization of airway cough receptors. This hypothesis is supported by the demonstration, in chronic tobacco cigarette smokers, of enhancement of cough reflex sensitivity within 2 weeks of smoking cessation.²² These studies suggest that cough reflex sensitivity is a dynamic phenomenon, able to be modulated by the presence or absence of stimuli such as cigarette smoke, even after prolonged exposure.²³ Thus, the aim of the present study was to evaluate the effect of

a single exposure to e-cig vapor on cough reflex sensitivity in healthy nonsmokers.

e-cigs are electronic nicotine delivery devices. A cartridge within the e-cig contains nicotine in a vehicle of distilled water, as well as either vegetable glycerin or propylene glycol. A lithium battery within the e-cig generates heat, thus vaporizing the nicotine solution. No combustion is involved in the creation of the nicotine-containing vapor that is inhaled by the user and promptly absorbed from the respiratory tract into the bloodstream.²⁴

Capsaicin, the pungent extract of red peppers, has been shown in over 3 decades of clinical experience to experimentally induce cough in a safe, dose-dependent, and reproducible manner.²⁵ Thus, capsaicin cough challenge testing has become an important tool in clinical research, allowing for the accurate measurement of the effect of a pharmacologic or other intervention on the sensitivity of the cough reflex.^{25,26} The standard end point measured in capsaicin cough challenge testing is the concentration of capsaicin inducing five or more coughs (C_5). In healthy volunteers, this end point has been demonstrated to be highly reproducible, in the short-term (20 min to 14 days) and long-term (months to years).²⁷ Standard capsaicin challenge methodology was used in this study to assess the effect of e-cig vapor exposure on cough reflex sensitivity.

Materials and Methods

Subjects

Thirty adult lifetime nonsmokers were enrolled after providing written, informed consent for this study, which was approved by the institutional review board of the Albert Einstein College of Medicine (institutional review board No. 2014-3288). Subjects were without history of asthma, gastroesophageal reflux disease, or symptoms suggestive of acute viral upper respiratory tract infection (common cold) or allergies within 4 weeks of enrollment. Subjects were not receiving medication known to affect cough reflex sensitivity.

Study Design

Upon enrollment, subjects underwent capsaicin challenge testing on day 1 to establish their baseline cough reflex sensitivity. On study day 2, subjects underwent an e-cig vaping session. While in a relaxed, seated position, subjects inhaled a total of 30 puffs (one puff every 30 s) from a disposable e-cig (Blu, Classic Tobacco flavor; Lorillard Technologies [Blu is now made by Fontem US, Inc]). The Blu e-cig is among the most, if not the most, commonly used e-cig in the United States. A disposable Blu e-cig contains 20 to 24 mg of nicotine and delivers approximately 400 puffs of nicotine-containing vapor. The ingredients of the vapor include distilled water, nicotine, vegetable glycerin, natural flavors, artificial flavors, and citric acid.²⁸ Thus, 30 puffs of the e-cig delivered approximately 1.5 to 1.8 mg of nicotine. In comparison, the estimated nicotine intake from a

tobacco cigarette is in the range of 1.07 to 2.6 mg, depending on the brand.^{29,30} Fifteen minutes after the conclusion of the e-cig session, subjects underwent capsaicin cough challenge. On study day 3, approximately 24 h after the vaping session, subjects underwent repeat capsaicin challenge. In addition, the number of coughs induced by each of the 30 puffs of the e-cig was tabulated. A cough number of five was assigned for at least five coughs.

A subgroup of eight subjects who demonstrated large degrees of cough reflex sensitivity inhibition after e-cig exposure (defined as at least a two doubling-concentration increase in C_5) underwent a repeat protocol identical to the above but with a disposable non-nicotine-containing e-cig with similar vehicle (Full Tobacco flavor; Blue Star). Subjects were unaware that the e-cig used in this portion of the study was nicotine free.

Capsaicin Cough Challenge

Capsaicin cough challenge testing was performed as previously described.^{25,27} Briefly, subjects inhaled single, vital-capacity breaths of ascending, doubling concentrations (range, 0.49-1,000 μ M) of aerosolized capsaicin solution, administered via a compressed air-driven nebulizer controlled by a dosimeter, with 1-min intervals between inhalations, until five or more coughs resulted in the 15 s following an inhalation. Placebo saline breaths were randomly interspersed between capsaicin doses to increase challenge blindness. The end point of capsaicin challenge testing is C_5 .

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