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Are Electronic Cigarette Users at Increased Risk for Cardiovascular Disease?

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The introduction of electronic cigarettes (e-cigarettes) in 2006 has created an entirely new public health dilemma. Although some public health activists believe that e-cigarettes represent a new addition to the armory of tobacco control and harm reduction, others are unsure how the widespread use of e-cigarettes will affect the prevalence of nicotine addiction and premature mortality owing to tobacco product use. The central issue in the debate is the disease risk imposed by e-cigarettes. Because e-cigarettes do not contain tobacco per se and do not burn tobacco, many of the toxic compounds produced during tobacco combustion are either eliminated or significantly reduced in abundance in e-cigarette aerosols. These devices produce little or no tar or carbon monoxide and only trace levels of metals and other toxicants abundant in combustible cigarettes. For this reason, proponents of e-cigarettes argue that many of the harmful health outcomes of combustible cigarettes, such as lung cancer, emphysema, and heart disease, are unlikely to be associated with long-term e-cigarette use. Indeed, Public Health England has declared[1] and the Royal College of Physicians has agreed[2] that e-cigarettes are likely to be 95% safer than conventional cigarettes. But apart from opinions, there is little direct evidence to assess the health impact of e-cigarettes.

Because e-cigarettes lack tar and other carcinogens, their carcinogenic effects may be lower than combustible cigarettes; however, it is unclear whether cardiovascular harm is similarly attenuated. Some cardiovascular toxicants present in tobacco smoke, eg, particulate matter and carbonyls such as formaldehyde, acetaldehyde, acetone, acrolein, and butanol, are also present in e-cigarettes.[3–5] By themselves, these can increase cardiovascular disease (CVD) risk by affecting blood pressure regulation, promoting coagulation, and accelerating the formation of atherosclerotic lesions.[6] Notably, nicotine present in most e-cigarettes is a strong vasoactive drug that can profoundly affect cardiovascular function and health. Indeed, it has been shown that smoking e-cigarettes increases heart rate[7,8] as well as diastolic and systolic blood pressure[8] to levels comparable with those observed with conventional cigarettes.[8] In contrast, other investigators have reported minimal changes in systolic blood

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pressure and no reduction in coronary reserve,[9] albeit with low nicotine delivery devices.[9] Adding to this debate, Moheimani et al[10] now report in this issue of *JAMA Cardiology* that habitual use of e-cigarettes increases the sympathetic tone and induces oxidative stress.[10]

In their study, Moheimani et al[10] studied young healthy adults who had used e-cigarettes for most days for a minimum of 1 year. They found that in comparison with nonusers, high-frequency (HF) component of the heart rate variability (HRV) was significantly reduced in e-cigarette users, suggesting diminished vagal tone. However, the HF component of HRV is dependent on changes in respiratory sinus rhythm and therefore is sensitive to changes in breathing pattern. Importantly, the authors also measured HRV during a controlled breathing period but found no changes in low frequency (LF) and the LF to HF ratio during controlled breathing period. To determine whether these changes in HRV were associated with oxidative stress, they measured the susceptibility of apolipoprotein B-containing lipoproteins to oxidation, a sensitive measure of systemic oxidative changes. They found that low-density lipoprotein from e-cigarette users was more susceptible to oxidation than that from nonusers. However, this increase in low-density lipoprotein oxidizibility was not associated with a statistically significant decrease in the activity of paraoxonase-1, which protects low-density lipoprotein against oxidation. No changes were observed in plasma levels of fibrinogen or C-reactive protein, which are indicators of systemic oxidative stress.

Although data from e-cigarette users were not compared with those from smokers of combustible cigarettes, the results of Moheimani et al[10] demonstrate that the use of e-cigarettes is not without consequence and might impose cardiovascular harm and increase CVD risk. Nevertheless, changes in HRV and low-density lipoprotein oxidizability are indirect indices of cardiovascular injury, and it remains unclear to what extent these changes represent an increase in CVD risk. Changes in HRV are robust predictors of cardiovascular mortality and have been considered to be an independent CVD risk factor. However, the meaning of the changes in LF and LF to HF is less clear, given the arguably limited reliability of LF and LF to HF as pure markers of cardiac autonomic influences. Extensive research suggests that LF may not be as reliable a measure of sympathetic or combined sympathetic and parasympathetic influences[11] as time-domain HRV, which was not reported by the authors. The LF to HF ratio is also an inconsistent marker of general sympathovagal balance and could reflect baroreflex-mediated cardiac autonomic modulation,[12] which itself is dependent not only on autonomic activation but also on baroreceptor sensitivity and blood pressure fluctuations. More significant to the evaluation of the potential cardiovascular injury of these changes are previous observations, pointed out by the authors[10] showing that HRV balance is shifted toward sympathetic predominance on oral nicotine ingestion. Because oral nicotine is relatively well tolerated even by individuals with advanced CVD, it is unclear whether changes in HRV alone could be regarded as an indication of substantial cardiovascular injury. However, oral nicotine also may not be innocuous because individuals who quit smokeless tobacco have been reported to decrease their CVD risk to an extent similar to those who quit smoking.[13] Moreover, an increase in heart rate could by itself accelerate atherosclerosis.[14] Hence, persistent changes in HRV observed in e-cigarette users reinforce the idea that nicotine, whether delivered by combustible cigarettes or e-cigarettes, is not a harmless drug but could have significant adverse cardiovascular effects.

The observations of Moheimani et al[10] showing oxidative stress in e-cigarette users further substantiate cardiovascular injury owing to e-cigarette use. These findings are in agreement with the results of a study by Carnevale et al[15] showing that smoking e-cigarettes decreases the bioavailability of nitric oxide and the levels of the antioxidant vitamin E while at the same time increasing the levels of the oxidant-generating enzyme nicotinamide adenine dinucleotide phosphate oxidase as well as the levels of 8-iso-prostaglandin F2α, an indicator of lipid peroxidation. Although collectively, such findings support of the notion that e-cigarette use increases oxidative stress, the reasons for this increase remain obscure. An increase in oxidative stress has also been reported in users of combustible cigarettes, but in tobacco-containing cigarettes, combustion generates a large number of long-lived quinone radicals. How e-cigarettes can induce oxidative stress in the absence of tar and other long-lived radicals remains unclear, and further studies are required not only to fully explore the reasons for the interesting observations of Moheimani et al[10] but also to assess in greater depth the cardiovascular effects of e-cigarettes. Such investigations are critical for evaluating how harmful e-cigarettes are and whether their widespread acceptance will decrease the incidence of cardiovascular disease or, by renormalizing smoking and promoting nicotine addiction, erode public health gains made by evidence-based tobacco control and regulation.

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