E-Cigarettes and Cardiovascular Risk: Beyond Science and Mysticism

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Abstract

Cigarette smoking is the most important cause of premature death, and it is currently listed as a major independent risk factor for cardiovascular disease. Because of restrictive measures and widespread control policies, tobacco companies are now using aggressive marketing strategies in favor of smokeless tobacco, including electronic nicotine delivery systems, which are also known as electronic cigarettes or e-cigarettes. Although the regular use of these devices appears less hazardous than traditional cigarettes or other forms of smokeless tobacco, recent studies have shown that various potentially harmful substances, especially nicotine, ultraparticles, and volatile organic compounds, may be effectively inhaled or liberated in exhaled air during repeated e-cigarette puffing. This would enhance the risk of cardiac arrhythmias and hypertension, which may predispose some users to increased risk of cardiovascular events, which may be further magnified by other potential adverse effects such as arrhythmias, increased respiratory, and flow respiratory resistance. Some cases of intoxication have also been described, wherein large amounts of nicotine and other harmful compounds may be effectively absorbed. As the use of e-cigarettes is continuously rising, and it is also considered a potentially effective method for smoking cessation, more focused research is urgently needed to definitely establish the cardiovascular safeness of these devices.

Keywords
- e-cigarette
- electronic cigarette
- cardiovascular disease
- risk factor
- tobacco

The Cigarette Smoke Epidemics

According to the latest available updates released by the American Heart Association (AHA), 21.3% of men and 16.7% of women aged 18 years or older are current cigarette smokers in the United States. Although the percentage of current cigarette smokers (i.e., 19.0% overall) has declined by nearly one-fifth since 1998, when the rate was 24.1%,[1] tobacco smoking causes nearly 19.1% of overall deaths in the United States, with approximately one-third of these attributable to cardiovascular disease. Even more impressive is that approximately 11% of cigarette smoking–related deaths are reportedly caused by second-hand (so called passive) smoke. The direct medical costs and lost productivity costs associated with smoking are estimated at approximately $96 and $97 billion, thus totaling an estimated $193 billion

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per year.[1] Cigarette smoking, either in active or passive form, is therefore considered the most important preventable cause of premature death in the United States as well as in most industrialized and developing countries and is currently listed as a "major" independent risk factor for cardiovascular disease.[2] Cigarette smoke contains thousands of chemicals such as nicotine, carbon monoxide (CO), tar, and several carcinogens among many others, which contribute to a kaleidoscope of negative effects on human biology, including hypertension, decreased exercise tolerance, progression of atherosclerotic lesions, and procoagulant effects.

Smokeless Tobacco

Smokeless tobacco is a vague term that refers to several tobacco products used by means other than smoking and includes snuff (loose tobacco particles or sachets), chewing (loose leaf, plug, and twist formulations), spit tobacco, oral compresses, and dry powders (e.g., moist, *nass*, *snus*, *gutkha*, or *gul* tobacco). These products usually contain several additives, some of which are added for flavor (e.g., nuts, vanilla, sugar, spices, and oils), and others to enhance pH (e.g., ammonium and sodium carbonate) and thus increase the concentration of unprotonated nicotine.[3] The nicotine and other compounds contained in formulations are typically absorbed across the buccal mucosa, whereas dry fine powder formulations of snuff can also be sniffed into the nose. Because of the different manufacturing techniques, products may vary broadly in chemical composition and relative nicotine content (e.g., approximately 10 mg/g of product in chewing tobacco, approximately 17 mg/g of product in dry snuff tobacco, approximately 13 mg/g of product in moist snuff tobacco, as compared with 7 to 13 mg/g of product in traditional cigarettes).[3] Although the absorption of combustion-derived carcinogenic substances such as benzo[a]pyrene and other polycyclic compounds is expectedly lower, other carcinogens such as nitrosamines have instead a relatively high concentration in smokeless tobacco products.[3]

The Electronic Cigarette

Because of the restrictive measures and widespread control policies, particularly in developed countries, tobacco companies are now using aggressive marketing policies in favor of smokeless tobacco for recovery from economical loss due to reduced income from traditional cigarette smoke. Along with more traditional and prevalent forms of smokeless tobacco, electronic nicotine delivery systems—also known as "electronic cigarettes" or "e-cigarettes"—were first commercialized in China nearly 10 years ago, and their market rapidly grew and spread, first through sales via the Web, and more recently, in tobacco shops and retail outlets. Basically, an e-cigarette is a device that looks and should feel like a real cigarette, but which does not burn tobacco. Within a tube containing a mouthpiece and a socket for cartridge insertion, a conventional e-cigarette also houses a battery, a heating element, a power source, and a pressure switch. The cartridge, which is device specific, typically contains 0 to 20 mg of nicotine (►**Fig. 1**). The refill kit, which may contain up to 1 g of nicotine in a small bottle, is used to fill the cartridge with replacement solution at higher doses than originally contained.[4] With notable differences among different brands and types, these devices also contain various amounts of humectants such as propylene glycol or glycerol to produce the vapor, flavors (e.g., mint, vanilla, fruit, and chocolate),[5] and even drugs such as rimonabant (i.e., a substance typically used for weight loss) and amino tadalafil (i.e., a drug analog of the commercially approved tadalafil, which is used to treat erectile dysfunction).[6]

With regard to the concordance between the content of e-cigarette refill bottles and what is stated on the label, Etter et al purchased and assessed 20 bottles of 10 different brands (19 were obtained from Web sites and shipped by regular mail by retailers and the remainder was obtained directly from the manufacturer).[7] The analysis, based on ultrahigh performance liquid chromatography and gas chromatography, was aimed to quantify nicotine content, known nicotine degradation products and potential impurities. The relative nicotine content of each bottle was rather similar to that claimed by the manufacturer and reported in the label, with a mean percentage concordance of 99.8% (95% confidence interval [CI], 97.6–101.9%) and a range between 85 and 121%. The remarkable concentration of nicotine-related impurities found in the bottles (between 0 and 4.4% of nicotine concentration, although most samples exhibited values between 1 and 2% of nicotine content) suggests, however, that oxidative degradation of the basic compound may have occurred during manufacturing of ingredients or final liquid, or that nondesirable interactions with the packaging material may have occurred along with inadequate handling and storage of bottles. Neither ethylene glycol nor diethylene glycol could be detected in fluids, which suggests that the overall quality of e-liquids may be somehow reassuring. Cameron et al analyzed nicotine solutions contained in seven different e-cigarettes by liquid chromatography/electrospray ionization tandem mass spectrometry[8] and found that the concentration of nicotine was equivalent to—or lower than—that marked or expected, given the manufacturer concentration ranges provided (i.e.,

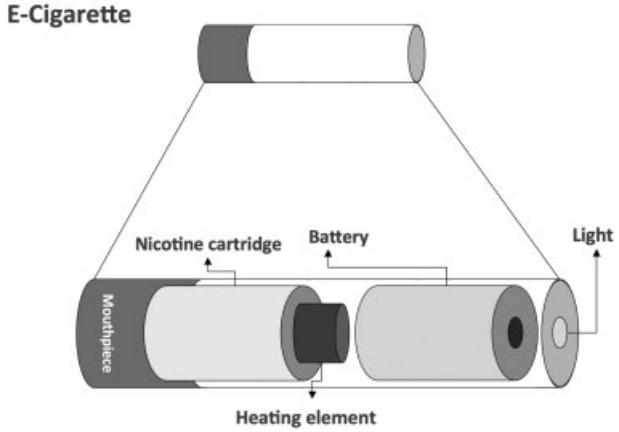

Fig. 1 Composition of a conventional electronic cigarette (e-cigarette).

between 41 and 93%). Nevertheless, the absolute level (i.e., from 8.5 to 22.2 mg/mL) was sufficient to be toxic or lethal should the product be orally ingested or transdermally absorbed and considering that the fatal dose of nicotine is 30 to 60 mg in adults and 10 mg in children.[5] In another recent study, Kim and Shin used liquid chromatography-tandem mass spectrometric to detect and measure tobacco-specific nitrosamines—which are well-established carcinogenic substances—in 105 replacement liquids of e-cigarettes produced by 11 companies.[9] The overall rate of detection of one or more of these harmful compounds was 93% (varying between 54 and 87% according to the different specific substance), with a maximum concentration of 86.92 μg/L, which was up to 10 times higher than that declared by manufacturers. In line with this finding, Williams et al found significant amounts of metal and silicate particles in cartomizer aerosol, which further supports the need for improved quality control in e-cigarette design and manufacture.[10]

The pharmacokinetics and pharmacodynamics of e-cigarettes have been investigated in some studies. Bullen et al earlier reported that the use of a 16-mg electronic nicotine delivery device increased serum nicotine to a peak of 1.3 ng/mL within 19.6 minutes as compared with 13.4 ng/mL in 14.3 minutes using a traditional tobacco cigarette.[11] Vansickel et al also assessed plasma nicotine and carbon CO concentration in 32 subjects who took 10 puffs of 16 mg or 18 mg electronic nicotine delivery devices compared with a traditional tobacco cigarette.[12] The mean plasma nicotine increased from a preadministration level of 2.1 ng/mL to a peak of 18.8 ng/mL 5 minutes after the use of traditional cigarette, whereas no significant changes could be observed for either e-cigarette device. Similarly, the mean CO increased from a preadministration level of 5.3 parts per million (ppm) to a peak of 16.2 ppm 15 minutes after use of traditional cigarette, but again, no significant changes could be found for both e-cigarettes. Passive vaping (vaporizing) has also been reported from consumption of e-cigarettes. Schripp et al analyzed the release of volatile organic compounds and (ultra)fine particles from an e-cigarette under near-to-real-use conditions,[13] and found a high amount of 1,2-propanediol along with moderate levels of 1,2,3-propanetriol, diacetin, nicotine, and ultrafine particles in exhaled air. Ingebrethsen et al also found that undiluted e-cigarette aerosols have particle diameters averaging between 250 and 450 nm, with approximate concentration of 10^9 particles/cm^3 range, which are figures globally comparable to those found in tobacco burning cigarette smoke.[14] Finally, Goniewicz et al recently assessed nicotine levels in vapor generated from 16 e-cigarettes differing for brands and models.[15] The mean nicotine amount in original unused cartridges was 10.3 mg (95% CI, 7.2–13.4 mg), that contained in refill solutions was 15.3 mg (95% CI, 11.6–18.9 mg), and that released to vapor with 150 puffs was 4.0 mg (95% CI, 2.6–5.4 mg). Overall, the effective vaporization of nicotine ranged from 21 to 85% of the relative amounts present in cartridges. By assuming that 15 puffs of e-cigarette may be more or less equivalent to smoking one tobacco cigarette, the overall amount of nicotine inhaled with an electronic cigarette would hence range between 0.025 and 0.77 mg. This is a lower amount than that absorbed by smoking a traditional tobacco cigarette (i.e., between 1.54 and 2.60 mg), but still represents a meaningful quantity that can be notably increased by enhancing puff strength or using higher amounts of refill(s). Taken together, these data provide clear evidence that a variety of harmful substances—especially nicotine, ultraparticles, and volatile organic compounds—may be effectively inhaled or liberated in the exhaled air during repeated e-cigarette puffing (►**Fig. 2**).

E-Cigarette and Cardiovascular Disease

The use of these devices for management of tobacco dependence is controversial due to a paucity of long-term safety results and randomized, controlled data. The typical profile of an e-cigarette user has been investigated by Dawkins et al in an online survey.[16] The vast majority of participants, up to 74%, reported not smoking for at least a few weeks as using the e-cigarette, whereas 70% of them reported a reduced urge to smoke. Approximately 72% of the participants were using a "tank" system, most commonly the eGo-C (Shenzhen Joyetech Co. Ltd., ShenZhen, China). The mean period of use was 10 months. A very low number of participants (i.e., 1%) reported exclusive use of nonnicotine-containing liquid. Indeed, the awareness and current use of these devices steadily grows. In Great Britain, for example, the current use of e-cigarettes among the overall general population has more than doubled between 2010 and 2012 (i.e., from 2.7 to 6.7%).[17]

Although it is usually considered less harmful than cigarette smoking for both cancer and cardiovascular disease, there is increasing evidence supporting the notion that smokeless tobacco may be less safe than conventionally supposed. The largest epidemiological study regarding the potential influence of smokeless tobacco on cardiovascular risk was published in 2010. In this large prospective trial, the incidence of cardiovascular disease was assessed in 14,498 participants of the Atherosclerosis Risk in Communities (ARIC) Study, aged 45 to 64 years at baseline.[18] Smokeless tobacco use was herein defined as "current and past use of chewing tobacco and snuff." During a median follow-up of 16.7 years, 2,572 cardiovascular events (i.e., acute coronary syndrome or stroke) were recorded. The current use of smokeless tobacco at baseline conferred a 1.27-fold (95% CI, 1.06–1.52) greater risk of cardiovascular events than the nonuse, even after adjustment for several demographic, socioeconomic, lifestyle, and tobacco-related variables. Even

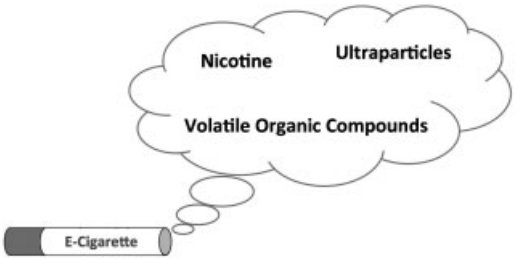

Fig. 2 Potentially toxic substances generated by electronic cigarettes.

more interestingly, although the risk of cardiovascular events was higher in smokers of traditional cigarettes (i.e., 1.46; 95% CI, 1.29–1.66), the cardiovascular rate associated with current use of smokeless tobacco was more than 30% higher than that for current cigarette smoking (i.e., 21/1,000 vs. 16/1,000 person-years), and this has been attributed to an acute response to the over 2,000 various chemical compounds contained in smokeless tobacco. In the earlier meta-analysis of Boffetta and Straif the relative risk for ever use of smokeless tobacco products was 1.13 (95% CI, 1.06–1.21) for myocardial infarction and 1.40 (95% CI, 1.28–1.54) for stroke, respectively.[19] A recent Policy Statement by the AHA concluded that data from the majority of available studies do not support an increased incidence of hypertension or nonfatal and fatal myocardial infarction in users of smokeless tobacco,[3] although data published by Yatsuya and Folsom[18] and the outcome of the meta-analysis by Boffetta and Straif[19] raise serious doubts about this conclusion.

So, although available data show that smokeless tobacco may carry a tangible cardiovascular risk for current users, these findings cannot be automatically translated to e-cigarettes, because of their peculiar manufacturing and composition. Unfortunately, the relatively recent commercialization has not permitted performance of large prospective studies and attainment of any reliable estimate of the potential cardiovascular risk of these devices. Nevertheless, some preliminary publications and case reports should raise widespread alertness regarding the cardiovascular safety of these devices.

Vardavas et al investigated whether the use of an electronic cigarette for 5 minutes would produce a significant effect on pulmonary function and fraction of exhaled nitric oxide in 30 healthy adult smokers[20] and reported an immediate decrease in fraction of exhaled nitric oxide along with enhanced total respiratory and flow respiratory resistances. These findings led the authors to conclude that the negative biological effects of short-term use of e-cigarettes may be similar to those observed with conventional tobacco smoking. Comparable findings were reported by Gennimata et al who assessed spirometry, static lung volumes, airway resistance, airway conductance, and a single breath nitrogen test in 32 consecutive subjects, 8 of whom never smoked, and 24 of whom were instead smokers (11 with normal spirometry and 13 with chronic obstructive pulmonary disease and asthma) immediately after smoking an e-cigarette for 10 minutes.[21] A statistically significant increase was observed in airway resistance combined with a significant decrease of airway conductance (especially in smokers and nonsmokers) but not in patients with chronic obstructive pulmonary disease and asthma. These results led the authors to conclude that the sudden increase in airway resistance may cause immediate harm after using the device, especially in selected categories of patients, such as those suffering from coronary artery disease. In a further study, Farsalinos et al assessed cardiac function in 20 healthy young daily smokers aged 25 to 45 years, before and after smoking 1 tobacco cigarette and 22 daily electronic cigarette users of similar age before and after using an e-cigarette with nicotine concentration of 11 mg/mL for 7 minutes.[22] The use of the e-cigarette did not cause significant alterations in any echocardiographic parameters, except for a modest increase of MV-A wave, whereas smokers of a tobacco cigarette exhibited a variety of significant abnormalities. This led the authors to conclude that an e-cigarette does not trigger acute adverse effects on cardiac function.

Although the e-cigarette may therefore be safer than traditional tobacco smoke and even other types of smokeless tobacco when used under ideal conditions, adverse effects together with occasional cases of poisoning by device refills have been described. In an interesting study, Hua et al collected short-term health effects produced by e-cigarette use through an analysis of original posts from three online e-cigarettes forums.[23] Overall, 387 different effects were identified, 318 of which (82%) were negative (the remaining were characterized as positive). The respiratory system was more frequently affected (74 cases), followed by mouth and throat ($n = 68$), the neurological system ($n = 52$), the sensorial system ($n = 39$), the digestive tract ($n = 36$), the muscular/skeletal ($n = 29$), and cardiocirculatory systems (17 chest symptoms, 2 circulatory). The more frequent cardiovascular complaints included chest pain or "pressure," arrhythmias, and abnormal blood pressure (namely hypertension). More specifically, blood pressure changes were reported by nearly 4% of users, wherein hypertension was the most frequent sign that was diagnosed by physicians.

Vansickel and Eissenberg assessed plasma nicotine concentration, heart rate, and subjective ratings of nicotine/product effects in eight e-cigarette users at baseline, after 10 puffs with a 30-second interpuff interval, after 1 hour after ad libitum puffing, and 2-hour afterward.[24] Compared with baseline, the concentration of plasma nicotine increased significantly within 5 minutes after the first puff (up to 10 ng/mL) and persisted as increased throughout the ad libitum puffing period (from 10–over 15 ng/mL). Similarly, the heart rate increase from 73 ± 2.0 to 78 ± 1.9 beats per minute (bpm) 5 minutes after the first puff, and persisted elevated throughout the following period. At variance with previous data, showing minimal or no nicotine delivery by e-cigarette, this study has a much higher practical significance, as the e-cigarette users not only were allowed to provide their preferred device and flavor/nicotine concentration, but they were also allowed to follow their typical pattern of consumption during the 1-hour ad libitum puffing period. Thus, effective nicotine delivery had occurred under this more "real-world" situation. A nicotinergic impact has also been documented by Flouris et al[25] who reported that the effect on serum levels of cotinine (a metabolite of nicotine) after active and passive e-cigarette smoking does not differ from that generated by a conventional tobacco cigarette.

As mentioned, some case reports have been published about the potential cardiovascular adverse effects of e-cigarettes, mostly attributable to improper use. Monroy et al described the case of a 70-year-old white woman with a medical history of hypertension, hyperlipidemia, osteoarthritis, and allergic rhinitis who developed paroxysmal atrial fibrillation, temporally associated with e-cigarette use.[26] As accurate investigations failed to show additional triggers, an improper use of a full-strength nicotine replacement device was identified as the

most probable source of arrhythmias. In fact, the refill bottle had never lasted as long as expected by the patient, a fact that was highly suggestive for incorrect (i.e., excessive) refill of e-cigarette cartridge, thus exposing her to a very high dose of nicotine, which is otherwise associated with a well-established proarrhythmic effect. When the patient ceased to use the e-cigarette, no further episodes of paroxysmal atrial fibrillation were reported. We have also recently described the case of nicotine poisoning in a 22-year-old girl, who reported to have mixed the content of an electronic cigarette refill with 60 mL of methadone, improperly bottled in a generic vial.[27] The spectrum of symptoms observed in the patient included tachycardia (115 bpm and sinus tachycardia at the electrocardiograph), hypertension (150/105 mm Hg), flushing, salivation, and nausea. Although the young girl had a favorable outcome, the small volume of the refill contents used highlight the serious risk of easy ingestion or injection of harmful—potentially lethal—doses of nicotine, thus posing a substantial threat over widespread and under regulated marketing of these devices and their refills (e.g., a typical 30 mL bottle refill solution may contain up to 18 mg/mL nicotine, which approximately corresponds to 540 mg of nicotine).

Conclusions

Strongly propelled by easy availability through the Web, the worldwide market of e-cigarettes continues to grow, despite limited information on their safety, adverse effects, and even efficacy for smoking cessation. Although e-cigarettes are expected to generate and/or release fewer dangerous substances than conventional tobacco cigarettes, and current evidence provides limited support for a comparative lessened increased cardiovascular risk in current users, there are some important issues that should be emphasized about the currently claimed safety of these devices.

Thus, although the use of e-cigarette appears more favorable than traditional cigarettes or smokeless tobacco products, recent data conversely attests that the more typical patterns of use may be associated with significant release of nicotine,[24] thus producing a plasma nicotine concentration which may ultimately approximate that of traditional cigarette smoking, because the minute nicotine particles contained in the vapor allow fast and effective delivery into the bloodstream. This would explain the enhanced risk of cardiac arrhythmias and hypertension, which may predispose some users—especially those with coronary atherosclerosis or other known cardiovascular risk factors—to a substantial risk of acute coronary syndrome, which may be further magnified by other potential adverse effects (i.e., arrhythmias, increased respiratory, and flow respiratory resistance) (►**Fig. 3**). Some cases of intoxication, wherein an amount of nicotine and other harmful compounds may be absorbed at a much larger extent than with traditional cigarettes, have also been reported. According to this data, e-cigarettes have been classified as "drug delivery devices" in several countries, and their marketing has been temporarily limited or even suspended until safety profile and efficacy will be finally established in clinical trials. The US Food and Drug Administration has also publicly discouraged the use of these devices in July 2009, raising serious concerns that e-cigarettes may be marketed to young people and lack appropriate health warnings.

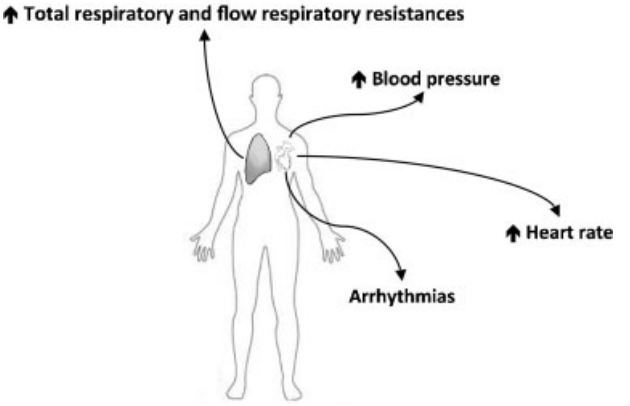

Fig. 3 Potentially harmful effects of electronic cigarettes on human biology.

Basically, their large and easy availability on the Web, a phenomenon that has several points in common with the "black market" of doping substances,[28,29] combined with the existence of a clear dose–response relationship effect on cardiovascular risk suggests that major caution regarding the use of these devices should be used, especially in persons at increased risk of developing cardiovascular events. The effects on blood pressure and heart rate are particularly concerning, as hypertension is a well-established cardiovascular risk factor,[2] whereas heart rate is a significant predictor of mortality in patients with known cardiovascular disease.[30] It is also noteworthy that e-cigarettes require stronger vacuums (suction) than conventional tobacco cigarette, and this effect remains unclear on enhanced absorption of dangerous substances and human health.[31] As the use of e-cigarettes is continuously rising, and it may be a potentially effective approach for smoking cessation, more focused research is urgently needed to definitely establish the cardiovascular safety of these devices. Should e-cigarettes be less harmful than traditional tobacco smoking or smokeless tobacco, then this would represent a favorable alternative for tobacco addictions, but may conversely pose serious threat on more fragile members of the society such as children and teens, who may be persuaded to start using electronic cigarette with unproven assumption of safety, become addicted to nicotine and eventually begin to smoke tobacco cigarettes, or worse abuse the level of active compounds in refill bottles with potential catastrophic outcome.

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