



Electronic Cigarettes: Impact on the Cardiovascular System



Tobacco smoking is a major public health threat for both smokers and nonsmokers. There is accumulating evidence demonstrating that smoking causes several human diseases, including those affecting the cardiovascular system. Indeed, tobacco smoking is responsible for up to 30% of heart disease–related deaths in the United States each year.¹ This is the single most preventable risk factor related to the development of cardiovascular disease, bringing about a trend toward tobacco harm reduction that started years ago.² As tobacco usage declined over time in the United States, industries introduced an alternative known as electronic cigarettes (e-cigarettes) claiming they were a healthier alternative to tobacco smoking.³

Since then, the number of e-cigarette users has increased significantly because of the perception that they serve as a healthy substitute to tobacco consumption with minimal or no harm, a lack of usage regulations (although that has now changed), and the appealing nature of these devices, among other reasons.⁴ Consequently, e-cigarettes became the most commonly used smoking products, especially among youth, with more than a 9-fold increase in usage from 2011 to 2015.⁵ Based on these considerations, it is clear that there are many unanswered questions regarding the overall safety, efficacy of harm reduction, and the long-term health impact of these devices.

Besides their potential negative health effects on users, there is increasing evidence that e-cigarettes emit considerable levels of toxicants, such as nicotine, volatile organic compounds, and carbonyls, in addition to releasing particulate matter (PM).^{6,7} Thus, they possess a potential harm to nonusers either through secondhand or thirdhand exposure. This is especially the case in vulnerable populations, such as children, elderly, pregnant females, and those with a history of

cardiovascular disease.⁸ Thus, it is critical to establish e-cigarettes' short- and long-term health effects on both users and nonusers. In this review, we will discuss the current state of literature regarding the potential negative cardiovascular effects of direct/active and passive e-cigarette exposure. Furthermore, we will review the possible impact of the individual constituents of the e-cigarette on hemodynamics and their contribution to the development of cardiovascular disease. The notion that e-cigarettes may negatively impact the cardiovascular system should uncover new avenues of research focused on establishing and understanding the safety of e-cigarette usage on human health.

E-Cigarettes

E-cigarettes, also known as vape pens, e-cigars, or vaping devices, are electronic nicotine delivering systems, which generate an aerosolized mixture containing flavored liquids and nicotine that is inhaled by the user.⁹ The extensive diversity of e-cigarettes arises from the various nicotine concentrations present in e-liquids, miscellaneous volumes of e-liquids per product, different carrier compounds, additives, flavors, and battery voltage.⁹ Regardless of the exact design, each e-cigarette device has a common functioning system, which is composed of a rechargeable lithium battery, vaporization chamber, and a cartridge (Figure 1). The lithium battery functions as the powerhouse; it is connected to the vaporization chamber that contains the atomizer⁹ (Figure 1). In order to deliver nicotine to the lungs, the user inhales through a mouthpiece, and the airflow triggers a sensor that then switches on the atomizer.^{9–11} Finally, the atomizer vaporizes liquid nicotine in a small cartridge (Figure 1) and delivers it to the lungs.⁹

With regard to their design, there are 4 generations of devices currently on the market.⁴ The first-generation e-cigarettes are the “ciga-like” devices, which are utilized mainly by new e-cigarette users; they are constructed of a cartomizer (cartridge and an atomizer) with a low-voltage battery (3.7 V).^{4,12–14} Second-generation e-cigarettes are primarily used by more-experienced users and are bigger in size with a refillable tank (unlike first-generation devices).^{4,13,14} Their battery voltage is adjustable, allowing users to use low or high voltage (3–6 V) during vaping.^{4,13,14} The third-generation

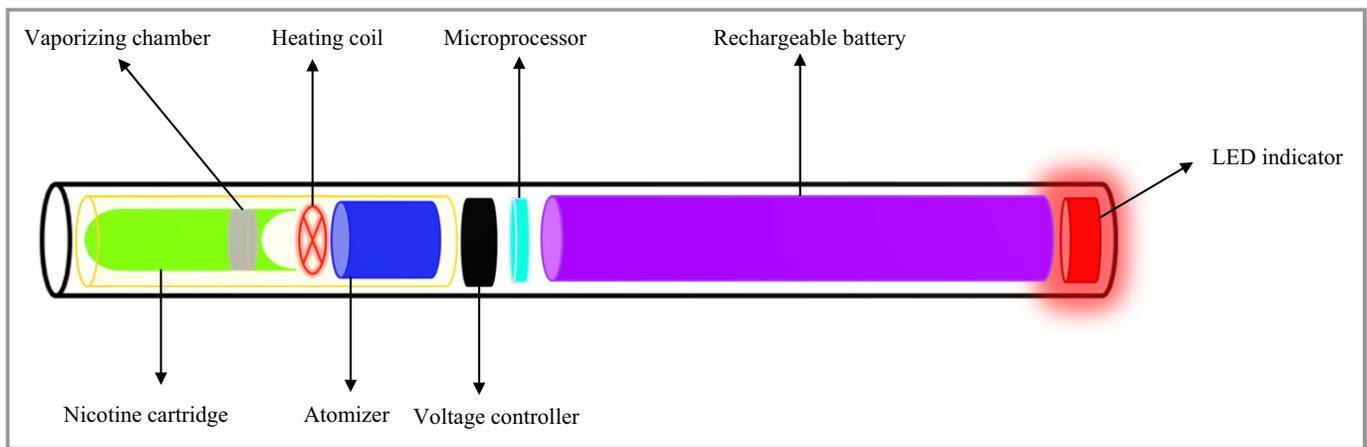


Figure 1. Typical e-cigarette design. E-cigarettes are usually composed of nicotine cartridge (e-liquid container), vaporizing chamber, a heating coil (heats e-liquid) followed by an atomizer (e-vapor generator), rechargeable battery and voltage controller (which will adjust the amount of nicotine delivered during vaping), microprocessor, and LED indicator—not present in all types—to activate the battery and visually mimic the conventional cigarette, respectively. LED indicates light-emitting diode.

devices are also known as mods and have the largest size batteries, with voltages up to 8 V.¹³ Finally, the fourth and most recent generation includes Sub ohm tanks (devices whose atomizer coils have a resistance of less than 1 ohm) and temperature control devices, which allow for temperature modulation during vaping. With these devices, the “vaper” can inhale huge puff volumes, leading to extremely high e-liquid consumption per puff.⁴

Taken together, there is diversity in e-cigarette designs, which has an effect on the levels of ingredients being delivered to the user and the environment (including nonusers). This variability also complicates our ability to assess the health consequences of e-cigarettes.

Prevalence of e-Cigarette Usage

Since their introduction in 2007, e-cigarettes have experienced widespread success among smokers, nonsmokers, pregnant females, and even youth. Their sales increased by 14-fold since 2008,¹⁵ contributing to scientists’ desire/necessity to evaluate their safety, population patterns, and usage reasons.¹⁶ Usage patterns vary depending on consumers’ age group.⁴ In adults, usage increased over the past decade to include 3.8% of US adults, of which almost 16% are current cigarette smokers, whereas 22% are former smokers.¹⁷ Importantly, almost 3.2% of individuals who never smoked before/naïve have tried e-cigarettes, reflecting exposure to harmful chemicals for “neoteric” purposes.^{17,18} In fact, adults primarily use e-cigarettes to discontinue smoking because they perceive them to be: (1) a healthier choice, which can reduce nicotine cravings, and (2) less harmful to nonusers in their proximity.^{4,19} As for seniors, it appears that e-cigarettes are used to stop smoking or to bypass smoke-free policies.^{20,21}

Usage of e-cigarettes among the youth is mainly linked to their curiosity and the “appealing” flavored nature of e-liquids.¹⁹ It is alarming that this group has the highest increase in usage¹⁸; 5.3% of all users are middle school students, and 16% are high school students. This is a 9- and 10-fold increase, respectively, since 2011.¹⁸ Because the brain is only fully developed by the age of mid-twenties, youths’ exposure to nicotine may disrupt their brain development, and hinder attention and learning, while elevating susceptibility for addiction to nicotine or other drugs such as cocaine.²²

Despite the known negative consequences of tobacco smoking, many pregnant females continue to use e-cigarettes based on their safety perception as compared with tobacco.²³ Ironically, given that nicotine contributes to the negative health consequences of smoking on newborns, e-cigarette use will likely expose the fetus to nicotine, leading to adverse effects, such as reduced cognitive deficits and perhaps even sudden infant death syndrome.^{22,24,25}

It is to be noted that aggressive marketing provoked a false perception, albeit has yet to be confirmed, about the effectiveness and safety of these devices, which further emboldened their use.²⁰ In light of the aggressive marketing and the fact that e-cigarettes use is growing among all populations, it is paramount to establish their safety profiles, especially in vulnerable populations, and take measures to ensure their protection.

Public Health and e-Cigarettes

The long-term health effects of e-cigarettes have not yet been documented in humans; however, the short-term negative effects have been suggested by several studies.^{8,9,26,27} These studies focused mainly on the cytotoxic profile of e-cigarettes

Table 1. Potential Effects of e-Cigarettes on Biological Systems

System	Effects of e-Cigarettes
Pulmonary system	Upper and lower respiratory tract irritation ^{9,26,27} Bronchitis, cough, and emphysema ^{9,26,27}
Immune system	Inflammation induction ²⁸ Reduce immune efficiency ²⁹
Central nervous system	Behavioral changes ⁹ Memory impairment (animal models) ^{9,10} Tremor and muscle spasms ¹⁰
Miscellaneous	Ocular irritation ⁹ Contact dermatitis and burns ^{9,31} Nausea and vomiting ^{9,31} Throat and mouth irritation ^{30,31}

and their effects on the respiratory tract,^{9,26,27} central nervous system,^{9,10} immune system,^{28,29} and a few others^{9,30,31} (Table 1).

As the primary system exposed to vapors from e-cigarettes, most reported health effects have centered on the pulmonary tract. Recent clinical and animal studies showed that (active or passive) e-vapors/e-cigarettes may cause irritation of both the upper and lower respiratory tract, in addition to inducing bronchospasm and cough^{9,32–34}; the latter effects may be attributed to a chain of inflammatory reactions through oxidative stress.²⁸

As for effects on other systems, e-cigarettes also reduce, in mice, the efficiency of the immune system, as reflected by the increased susceptibility to infection with influenza A and *Streptococcus pneumoniae*.²⁹ As for the central nervous system, e-cigarettes may alter brain functions, which affects the mood, learning abilities, memory, and could even induce drug dependence in both humans and animals.^{35–37} E-cigarettes may also directly damage neurons and cause tremor and muscle spasms.⁹

Carcinogenicity, mostly manifested in the lungs, mouth, and throat,³⁰ is another important aspect of the e-cigarette's negative health profile; this may be linked to nitrosamines, propylene-glycol (the major carrier in e-liquids), and even some flavoring agents.^{9,31} In fact, one study indicated that after being heated and vaporized, propylene glycol may transform into propylene oxide, which is a class 2B carcinogen. Moreover, e-liquid exposure was found to exert a direct cytotoxic effect on human embryonic stem cells and mouse neural stem cells, highlighting a potential harm for pregnant females.^{15,32} Other adverse effects include nausea, vomiting, and contact dermatitis, as well as eye, mouth, and throat irritation.^{9,31} It is noteworthy that the harm related to e-cigarette usage reaches further beyond “beings” to include fire hazards and explosions; issues the public tends to underestimate.^{38,39}

In summary, there is increasing evidence that short term e-cigarette exposure exerts deleterious effects on multiple biological systems, but the mechanism by which these effects occur is presently unknown. While the long-term effects have not yet been studied, one can predict that e-cigarettes will likely cause more harm if used for extended periods, a notion that also warrants investigation.

The Impact of e-Cigarettes on the Cardiovascular System

Cardiovascular disease is the major cause of death among smokers¹ and is responsible for as much as 30% of heart disease-related deaths in the United States each year.¹ As smokers considered safer alternatives to help them quit, they started using e-cigarettes, in part, because they have “lower” levels of harmful constituents.¹⁹ Nevertheless, this notion should be reconciled in light of the high “sensitivity” of the cardiovascular system and evidence of a nonlinear dose-response relationship between tobacco exposure and development of cardiovascular disease. Thus, even exposure to low levels of harmful constituents could have a pronounced effect, and, consequently, the reduction of such materials in e-cigarettes does not assure a proportional harm reduction.⁴⁰ Conversely, exposure to toxicants may not necessarily translate into a negative health effect.

It is therefore paramount to evaluate e-cigarette's short- and long-term safety on the cardiovascular system, especially given the limited studies in this area and/or their controversial findings.²⁸ Several studies suggest that e-cigarette use acutely and negatively (increased) impacted vital signs, such as heart rate^{41,42} and blood pressure.^{43,44} In this regard, Andrea et al showed that heart rate acutely increased after e-cigarettes use by smokers,⁴¹ which was also observed in a separate study.⁴² Additionally, Yan et al found that e-cigarettes elevated both diastolic blood pressure and heart rate in smokers, but to a lesser extent when compared with tobacco cigarettes.⁴³

It was also found that endothelial cell dysfunction and oxidative stress, which play important roles in the pathogenesis of cardiovascular disease,⁴⁵ are associated with e-cigarettes, even a single use, but the effect was less pronounced compared with cigarette smoking.⁴⁶ On the other hand, relative to cigarette smoking, e-cigarette use caused a comparable and rapid increase in the number of circulating endothelial progenitor cells, which could be attributed to acute endothelial dysfunction and/or vascular injury.⁴⁷ Given that platelets are key players in the development of cardiovascular disease—especially thrombosis and atherosclerosis—a recent *in vitro* study evaluated the effects of e-cigarettes on these cells.⁴⁸

Consequently, e-cigarette vapor extracts were found to enhance activation (aggregation and adhesion) of platelets from healthy human volunteers.⁴⁸

Alternatively, some studies have shown that short-term exposure to e-cigarettes has no cardiovascular harm.^{49–51} These studies found that acute exposure to e-cigarettes had no immediate effects on the coronary circulation, myocardial function, and arterial stiffness.^{10,49,50} Another study revealed no significant changes in smokers' heart rate after acute use of e-cigarettes.⁵² However, the discrepancy in findings should be examined in the context of evidence indicating that vaping topography (e-cigarette usage patterns such as inhalation duration and the magnitude of inhaled volume) and user's experience are critical factors in determining the health effects of e-cigarettes.^{39,53} The discrepancy in the results, aside from the user's experience and vaping topography, which could be attributed to differences in sample size, study groups (former smokers' versus nonsmokers), exposure's nature (acute versus prolonged), and wide variety of e-cigarette products, makes it difficult to draw conclusions regarding the cardiovascular health consequences of e-cigarettes. Of note, the long-term effects of e-cigarettes have not been studied, nor has the mechanism(s) by which they exert their effects on the cardiovascular system.

Although some studies support and promote the idea that e-cigarettes could be a safer alternative to tobacco, it is important to consider (and address) the public safety of these devices to nonusers who are in proximity and would be subject to secondhand vaping/exposure.⁵⁴ Furthermore, a new threat, thirdhand vaping/exposure, has been discovered; it arises from exposure to e-cigarette residues remaining on surfaces in areas where vaping took place.⁵⁵ Given that secondhand and even thirdhand exposure to tobacco smoke exerts toxicity, including the cardiovascular system,⁵⁶ whether e-cigarettes are a source of secondhand or thirdhand vapors was investigated. Subsequent studies provided substantial evidence that e-cigarettes are not an emission-free device; instead, they negatively affect indoor air quality. Specifically, e-cigarette vaping was found to release various potentially noxious constituents.^{57,58}

Although the indoor use of e-cigarettes was found to result in lower levels of "secondhand and thirdhand" residues, compared with tobacco smoke,⁵⁹ these hazards are still a health threat to those who are involuntarily exposed (nonusers). The latter notion should be considered with survey findings that e-cigarette users (unfortunately) do not consider laws that prohibit tobacco smoking to apply to them and hence vape in smoke-free areas.⁶⁰ This is consistent with another survey that showed a large proportion of middle and high school students have been exposed to secondhand vapors.⁶¹ Thus, research should be initiated to evaluate health

effects of secondhand and thirdhand vaping, which would, in turn, inform (stricter) e-cigarette regulations.

The Impact of e-Cigarette Toxicants/Constituents on the Cardiovascular System

There are limited studies on the health effects of e-cigarettes, particularly on the cardiovascular system. Therefore, to gain a better understanding of their possible/potential harm, we sought to review the effects of constituents/toxicants known to exist in e-cigarettes. In this regard, e-liquids and e-vapors are a source of a large number of these chemicals,^{7,10,53,57,62–66} affecting several biological systems^{37,43,67–88} (Table 2). The levels of some of these toxicants in e-cigarette aerosols are claimed to be lower than in tobacco smoke. For instance, several studies have shown that e-cigarette usage results in lower volatile organic compounds levels compared with the combustible cigarette.^{64,89,90} Notably, the levels of e-cigarette chemicals appear to vary between studies, attributed to the wide range of products on the market, different nicotine concentrations, study designs, vaping techniques (puffing topography), and users' experiences.⁹¹ Nevertheless, most studies do support the presence of carbonyl compounds, nicotine, and particulate matter in e-cigarette liquids and/or vapors,^{8,9} and those will be the focus of the discussion in the following sections.

The Impact of Nicotine on the Cardiovascular System

Nicotine, which is the major constituent in most smoking products, is considered a strong alkaloid that can be absorbed by various routes: oral mucosa, lungs, skin, or gut.⁹³ After absorption, nicotine is metabolized by the liver into cotinine as one of the metabolites.⁹⁴ Most e-liquids contain nicotine at concentrations that vary between 0 and 36.6 mg/mL.⁹⁵ Interestingly, it has been reported that several e-cigarette brands inaccurately labeled nicotine concentration,⁹⁶ and, in fact, some of the "nicotine free" brands apparently contain some.⁸ As expected, e-liquids with higher nicotine concentrations deliver more nicotine than those with lower concentrations.^{43,97}

Nicotine delivery to the human body is affected by other factors, such as the type of device used.³⁹ Thus, studies on first-generation e-cigarettes reported delivery of low concentrations of nicotine to the bloodstream,⁹⁸ unlike newer-generation devices (equipped with a high-capacity battery).¹³ To this end, Farsalinos et al showed a 35% to 72% increase in nicotine delivery with newer generations of e-cigarettes, relative to first-generation devices.¹³ Furthermore, although studies have shown that conventional cigarettes result in

Table 2. Chemicals Emitted in e-Cigarette Vapors and Their Potential Health Effects

	Chemical	Detected Concentration Range	Biological System Affected
	Nicotine	ND to 36.6 mg/mL ^{10,62,63}	Lung tumor promoter ⁶⁷ Addiction ⁶⁷ Gastrointestinal carcinogen ⁶⁷ Raises blood pressure and heart rate ⁶⁸ Reduce brain development in adolescents ³⁷
	Cotinine	ND*	Reduce fertility and reproduction ⁶⁹
Aldehydes	Acetaldehyde	0.11 to 2.94 µg/15 puffs ^{53,64,65}	Carcinogen ⁷⁰ Aggravation of alcohol-induced liver damage ⁷¹
	Acrolein	0.044 to 6.74 µg/15 puffs ^{53,64,65}	Ocular irritation ⁷² Respiratory irritation ⁷² Gastrointestinal irritation ⁷²
	Formaldehyde	0.2 to 27.1 µg/15 puffs ^{53,64,65}	Carcinogen ⁶⁸ Bronchitis, pneumonia, and increase asthma risk in children ^{73,74} Ocular, nasal, and throat irritant ⁷⁴
	o-Methyl benzaldehyde	ND to 7.1 µg/15 puffs ⁷	Unknown
	Acetone	ND to 91.2 ⁷	Gastric distress ⁷⁵ Weakness of extremities and headache ⁷⁵ Ocular irritation ⁷⁵
Volatile organic compounds	Propylene glycol	0 to 82.875 mg/15 puffs ⁷	Throat and airways irritation. ⁷⁶ Carcinogen ⁶⁸ Gastric distress ⁶⁸ Increase asthma risk in children ⁶⁸ Ocular irritation ⁶⁸
	Glycerin	75 to 225 µg/15 puffs ⁵⁷	Lipoid pneumonia ⁷⁷ Ocular, dermal, and pulmonary irritant ⁷⁸
	3-Methylbutyl-3-methylbutanoate	1.5 to 16.5 µg/15 puffs ⁵⁷	Unknown
	Toluene	<0.63 µg/15 puffs ⁶⁴	CNS damage ⁷⁹ Renal damage ⁸⁰
Nitrosamines	NNN	0.8 to 4.3 ng/e-cigarette ⁶⁴	Carcinogen ⁸⁷
	NNK	1.1 to 28.3 ng/e-cigarette ⁶⁴	Carcinogen ⁸⁷
Metals	Chromium	ND to 0.0105 µg/15 puffs ^{7,66}	Pulmonary irritation and inflammation, nasal mucosa atrophy and ulcerations ⁸¹ Nasal mucosa atrophy, reduce fertility and reproduction ⁸²
	Cadmium	ND to 0.022 µg/15 puffs ^{64,66}	Increase risk of lung cancer ⁸³ Pulmonary and nasal irritation ⁸³
	Lead	0.025 to 0.57 µg/15 puffs ^{64,66}	Hypertension induction ^{83,84,88} Renal damage ⁸⁸ CNS damage ^{84,88}
	Nickel	0.0075 to 0.29 µg/15 puffs ^{64,66}	Carcinogen ⁴³ CNS and pulmonary damage ⁸⁵ Renal and hepatic toxicity ⁸⁵

ND indicates not detected; CNS, central nervous system; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-nitrosamines.

*Variable concentrations found in plasma after using e-cigarettes.⁹²

quicker and 60% to 80% higher plasma nicotine levels,^{45,98,99} e-cigarettes vaping still could result in comparable levels,⁹² especially with experienced smokers who can adjust the topography of vaping.^{53,62,100,101} However, e-cigarette users take a longer time to reach such levels.^{53,92} Consistent with its systemic uptake, comparable saliva and plasma levels

were reported for cotinine, which is considered one of the major metabolites and a marker of nicotine, in both e-cigarette users and conventional smokers.^{92,102,103} Collectively, these studies support the notion that e-cigarette usage results in increased nicotine delivery to the human body.

Studies with conventional cigarettes showed that nicotine increased the risk of cardiovascular disease in smokers, including the development of acute coronary disease,⁴⁶ elevated blood pressure,¹⁰⁴ and heart failure.¹⁰⁵ As for nicotine effects on thrombogenesis, it seems to be controversial, with studies suggesting it to be elevated,^{106,107} reduced,¹⁰⁸ or not affected¹⁰⁹; but this discrepancy could be attributed to the dose of nicotine used,¹¹⁰ route of administration,¹¹¹ and the method used to measure platelet function. Additionally, it was established that nicotine induces endothelial dysfunction,¹¹² angiogenesis,¹¹³ inflammation,¹¹⁴ and lipogenesis, which may increase thrombosis risk. Conversely and interestingly, nicotine delivered from nicotine replacement therapy was not found to be associated with increased cardiovascular diseases risk.¹⁰⁴ This finding could be attributed to the standardized dose-delivery system of nicotine replacement therapy, in which the nicotine dose is reduced over a short period of time.¹⁰⁴ Thus, it seems that the cardiovascular effects of nicotine depend on the dose delivered and its distribution kinetics.^{115–117} Given that the pharmacokinetics of nicotine delivery to human body by e-vaping seems to be different from tobacco smoking, both in the magnitude and the speed by which peak levels are reached,¹¹⁸ it is essential to evaluate whether “e-vaped” nicotine has an effect on cardiovascular system.

Unfortunately, studies on e-cigarette nicotine effects have been limited, and controversial. A study by D’Ruiz et al indicated an elevation in heart rate after using (different brands of) e-cigarettes, which correlated with elevation in plasma nicotine levels. This is consistent with findings that both heart rate and plasma nicotine were elevated after 5 minutes of the first puff, and throughout 1 hour of the ad-lib period in e-cigarette users.⁴³ A separate study found no changes in heart rate in e-cigarette users, and no increase in nicotine plasma levels were observed.⁵² However, these “guilt by association” studies do not provide a direct cause-and-effect relationship between nicotine concentration and human hemodynamics. This notion seems to be consistent with a recent *in vitro* study by Rubenstein et al, which indicated that the enhanced activity of human platelets upon exposure to e-vapor extracts was independent of nicotine.⁴⁸ It is clear that further investigation is warranted to address and better understand the short- and long-term effects of nicotine delivered by e-cigarettes on the cardiovascular system.

Additional concerns related to e-cigarettes include nicotine dependence and toxicity, given that the nicotine concentrations found in plasma of e-cigarette smokers are high enough to produce and maintain nicotine dependence, especially in youth. This may explain why many adolescents shift to tobacco smoking in their adulthood or cannot abandon vaping easily.²² E-cigarettes may also present higher risks of nicotine toxicity, especially for children, because some incidents of

ingesting e-liquids were reported.^{9,119} In fact, the number of calls to poison centers for ingestion of e-liquids increased from “one per month in September 2010 to 215 per month in February 2014”.¹²⁰ Thus, the Child Nicotine Poisoning Prevention Act was initiated in January 2016; this required e-cigarette manufacturers to use child-resistant e-liquid packaging.

Concerns also exist for passive exposure to nicotine (nonusers); there is considerable evidence that e-vapors are a source of nicotine contamination.¹⁰³ Indeed, examination of indoor air quality revealed a significant elevation of air nicotine concentrations, which was commensurate with an increase in nicotine levels in plasma and saliva of nonusers.⁹⁰ In agreement with these results, salivary concentrations of cotinine were found to be elevated in nonusers living with e-cigarette users.^{103,121} In addition to this, a detectable amount of nicotine was found on the surfaces of e-cigarette users’ homes, suggesting a potential risk for thirdhand exposure.^{55,59} Taken together, these data advocate that e-cigarettes are a source of secondhand and thirdhand exposure to nicotine, especially in sensitive or vulnerable populations, regardless of whether its levels from passive exposure to e-vapors are similar or lower than those from tobacco smoke.

The Impact of Carbonyl Compounds on the Cardiovascular System

In addition to nicotine, e-cigarettes emit other potentially harmful constituents like carbonyls; this includes aldehydes, such as formaldehyde, acetaldehyde, and acrolein,^{64,122} which result from thermal degradation of propylene glycol and glycerol (most commonly used solvents in e-liquids¹²³). As was the case with nicotine, newer generations of e-cigarettes reportedly result in comparable carbonyls levels relative to cigarettes (voltage dependent).^{122,124} In this regard, whereas some studies showed that levels of aldehydes increased significantly under high voltage, or “dry-puff” conditions,^{122,125} recent studies confirmed their presence even under normal puffing conditions.¹²⁶ Interestingly, levels of the acrolein metabolite, 3-HPMA, were found to be elevated in urine samples obtained from e-cigarette smokers when compared with nonsmokers, confirming its systemic delivery to the human body.¹²⁷ On the other hand, levels of 3-HPMA were reduced by 83% when tobacco smokers switched to e-cigarettes and were similar to levels observed in those who quit smoking.¹²⁸ The presence of the aforementioned aldehydes represents a major health concern; in fact, formaldehyde was classified as a carcinogen and acetaldehyde as a potential carcinogen by the International Agency for Research on Cancer.¹²⁹

Aside from their cytotoxic effects, animal studies suggest that aldehydes exert various negative cardiovascular

effects.^{130–132} Given the limited clinical studies evaluating the effects of e-cigarette aldehydes on the human cardiovascular system, we will rely on and extrapolate evidence from non-e-cigarette sources. In this regard, animal studies revealed that formaldehyde exposure altered the heart rate,¹³² by a sympathetic nerve activity,¹³² and it also altered blood pressure¹³³ and cardiac contractility.¹³¹ Additionally, subacute and chronic inhalation of formaldehyde was associated with cardiac oxidative stress and, consequently, cardiac cell damage.¹³⁴ With regard to platelets, it was shown that total platelet count significantly increased in mice exposed to formaldehyde gas¹³⁰; this effect should be considered in the context of the importance of platelets in hemostasis and their role in thrombotic disorders. As for acetaldehyde, elevated blood pressure and heart rate were reported in animals following inhalation of variable doses, which could be attributed to its sympathomimetic effect.^{135,136} It is noteworthy that formaldehyde and acetaldehyde concentrations used in these studies are comparable to the levels generated by e-cigarettes. Collectively, studies clearly suggest potential harm from exposure to aldehydes, which could serve as a basis for future and further studies focusing on the cardiovascular consequences of their chronic exposure in real-life e-cigarette settings.

Exposure from smoking and other sources to acrolein, the other carbonyl, is associated with a wide range of cardiovascular toxicity.¹³⁷ Thus, inhalation of only 3 ppm of acrolein caused an increase in systolic, diastolic, and mean arterial blood pressure in an animal model.¹³⁸ Furthermore, acrolein-mediated autonomic imbalance caused an increase in the risk of developing arrhythmia in rats.¹³⁹ Additionally, it has been suggested that acrolein can directly induce myocardial dysfunction and cardiomyopathy.¹⁴⁰ As for the mechanisms of acrolein-induced cardiotoxicity, the following is some of what has been proposed thus far: the formation of myocardial protein-acrolein adduct, induction of oxidative stress signaling, upregulation of proinflammatory cytokines, and inhibition of cardioprotective signaling.^{140,141}

In line with the negative effects on the vasculature, acrolein can result in vascular injury by impairing vascular repair capacity, as well as increasing the risk of thrombosis and atherosclerosis, a possible result of endothelial dysfunction, dyslipidemia, and platelet activation, among others.^{142–144} Moreover, Sithu et al found that inhalation of acrolein vapor, generated from either acrolein liquid or tobacco smoke, results in a prothrombotic phenotype in mice.¹⁴⁵ Acute (5 ppm for 6 hours) or subchronic (1 ppm for 6 hours/day for 4 days) exposure to acrolein, regardless of its source, induced platelet activation and aggregation.¹⁴⁵ Additionally, an increase in acrolein-protein adduct in platelets was observed, which suggests its systemic delivery and that it exerts a direct effect on platelets.¹⁴⁵ In support of this notion,

a human study revealed a correlation between levels of acrolein metabolite (ie, 3-HPMA) and platelet-leukocyte aggregates, in addition to increased risk of cardiovascular diseases.¹⁴⁶ The effects of acrolein on the cardiovascular system are summarized in Figure 2.

Although acrolein sources were different in these studies, to gain insight regarding their relevance and applicability to e-cigarettes, we converted the concentrations emitted from e-cigarettes to ppm, as reported by several studies, taking into account puff volumes^{64,147–149} (Table 3). Thus, based on the average of 120 puffs/day reported in the literature,¹⁰¹ our calculated levels of acrolein emitted by e-cigarette users per day were found to vary between 0.00792 and 8.94 ppm/day (Table 3). Because its harmful cardiovascular levels fall within this range, acrolein emitted from e-cigarettes may produce similar harm, which warrants investigation.

As mentioned before, an additional concern, that is often forgotten or ignored, is that e-cigarettes can be a source of secondhand or thirdhand exposure to aldehydes (and other toxicants) for nonusers.^{150,151} Indeed, under human puffing conditions, indoor air quality was found to be reduced, attributed to aldehydes emission in e-cigarette vapors.⁵⁷ Even though detected levels were low, they may still pose a health concern, especially in people with a history of cardiovascular disease, as well as in children, casino/housekeeping workers, and in pregnant women. Hence, the safety of exposure to low levels of aldehydes for extended periods of time needs to be examined in nonusers who live with e-cigarette users or work in places where their use is allowed.

The Impact of PM on the Cardiovascular System

Another health concern related to e-cigarette usage is the generation of fine and ultrafine particles, known as PM, which represents the solid and liquid particles suspended in the air. PM_{2.5}, which includes particles with a diameter of 2.5 μm or less, will be the focus of this section because of their small size; this enables them to easily penetrate airways and reach circulation, thereby causing a potential hazard to the respiratory and cardiovascular systems.¹⁵² Several studies evaluated their presence in e-cigarette vapors and concluded that significant levels of PM_{2.5} are indeed exhaled by e-cigarette users.⁵⁸ The number of particles and size distribution in emitted PM in e-vapors were found to vary depending on the e-liquid, nicotine concentration, and puffing topography^{12,101,153} and seem to be comparable to those generated from tobacco smoke.^{153,154}

Several studies, conducted under controlled conditions that almost resemble real-life settings, revealed a significant increase in PM_{2.5} concentrations in rooms and/or experimental chambers in which e-cigarettes were consumed by

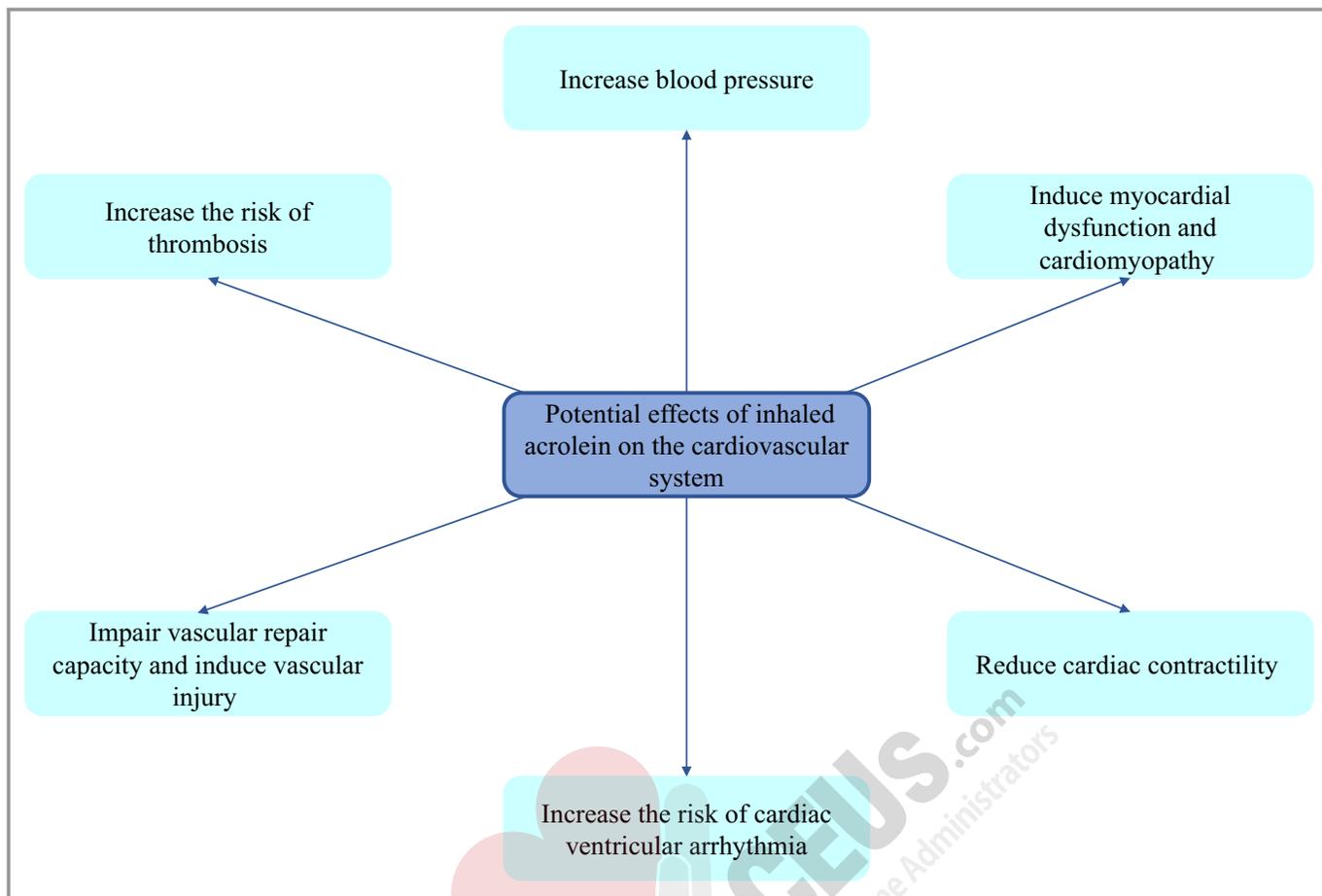


Figure 2. Effects of acrolein on the cardiovascular system. Wide ranges of cardiovascular effects of acrolein inhalation from smoking and ambient air pollution are reported in animal studies.^{138,139,142,146}

human subjects.^{57,65,90} This highlights e-cigarettes as a source of PM_{2.5} secondhand exposures.^{57,65,90} In fact, PM_{2.5} concentrations increased dramatically (125–330-folds) in hotel rooms where e-cigarette use was allowed for 2 days, compared with the same rooms before active vaping occurred.¹⁵⁵ Surprisingly, these concentrations of PM_{2.5} are higher than the reported values from tobacco smoking

in Hookah cafes and indoor bars.¹⁵⁵ On the other hand, it has been shown that the level of PM_{2.5} in houses of e-cigarette users was 95% lower than those from homes of conventional cigarette users.⁵⁸ Collectively, these studies provide evidence that e-cigarette users do indeed exhale PM_{2.5}, thus putting themselves as well as nonusers under health risks.

Table 3. Acrolein Concentrations Emitted in e-Cigarette Vapors

Reference	Puff Volume	Acrolein Concentration/15 puffs*	Acrolein Concentration/d (120 puffs)	Acrolein Concentration ppm [†]	Acrolein Concentration ppm/d (120 puffs)
Goniewicz et al ⁶⁴	70 mL	0.07 to 4.19 µg	0.564 to 33.516 µg	6.6×10^{-5} to 0.0039	0.00792 to 0.468
Uchiyama et al ¹⁴⁷	55 mL	3.15 to 24 µg	25.2 to 192 µg	0.0038 to 0.029	0.456 to 3.48
Gillman et al ¹⁴⁸	55 mL	0.3 to 82.5 µg	2.4 to 660 µg	0.00036 to 0.1	0.0432 to 12
Flora et al ¹⁴⁹	55 mL	61.5 µg	492 µg	0.0745	8.94

*15 puffs=1 conventional cigarette.

[†]ppm=µg/mL, to convert µg/puff to ppm, we divided the concentration (µg) by the volume of each puff (mL).

$$\text{ppm} = \frac{\text{concentration } (\mu\text{g})}{\text{volume (mL)}}$$

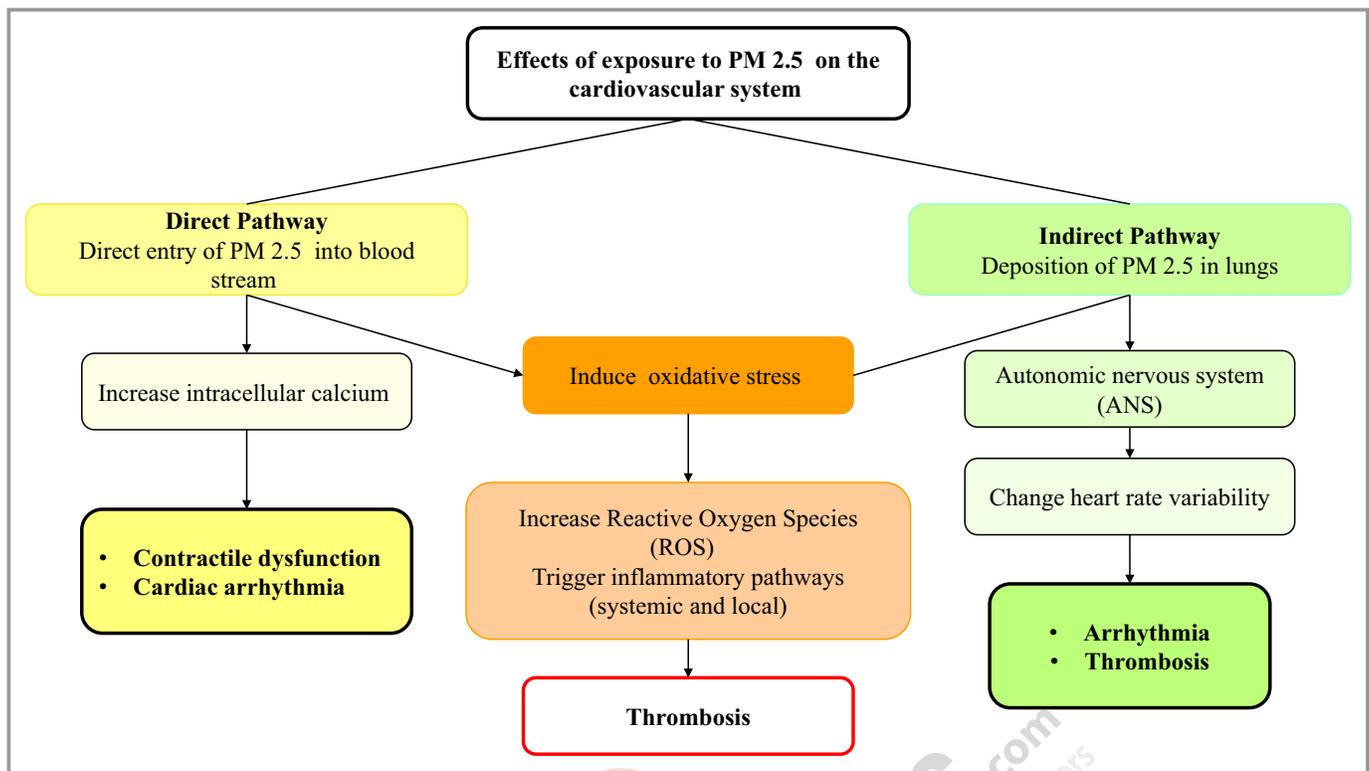


Figure 3. Effects of particulate matter (PM_{2.5}) on the cardiovascular system. PM_{2.5} exposure from tobacco and environment/ambient negatively affects the cardiovascular system either directly or indirectly. The direct pathway is mediated by the delivery of PM_{2.5} into the bloodstream. The indirect pathway is attributed to deposition of PM_{2.5} in lungs and a modulation of autonomic nervous system. Oxidative stress is triggered by both pathways and induces local and systemic inflammatory processes. PM_{2.5} indicates particulate matter less than 2.5 microns in diameter.

Epidemiological and clinical studies suggest a strong association between human exposure to PM_{2.5} and the risk of cardiovascular disease development. Specifically, these studies showed that exposure to PM_{2.5} from ambient air pollution and/or tobacco smoking is linked to hypertension,¹⁵⁶ coronary artery disease,¹⁵⁷ myocardial infarction,^{158,159} atherosclerosis,¹⁵⁶ arrhythmia,¹⁶⁰ as well as mortality relative risk.^{161,162} Interestingly, risk of atherosclerosis was reported to increase with long-term exposure to ambient air PM_{2.5}, and to be higher in elderly, female, and nonsmoker participants,¹⁶³ underscoring the sensitivity of special populations. This notion is consistent with reports that exposure of the elderly population with a history of cardiovascular disease to PM_{2.5} for only 28 days was accompanied with higher resting cerebrovascular resistance and increased mean arterial blood pressure.¹⁶⁴

The physiomechanisms underlying the aforementioned effects are divided into a direct and indirect pathway, as summarized in Figure 3.¹⁵⁶ The direct pathway is mediated by the delivery of PM_{2.5} into the bloodstream, thereby targeting multiple organs.^{165,166} Thus, if ion channels and calcium regulation are affected by PM_{2.5}, it could lead to contractile dysfunction and arrhythmia,^{165,167} whereas vascular dysfunction and thrombus formation can result from producing local

oxidative stress and inflammation.^{168–170} Regarding the indirect pathway, PM_{2.5}-induced cardiovascular toxicity is associated with the development of inflammatory responses and modulation of the autonomic nervous system.¹⁶⁷ Thus, deposition of PM_{2.5} on alveoli was found to trigger the release of a host of proinflammatory mediators, vasoactive molecules, and reactive oxygen species into the circulation. These will subsequently affect vascular integrity and induce thrombogenesis.^{168,170} As for PM_{2.5} modulation of the autonomic nervous system, it results in increased vasoconstriction and change in heart rate variability, which will potentially enhance the risk of developing arrhythmias and thrombosis.¹⁷¹

Importantly, it has been found that the dose-response relationship between PM exposure and cardiovascular mortality is also nonlinear,¹⁷² and that a consequential adverse cardiovascular outcome can happen as a result of exposure to low levels.¹⁷² Interestingly, it was suggested that PM_{2.5} is responsible for more than 90% of the predicted harm caused by thirdhand smoke pollutants.¹⁷³ Although, clearly, PM_{2.5} from ambient air pollution and smoking exerts harmful effects on the cardiovascular system, its mere presence—as a result of e-cigarette use—does not mean that it will have an effect; this issue should be investigated.

Studies have shown that e-cigarette PM2.5, even from a single puff, undergoes cardiopulmonary delivery into the systemic circulation,¹⁷⁴ resulting in a significant amount of deposition in the respiratory tree.¹⁷⁵ Furthermore, in vitro experiments documented a venous absorption between 7% and 18% of the total e-aerosol and arterial absorption through the alveoli between 8% and 19%.¹⁷⁴ Finally, a recent in vitro study concluded that PM2.5 may be the primary constituent that mediates e-cigarette-induced platelet activation and aggregation.⁴⁸ Based on these considerations, it is important to examine the negative health effects of short- and long-term (active and passive) exposure to e-cigarettes PM2.5.

Recent Regulatory Updates

Because of the growing evidence that e-cigarettes' present potential harm to public health, and the "skyrocketing" usage among youth, the US Food and Drug Administration issued new legislation (on August 8, 2016) that extended their regulations to e-cigarettes. This is expected to protect public health, minimize the risks associated with e-cigarettes and reduce youth's exposure to these devices. Under this expansion, manufacturers will be required to report all ingredients and undergo a premarket review to obtain permission to market their products.¹⁷⁶ Furthermore, selling of e-cigarettes to those aged <18 years is now prohibited, as is selling any tobacco products in vending machines (unless in an adult-only facility).¹⁷⁶ Of note, the tobacco 21 movement, a regulation that advocates for raising the minimum legal sale age for tobacco products to 21, was followed during 2016 only in 2 states (California and Hawaii). However, as of March 2017, the pattern is expanding to include at least 220 localities across the United States.¹⁷⁷ Nonetheless, and unfortunately, e-cigarettes are still available for purchase from online vendors, which would be the first alternative for youth. Thus, this aspect/"loophole" should be covered/closed by state legislation or by stricter rules from the US Food and Drug Administration.

The Public Health and Tobacco Policy Center report revealed that even though 31 states have (state) restrictions and laws addressing where e-cigarettes usage is allowed, only 10 of 31 prohibited their use wherever tobacco is prohibited effective January 2017. The majority of the remaining states prohibit vaping in schools, day care facilities, and a few on campuses.¹⁷⁸ However, concerns remain regarding the use of e-cigarettes at work and public places across the country, which results in exposing nonusers to potentially harmful vapors.

Conclusion

Although much is known about smoking-induced cardiovascular toxicity, little is known about that of e-cigarettes. This is

an issue that continues to be a subject of debate. Nevertheless, based on the current body of evidence, e-cigarettes are not emission free (as some believe) and, in fact, they emit various potentially harmful and toxic chemicals. Whether or not the levels of these toxicants are lower than traditional smoking remains controversial. In this connection, recent studies showed that e-cigarettes-emitted chemicals reach levels comparable to tobacco smoke, and those levels vary depending on multiple factors, including types of devices, e-liquid, vaping topography, and vaping experience.¹⁷⁹ Given the sensitivity of the cardiovascular system and its "smoke" nonlinear dose-response/toxicity relationship, it is important to evaluate the cardiovascular safety of e-cigarettes.

Although it was originally argued that e-cigarettes are "harm free," the present prevailing belief is that they are "reduced harm" alternatives to conventional cigarettes. This latter notion is still debatable and not supported by conclusive evidence, especially considering the wide variation between e-cigarette products. Even if that were the case, their harm can still extend to innocent/bystander nonsmokers through secondhand and thirdhand vaping, including children, pregnant women, casino/housekeeping workers, and people with preexisting cardiovascular and other diseases.

The widespread and increasing usage of e-cigarettes in the United States is concerning because of the lack of studies on the long-term health effects of these devices on biological systems. Therefore, future research should establish, under real-life conditions, not only the long-term, but also the short-term negative effects of e-cigarette usage, on both users (active) and nonusers (passive), and provide mechanistic insights regarding these effects. These should, in turn, guide and shape policy for further evidence-based vaping control. Ultimately, we hope to underscore the need for prevention of exposure to various forms of vaping, especially in vulnerable populations like children and youth



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