The rise of electronic cigarettes: A brief look at their cardiovascular effects and what makes them so popular

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Abstract:

Electronic cigarettes (ECs) have quickly gained popularity among adolescents and adults, and have begun to replace conventional cigarettes as a source of nicotine. Although little is known about the impact of the exposure of chemical constituents of ECs, two major constituents, propylene glycol and vegetable glycerin have been implicated as formaldehyde-releasing agents. The wide variety of EC flavours appeal to users of all ages with reports showing a positive correlation between EC use and sweet flavorings. In addition, although marketing strategies advertise ECs as tools to facilitate smoking cessation, the evidence supporting this role is weak. In terms of its effect on users with pre-existing cardiovascular diseases, the data is conflicting regarding whether ECs have an impact on cardiovascular function. Although it is obvious that their safety and efficacy needs to be better understood, it is nonetheless essential to review what the research conducted so far has shown.

Despite the prevalence of conventional cigarette smoking by adolescents and adults at historically low numbers, public health agencies across North America are grappling with a new and different type of problem – the use of electronic cigarettes (ECs) [1]. The mid to late 2000s saw a rapid increase in the use of these battery-powered electronic devices which heat liquids (mainly propylene glycol, glycerol, and nicotine solution) stored in a disposable cartridge into a vapour form for inhalation [2]. This is in contrast to conventional combustible cigarettes which deliver nicotine primarily through the burning of tobacco and are widely known as a risk factor for several preventable diseases including cardiovascular and pulmonary diseases, and certain types of cancers [3]. ECs have quickly risen in popularity with over 15.4% of the U.S. adult population having tried them at least once in the past [4]. Although heavily marketed as a 'healthy' alternative to conventional cigarettes due to their ability to deliver nicotine without the burning of tobacco and as an inexpensive smoking-cessation tool, recent evidence questions their safety, leading to the introduction of stringent regulations across North America [5]. Under the new proposed rules which took effect in 2014, the U.S. Food and Drug Administration (FDA) banned the sale of ECs to individuals under the age of 18 and regulated the sale of ECs as tobacco products [3]. As of 2017, Canada has prohibited manufacturing and sale of ECs containing nicotine [6]. In spite of such regulations, ECs remain widely available online and in retail outlets which calls for the need to better understand the effects on both short- and long-term health.

Chemical constituents of ECs

In a conventional cigarette, majority of the smoke toxicants are generated due to the burning or combustion of tobacco containing nicotine at temperatures around 700-950 °C [7]. The smoke from this reaction contains over 7,000 chemicals, 69 of which are known carcinogens that have been implicated in major diseases [8]. In contrast, ECs differ in product design such that they do not burn or contain natural tobacco [9]. Instead, they deliver nicotine directly through the heating of the EC-liquid solution containing nicotine, flavourings, and other products which produce an aerosol of ultrafine particles (often called "vapour") which are then inhaled by the user [9,10]. It is still unknown whether these ultrafine particles produce similar toxicity effects to those generated by conventional cigarette smoke [11]. However, the available evidence suggests that ultrafine particles from air pollution and tobacco smoke encourage pulmonary inflammation and consequently increase the risk of cardiovascular and respiratory diseases, even after short-term exposure [11].

Despite the variability in EC-liquid composition due to a wide range of nicotine and flavouring concentrations used, two nicotine-solvent compounds, propylene glycol and vegetable glycerin, represent the majority of the EC-liquid volume [10,12]. Although these two ingredients have been approved by the FDA for commercial use, their role in ECs has not been well characterized [13]. Evidence has shown that repeated exposure to propylene glycol can cause irritation

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of the respiratory airways [13]. To make matters worse, the degradation of propylene glycol and glycerin during the heating of ECs in the presence of oxygen produces formaldehyde and acetaldehyde, which are known human carcinogens, at levels approaching those from conventional cigarettes [14]. In comparison, the emission levels of other smoke toxicants such as volatile organic compounds and tobacco-specific nitrosamines remain either undetectable or as a fraction of what is typically found in conventional cigarette smoke [14,15]. A study looking at EC vapours found that over 2% of the solvent molecules from the aerosol vapours were converted from propylene glycol and glycerol into formaldehyde-releasing agents [14]. Although the disposable cartridges themselves have shown to have zero or only trace amounts of these harmful chemicals, heating of propylene glycol in the EC cartridge may result in the formation of these chemicals [16]. Although it is unknown how formaldehyde-releasing agents affect the respiratory tract, the classification of formaldehyde as a group 1 carcinogen calls for a more detailed understanding of its role in ECs [14]. Results from toxicological studies show the presence of formaldehyde in conventional cigarettes as well, where it is known to be generated during tobacco combustion from saccharides such as sugars and cellulose used as tobacco ingredients [17]. If formaldehyde-releasing products from ECs do carry the same risk per unit of formaldehyde as gaseous formaldehyde from conventional cigarettes, then long-term vaping may lead to a 5 times increase in lifetime cancer risk compared to long-term conventional cigarette smoking [14]. This data was based on earlier studies looking at daily exposure of formaldehyde from ECs and was derived using protocols from Health Canada and the International Organization for Standardization, and the Massachusetts Department of Public Health [14] . In addition, EC smokers experience an increase in serum cotinine levels which are comparable to levels seen in conventional cigarette users [18]. Cotinine is a major alkaloid metabolite of nicotine and has been used as a biomarker for tobacco exposure in humans [18]. These findings demonstrate that the popular claim that EC emissions are "only water vapour" is false [19].

Impact of the wide availability of EC flavours

The availability of over 7,000 EC flavours make them one of the most frequently used flavoured tobacco product around the world [20]. In a 2014 study, 81% of the youth attributed the flavour availability as the primary reason for their initial use and/or continued use of ECs [21]. Multiple studies have found that the addition of flavours increase the palatability of the liquid in the ECs [22]. In one study, higher ratings of perceived sweetness of different EC flavours were positively associated with liking the product [22]. Another study looking at EC flavour preferences of a high-school in the U.S. found that adolescents were significantly more likely to prefer flavours perceived as sweet, such as "fruit," "candy/dessert," and "vanilla" compared to adults [23]. In the past, the disproportionate preference of flavoured tobacco cigarettes by the youth population led to their ban by the FDA [23]. The wide availability of flavours can create the perception that their addition makes the ECs less harmful and therefore contribute to the increased popularity among youth [22].

ECs as a smoking cessation tool

The tobacco industry has marketed ECs as a lower-risk smoking-cessation tool for individuals who would otherwise be reluctant to quit smoking [24]. This includes promoting them as a healthier alternative on social media sites such as YouTube, Facebook and, Twitter which do not require age verification from its users, and through banners on entertainment websites visited frequently by youth [24]. However, data from epidemiological studies have been inconsistent in terms of whether the use of ECs are associated with long-term abstinence from cigarette smoking [10]. Although some population-based surveys have found a positive correlation between EC use and quit attempts, other longitudinal studies report no such association [10]. A randomized control trial conducted in the U.K. found that EC smoking led to significantly higher rates of abstinence (18.0%) compared to those using nicotine-replacement products (9.9%) at a 1-year follow up [25]. Nicotine replacement products include nicotine-patches, gums, and lozenges which are commonly used as smoking cessation tools by individuals looking to quit conventional smoking [25]. However, these findings are contradicted by results from a randomized trial from New Zealand where adult smokers interested in quitting smoking achieved similar levels of smoking abstinence after 6-months using ECs compared to those given nicotine patch vouchers [26]. Meta-analyses of these studies suggest that there is little evidence to support the idea that nicotine-containing ECs help with smoking-cessation [27]. However, the number of attempts at smoking-cessation may be dependent on the type of EC device used, the amount of nicotine in the product, as well as the frequency of use [10]. Cross-sectional data shows that individuals who use the earlier versions of ECs tend to be dissatisfied with their device and show lower cessation rates compared to those who use newer versions which allow them to customize flavours and nicotine strength [28]. Similarly, the amount of nicotine emitted per puff second (nicotine flux) by an EC can influence cessation rates [29]. Certain brands with low "nicotine flux" may not provide enough nicotine replacement for a smoker to quit, and others might provide too much leading to undesired side effects such as nausea [29]. However, the studies on the use of ECs as a smoking cessation aid has only been conducted in adult populations and remains untested in youth [24].

Effects of ECs on the cardiovascular system

There is substantial evidence supporting the adverse effects of conventional cigarettes on cardiovascular health. A key question is whether similar effects are evident with ECs. Although oxidative stress and endothelial dysfunction is more pronounced with conventional smoking, the use of ECs could

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predispose individuals to adverse cardiovascular conditions, and has been linked to short-term pulmonary inflammatory reactions [30]. Increased aortic stiffness was observed following a 30-minute session use of EC, which was similar to the effects observed after 5-minutes of smoking tobacco [31]. However, since arterial stiffness returned to normal within 30 minutes after EC use, this may be only a short-term association [31]. Limited preclinical studies using mouse models have aimed to establish the impact of chronic EC use on cardiovascular health. Mice subjected to 8 months of chronic EC use at low levels exhibited significantly increased arterial stiffness and reduced vascular relaxation to a vasodilator [32]. Similarly, exposure to EC vapour increased systemic inflammation, systolic blood pressure, and showed an upward trend in diastolic blood pressure [33]. However, most of the current data on the cardiovascular effects of ECs comes from preclinical and cross-sectional studies. The results from these preclinical cell-culture and animal studies need to be replicated in human subjects in an ethical manner to assess for safety and efficacy of ECs. Similarly, since cross sectional studies rely on observational data from specific points in time, it is not yet possible to infer causation.

In addition to looking at EC use by the general population, it is also important to evaluate their impact on chronic tobacco users with pre-existing chronic obstructive pulmonary disease [COPD]. One recent retrospective study found evidence of a reduction in respiratory conditions including decreased respiratory infections and absence of deterioration in respiratory physiology [34]. They also reported improved general health and physical activity in COPD patients who reduced their tobacco consumption after switching from conventional cigarettes to ECs [34]. Similar improvements in health outcomes has been reported by an internet-based survey of individuals with COPD, majority of whom were smokers who attempted to avoid the adverse effects of smoking by switching to ECs [35]. These positive findings are in contrast with studies conducted in preclinical cell culture and animal models. For example, a study conducted using A/J mice widely used in cancer research due to their tendency to develop tumours, found increased cytokine expression, airway hyper-reactivity and lung-tissue destruction after prolonged exposure to nicotine-containing glycerol or propylene glycerol [36]. Another mouse study found a significant decrease in bacterial clearance from the lungs of the animals exposed to EC vapour for one week following infection with Streptococcus pneumonia [37]. It is well-known that patients with COPD experience exacerbated viral and bacterial complications which are a major cause of COPD-related morbidity and mortality [37]. Therefore, if EC use can impair immune responses against infections in mouse models, it is possible that they can accelerate disease progression in patients with COPD [37]. The contradictory findings among studies makes it difficult to get a clear understanding of the effects of ECs. Such differences result from a lack of defined models for EC exposure in both in vitro and in vivo studies and due to methodological drawbacks including differences in EC devices or in the concentration of EC vapour used [38,39].

Concluding remarks

With the continuous rise in the use of ECs by the youth population, it is concerning that their potential health effects remain to be fully elucidated. Although multiple studies have looked at the chemical constituents of ECs, the research has been conducted under controlled conditions which may not be the best representation of actual EC use [40]. It is becoming clear that the appeal of wide selection of flavours, including non-tobacco flavours such as candy, fruit, and dessert, likely appeal to consumers of all ages and may play a part in the initiation of EC use especially in youth [21]. An argument often posed by the proponents of ECs is their supposed role in smoking-cessation [41]. However, current evidence supporting their smoking-cessation role is weak and may provide the same benefit as nicotine replacement products available on the market [41]. Finally, while cross-sectional studies suggest there is a slight advantage of ECs over conventional cigarettes in individuals with pre-existing cardiovascular conditions, this evidence does not allow for strong conclusions to be drawn [42]. Any correlation between ECs and cardiovascular health is further complicated by short-term animal studies showing endothelial dysfunction following EC consumption [42].

With hundreds of EC brands dominating the market, it is important to develop a mathematical model which can accurately predict EC nicotine emissions and account for the variability in device design, ingredients in the EC-liquid solution, and user behaviour [40]. This would allow researchers to standardize parameters of the EC devices and generate results to determine causal relationships [40]. Furthermore, although observational studies can gather information on large number of users, randomized control trials can allow for experimental control over variable factors such as a user's nicotine dependence and previous attempts at smoking cessation [40]. Although these studies are conducted under idealized conditions and might not accurately depict real-time use of ECs, they are still needed to confirm the results shown in observational studies. Nonetheless, it is important to recognize the gaps in knowledge and use them as the foundation for future studies to accurately characterize the risks of ECs.

References

1. Drope J, Cahn Z, Kennedy R, Liber AC, Stoklosa M, Henson R, et al. Key issues surrounding the health impacts of electronic nicotine delivery systems (ENDS) and other sources of nicotine. CA Cancer J Clin [Internet]. 2017 Nov [cited 2020 Feb 6];67(6):449–71. Available from: http://doi.wiley.com/10.3322/caac.21413
2. Korfei M. The underestimated danger of E-cigarettes - also in the absence of nicotine. Vol. 19, Respiratory Research. BioMed Central Ltd.; 2018.
3. Rom O, Pecorelli A, Valacchi G, Reznick AZ. Are E-cigarettes a safe and good alternative to cigarette smoking? Ann N Y Acad Sci [Internet]. 2015 Mar 1 [cited 2020 Mar 23];1340(1):65–74. Available from: http://doi.wiley.com/10.1111/nyas.12609

4. QuickStats: Percentage* of Adults Who Ever Used an E-cigarette† and Percentage Who Currently Use E-cigarettes,§ by Age Group - National Health Interview Survey, United States, 2016¶. MMWR Morb Mortal Wkly Rep. 2017 Aug 25;66(33):892.
5. Worku D, Worku E. A narrative review evaluating the safety and efficacy of e-cigarettes as a newly marketed smoking cessation tool. SAGE Open Med. 2019 Jan;7:205031211987140.
6. Barry AR. Do the benefits of electronic cigarettes outweigh the risks?: The "cON" side. Vol. 71, Canadian Journal of Hospital Pharmacy. Canadian Society of Hospital Pharmacists; 2018. p. 45–7.
7. Mallock N, Pieper E, Hutzler C, Henkler-Stephani F, Luch A. Heated Tobacco Products: A Review of Current Knowledge and Initial Assessments. Vol. 7, Frontiers in Public Health. Frontiers Media S.A.; 2019.
8. U.S.DHSS. How Tobacco Smoke Causes Disease The Biology and Behavioral Basis for Smoking-Attributable Disease A Report of the Surgeon General. Public Health. 2010.
9. Glynos C, Bibli S-I, Katsaounou P, Pavlidou A, Magkou C, Karavana V, et al. Comparison of the effects of e-cigarette vapor with cigarette smoke on lung function and inflammation in mice. Am J Physiol Cell Mol Physiol [Internet]. 2018 Nov 1 [cited 2020 Mar 25];315(5):L662–72. Available from: https://www.physiology.org/doi/10.1152/ajplung.00389.2017
10. Chaffee BW. Electronic Cigarettes: Trends, Health Effects and Advising Patients Amid Uncertainty. J Calif Dent Assoc [Internet]. 2019 Feb [cited 2020 Feb 6];47(2):85–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30976150
11. Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. Circulation [Internet]. 2014 May 13 [cited 2020 Feb 6];129(19):1972–86. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24821826
12. Clapp PW, Jaspers I. Electronic Cigarettes: Their Constituents and Potential Links to Asthma. Vol. 17, Current Allergy and Asthma Reports. Current Medicine Group LLC 1; 2017. p. 79.
13. Czoli CD, Goniewicz ML, Palumbo M, Leigh N, White CM, Hammond D. Identification of flavouring chemicals and potential toxicants in e-cigarette products in Ontario, Canada. 1997 [cited 2020 Feb 6]; Available from: https://doi.org/10.17269/s41997-019-00208-1
14. Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde in e-cigarette aerosols [Internet]. Vol. 372, New England Journal of Medicine. Massachussetts Medical Society; 2015 [cited 2020 Mar 25]. p. 392–4. Available from: http://www.nejm.org/doi/10.1056/NEJMc1413069
15. Margham J, McAdam K, Forster M, Liu C, Wright C, Mariner D, et al. Chemical Composition of Aerosol from an E-Cigarette: A Quantitative Comparison with Cigarette Smoke. Chem Res Toxicol [Internet]. 2016 [cited 2020 Apr 17];29(10):1662–78. Available from: https://pubs.acs.org/sharingguidelines
16. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control. 2014 Mar;23(2):133–9.
17. Baker RR. The generation of formaldehyde in cigarettes-Overview and recent experiments. Food Chem Toxicol. 2006 Nov 1;44(11):1799–822.
18. Kaur G, Pinkston R, McLemore B, Dorsey WC, Batra S. Immunological and toxicological risk assessment of e-cigarettes. Eur Respir Rev [Internet]. 2018 [cited 2020 Feb 6];27(147). Available from: http://ow.ly/y3ee30hH2aB
19. Fernández E, Ballbè M, Sureda X, Fu M, Saltó E, Martínez-Sánchez JM, et al. Particulate Matter from Electronic Cigarettes and Conventional Cigarettes: a Systematic Review and Observational Study. Curr Envir Heal Rpt [Internet]. 2015 [cited 2020 Feb 6];2:423–9. Available from: http://www.pubmed.org
20. Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, et al. Four hundred and sixty brands of e-cigarettes and counting: Implications for product regulation. Tob Control. 2014;23:iii3–9.
21. Schneller LM, Bansal-Travers M, Goniewicz ML, McIntosh S, Ossip D, O'connor RJ. Use of flavored E-cigarettes and the type of E-cigarette devices used among adults and youth in the US—results from wave 3 of the population assessment of tobacco and health study (2015–2016). Int J Environ Res Public Health. 2019 Aug 1;16(16).
22. DeVito EE, Krishnan-Sarin S. E-cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure. Curr Neuropharmacol. 2017 Oct 19;15(4):438.
23. Morean ME, Butler ER, Bold KW, Kong G, Camenga DR, Cavallo DA, et al. Preferring more e-cigarette flavors is associated with e-cigarette use frequency among adolescents but not adults. PLoS One. 2018 Jan 1;13(1).
24. Activities of the E-Cigarette Companies. In: E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General [Internet] [Internet]. Atlanta (GA); 2016 [cited 2020 Apr 16]. p. 147–80. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538679/
25. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Smith KM, Bisal N, et al. A randomized trial of E-cigarettes versus nicotine-replacement therapy. N Engl J Med [Internet]. 2019 Feb 14 [cited 2020 Apr 16];380(7):629–37. Available from: http://www.nejm.org/doi/10.1056/NEJMoa1808779
26. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, et al. Electronic cigarettes for smoking cessation: A randomised controlled trial. Lancet. 2013;382(9905):1629–37.
27. Glantz SA, Bareham DW. E-Cigarettes: Use, Effects on Smoking, Risks, and Policy Implications. Annu Rev Public Health. 2018 Apr;39(1):215–35.
28. Giovenco DP, Delnevo CD. Prevalence of population smoking cessation by electronic cigarette use status in a national sample of recent smokers. Addict Behav. 2018 Jan 1;76:129–34.
29. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations between E-Cigarette type, frequency of use, and quitting smoking: Findings from a longitudinal online panel survey in Great Britain. Nicotine Tob Res. 2015;17(10):1187–94.
30. Macdonald A, Middlekauff HR. Electronic cigarettes and cardiovascular health: What do we know so far? Vol. 15, Vascular Health and Risk Management. Dove Medical Press Ltd.; 2019. p. 159–74.
31. Vlachopoulos C, Ioakeimidis N, Abdelrasoul M, Terentes-Printzios D, Georgakopoulos C, Pietri P, et al. Electronic Cigarette Smoking Increases Aortic Stiffness and Blood Pressure in Young Smokers. Vol. 67, Journal of the American College of Cardiology. 2016. p. 2802–3.
32. Olfert IM, De Vallance E, Hoskinson H, Branyan KW, Clayton S, Pitzer CR, et al. Chronic exposure to electronic cigarettes results in impaired cardiovascular function in mice. J Appl Physiol. 2018;124(3):573–82.
33. Crotty Alexander LE, Drummond CA, Hepokoski M, Mathew D, Moshensky A, Willeford A, et al. Chronic inhalation of e-cigarette vapor containing nicotine disrupts airway barrier function and induces systemic inflammation and multiorgan fibrosis in mice. Am J Physiol - Regul Integr Comp Physiol. 2018;314(6):R834–47.
34. Polosa R, Morjaria JB, Caponnetto P, Prosperini U, Russo C, Pennisi A, et al. Evidence for harm reduction in copd smokers who switch to electronic cigarettes. Respir Res [Internet]. 2016 [cited 2020 Apr 16];17(1). Available from: www.who.int/whosis/whostat/2008/en/
35. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: A worldwide survey of more than 19,000 consumers. Int J Environ Res Public Health. 2014 Apr 22;11(4):4356–73.
36. Garcia-Arcos I, Geraghty P, Baumlin N, Campos M, Dabo AJ, Jundi B, et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. Thorax [Internet]. 2016 [cited 2020 Apr 16];71(12):1119–29. Available from: http://dx.doi.org/10.1136/thoraxjnl-2015-208039
37. Sussan TE, Gajghate S, Thimmulappa RK, Ma J, Kim JH, Sudini K, et al. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. PLoS One. 2015;10(2).
38. Morjaria JB, Mondati E, Polosa R. E-cigarettes in patients with COPD: Current perspectives. Vol. 12, International Journal of COPD. Dove Medical Press Ltd.; 2017. p. 3203–10.
39. Bozier J, Rutting S, Xenaki D, Peters M, Adcock I, Oliver BG. Heightened response to e-cigarettes in COPD. ERJ Open Res. 2019 Feb;5(1):00192–2018.
40. Breland A, Soule E, Lopez A, Ramôa C, El-Hellani A, Eissenberg T. Electronic cigarettes: what are they and what do they do? Vol. 1394, Annals of the New York Academy of Sciences. Blackwell Publishing Inc.; 2017. p. 5–30.
41. Bhatnagar A, Payne TJ, Robertson RM. Is There A Role for Electronic Cigarettes in Tobacco Cessation? [Internet]. Vol. 8, Journal of the American Heart Association. American Heart Association Inc.; 2019 [cited 2020 Apr 18]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/31203709

https://doi.org/10.29173/hsi292

42. Buchanan ND, Grimmer JA, Tanwar V, Schwieterman N, Mohler PJ, Wold LE. Cardiovascular risk of electronic cigarettes: a review of preclinical and clinical studies. Cardiovasc Res [Internet]. 2019 Nov 7 [cited 2020 Feb 11];116(1):40–50. Available from: https://academic.oup.com/cardiovascres/advance-article/doi/10.1093/cvr/cvz256/5613736