Safety Assessment of Electronic Cigarettes and Their Relationship with Cardiovascular Disease

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Abstract: Electronic cigarettes (e-cigarettes) are sometimes considered as an adjunct to quitting smoking, and the number of people using e-cigarettes among young people and adults is increasing rapidly. However, limited knowledge exists about the long-term health effects of e-cigarette use. Both animal models and human studies have demonstrated that e-cigarette, especially nicotine, is closely associated with cardiovascular diseases. However, there is not that much research focus on the mechanism of how e-cigarettes affect cardiovascular disease. Some studies have demonstrated that the content of e-cigarette, especially nicotine and flavouring additive may result in cardiovascular disease due to damage in the endothelium. The relationship between e-cigarette usage and hypertension has been nearly confirmed, which might be the potential cause of other cardiovascular diseases. This review aims to summarize the trends and existing scientific information on the use of e-cigarettes, focusing on potential cardiovascular health risks and benefits, characteristics related to the use of e-cigarettes, and key areas for future research.

1. Introduction

Electronic cigarettes (e-cigarette), a portable device that looks like cigarettes, provide nicotine vapour to users by a heating liquid containing, but not limited to, propylene glycol or glycerine, nicotine, and flavouring ingredients [1]. It has been widely used as a replacement for conventional cigarettes. However, number of studies have proved that the degree of injury that e-cigarette bring to the body is not lower than that of conventional cigarettes.

E-cigarettes have been listed in the United States since 2007. The supply and use of e-cigarettes lag behind other industrialized countries, but they have increased rapidly in recent years. Global usage is growing exponentially. Among adults who also use traditional cigarettes, the use rate of e-cigarettes is the highest. Youth e-cigarette use in the United States doubled or tripled every year between 2011 and 2014, and by 2014, e-cigarette use had surpassed conventional cigarette use in youth. By 2015, up to 16% of young high school students in the United States had used e-cigarettes in the past 30 days, The United States Secretary of Health issued a report, pointing out that the use of e-cigarettes by adolescents and young people has been regarded as a major public health problem, and emphasizing the need to strengthen prevention and education to reduce the use of e-cigarettes by young people [2-4].

Cardiovascular diseases (CVDs) are a set of disorders involves heart and blood vessels. CVDs include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, and deep vein thrombosis and pulmonary embolism. CVD is the major cause of mortality and early death in China, accounting for 40% of all fatalities. The risk factors of CVD have been studied widely. Major modifiable risk factors for cardiovascular disease include high blood pressure, smoking habits, diabetes, and lipid abnormalities. Tobacco usage is a major risk factor for cardiovascular disease (CVD) and the primary preventable cause of death globally [5]. According to World Health Organisation (WHO), tobacco use has a well-established causal relationship with CVD morbidity and death. High blood pressure is linked to the most substantial evidence for causation and has a high incidence of exposure among them [6].

Besides, mixed evidence suggests that e-cigarette may promote smoking cessation attempts, and recent evidence supports the view that e-cigarette may also help TC quit smoking. In addition, the possible benefits of e-cigarette as a smoking cessation aid must be balanced with its increasing popularity among people who never smoke, especially adolescents [7].

Therefore, in this review, we summarise the known effects of e-cigarette on cardiovascular health and areas for further research and discuss the effects of e-cigarette on public health.

2. E-cigarette and Cardiovascular Disease

2.1 E-cigarette and atherosclerosis

Atherosclerosis is a disease in which plaque builds up inside the arteries [8], which might result in major complications such as a heart attack, stroke, or even death. Endothelial cells are the basis of regulating vascular tension, inflammation, vascular growth, platelet aggregation and coagulation. Endothelial cells produce important vasodilators with anti-atherosclerotic and anti-aggregation properties, such as nitric oxide and prostacyclin. Endothelial dysfunction (impaired biochemical pathway of endothelial cells) is a feature of coronary artery disease, a predictor of atherosclerosis and future cardiovascular events [9]. Electronic cigarettes contain nicotine, particulates, and other compounds [10]. The addictiveness of nicotine is known to all. Nicotine induces the release of catecholamine and cortisol, and causes hemodynamic changes (increase in heart rate, rise in blood pressure, and the vasoconstriction) [11]. Researchers at Danderyd hospital in Sweden found that smoking e-cigarettes only 10 times could lead to vascular damage. Subsequently, they further studied the effects of inhaling e-cigarettes 30 times on healthy people. Magnus Rudbeck, a doctor at Danderyd hospital who participated in the study, believes that e-cigarette users have poor vascular elasticity, which may lead to heart disease and stroke [12]. Farsalinos, K.E. et al. studied the acute effect of e-cigarette on the cardiovascular system of the contacts [13]. The results showed that the cardiac output and blood pressure (nicotine content of 11mg / ml) of the contacts increased slightly; when the smoker's heart contracts, the cardiac output and heart rate increase significantly. They also verified the toxic effect of atomized e solution on cultured cardio myocytes by MTT test [13].

Also, vascular smooth muscle cell (VSMC) plays a significant role in atherosclerosis by generating a new neointima layer [14]. Study shows nicotine will be adjusting the function of VSMCs. To be more specific, nicotine appears to cause VSMCs to undergo a phenotypic flip, causing migration into the intima, or inner layer of the artery [15-16]. When the potent vasoconstrictor Angiotensin II (Ang II) work with nicotine, a strong compounding effect on VSMC will be generated, which causing atherosclerosis [17]. Flavours additive adds another degree of complication when it comes to evaluating the risk of hazardous health impacts [18]. Thus, Gideon St. Helen et al. concluded that flavours increase nicotine intake through flavour preference, which may change nicotine absorption rate via pH effects, and lead to e-cigarette heart rate acceleration and subjective effects. Centner et al. also claimed that by the way, atherosclerosis is closely associated with hypertension as well [14]. The endothelium is damaged by untreated hypertension, which leads to cell multiplication, vascular remodelling, and immune cell recruitment [19]. Moreover, hypertension can lead to loss of vasomotor activity, which eventually develop to arterial constriction, partly through the production of free radicals, inflammation, and the creation of foam cells and atherosclerotic plaque.

2.2 E-cigarette and hypertension

The long-term impacts of smoking on blood pressure remain unknown. After acute ventilator ventilation in humans, a brief increase in systolic blood pressure was observed. After a large number of exposures to electronic flue gas sol in mice and in vitro studies, accelerated aortic stiffness and abnormal vascular inflammation were reported respectively. If confirmed in humans, both of these conditions may lead to hypertension [20-21].

Numbers of intervention studies demonstrated that there is a short-term association between e-cigarette usage and increase in blood pressure, both systolic blood pressure (SBP) and diastolic blood pressure (DBP), immediately to a period after exposure to e-cigarette containing nicotine [22].

Currently, smokers with standard to normal hypertension (120 – 139 / 75 – 89 mmHg) have a higher risk of cardiovascular disease than non-smokers with average to normal hypertension [5]. Additionally, tobacco usage increases arterial stiffness, which lasts for a decade after smoking cessation; persistent arterial stiffness is also associated with a higher risk of CVD events [23].

One possible explanation would be nicotine in the e-cigarette vapour activates the sympathetic nervous system, resulting increase in heart rate, blood pressure, sympathetic nerve activity (SNA) and myocardial contractility [24-25]. The relative balance between the direct sympathetic excitation effect of tobacco smoke and the opposite sympathetic inhibition effect mediated by baroreflex determines the overall effect of acute smoking and nicotine exposure on SNA.

Another possible explanation would be flavouring chemicals in e-cigarette result in oxidative stress causes endothelial dysfunction [26-27]. Although the processes behind endothelial dysfunction are complex, a growing number of research shows that increased reactive oxygen species (ROS) generation contributes significantly to this phenomenon of endothelial dysfunction in a variety of ways. In particular, ROS may react with NO, reducing its bioavailability [28]. Which hurts the response of vascular smooth muscle to the vasodilators, increased vasoconstrictor substance synthesis or boosted shear stress. Some experts also mentioned that increased ROS or oxidative stress is linked to classic and nontraditional risk factors for cardiovascular events.

2.3 E-cigarette and hyperlipidemia

Hyperlipidemia involves an imbalance of cholesterol levels, including low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) in the blood. LDL-C and HDL-C regulate the amount of cholesterol in the body and an imbalance can increase the risk of cardiovascular events [29].

Smoking can lead to dyslipidemia, which is a modifiable risk factor. Nicotine has adverse effects on blood lipid, which can lead to adenylate cyclase activation and triglyceride decomposition in adipose tissue. The study found that the total lipid composition of rats exposed to e-cigarette smoke increased significantly, the content of saturated fatty acids increased significantly, while the content of unsaturated fatty acids decreased significantly, and the induction of insulin resistance [30-32].

There are few studies on hyperlipidemia caused by e-cigarettes, but it is well known that hyperlipidemia is also a risk factor for atherosclerosis, hypertension, and other chronic diseases. Thus, it is worth doing more research to further explore its impact mechanism

3. Conclusions

Traditional cigarettes have a history of hundreds of years. As e-cigarettes have been on the market for only a few years, the long-term impact on people's health is still unknown. The small sample size in population survey and epidemiological statistical analysis limits the research on its safety. WHO (2021) the latest tobacco report that e-cigarettes are harmful, and there is no sufficient evidence to prove that they can be used as a tool to quit smoking [33]. In vivo and in vitro evidence has confirmed that the ingredients are harmful to the respiratory and cardiovascular systems. Our study further proved that there is an association between e-cigarette smoke and some cardiovascular diseases. The possible mechanism is that nicotine contained in e-cigarette affects endothelial cells, vascular smooth muscle cells, causes oxidative stress disorder, or activates the sympathetic nervous system, affects sympathetic nerve activity, and finally leads to abnormal cardiovascular diseases. However, at present, the research on e-cigarette is still fragmented and incomplete, and there is no systematic evaluation on its safety. In addition, due to the lack of quality control and authorization policies, it is not convenient for further research and development. Finally, given the concerns of teenagers about the increased use of e-cigarettes, it is necessary to further strengthen the supervision of these products to limit the availability, as well as the supervision of liquids and condiments.

References

[1] Bold, K., Krishnan-Sarin, S., & Stoney, C. (2018). E-cigarette use as a potential cardiov ascular disease risk behavior. American Psychologist, 73(8), 955-967. Https: // doi.org/ 10.1 037 / amp0000231.

[2] Grana, R., & Ling, P. (2014). “Smoking Revolution”. American Journal of Preventive M edicine, 46(4), 395-403. Https: // doi.org/10.1016/j.amepre.2013.12.010.

[3] Singh, T., Arrazola, R., Corey, C., Husten, C., Neff, L., Homa, D., & King, B. (2016). Tobacco Use Among Middle and High School Students — United States, 2011–2015. MM WR. Morbidity and Mortality Weekly Report, 65(14), 361-367. Https: // doi.org/10.15585/m mwr.mm6514a1.

[4] Glantz, S., & Bareham, D. (2018). E-Cigarettes: Use, Effects on Smoking, Risks, and P olicy Implications. Annual Review of Public Health, 39(1), 215-235. Https: // doi.org/ 10.11 46/ annurev-publhealth-040617-013757.

[5] Kondo, T., Nakano, Y., Adachi, S., & Murohara, T. (2019). Effects of Tobacco Smokin g on Cardiovascular Disease. Circulation Journal, 83(10), 1980-1985. Https: // doi.org / 10.1 253/circj.cj-19-0323.

[6] Fuchs, F., & Whelton, P. (2020). High Blood Pressure and Cardiovascular Disease. Hype rtension, 75(2), 285-292. https://doi.org/10.1161/hypertensionaha.119.14240

[7] MacDonald A, Middlekauff HR. Electronic cigarettes and cardiovascular health: what do we know so far? Vasc Health Risk Manag. 2019; 15: 159-174 https://doi.org/10.2147/VHRM.S175970

[8] Libby, P., Buring, J., Badimon, L., Hansson, G., Deanfield, J., & Bittencourt, M. et al. (2019). Atherosclerosis. Nature Reviews Disease Primers, 5(1). https://doi.org/10.1038/s41572-0 19-0106-z

[9] Münzel, T., Hahad, O., Kuntic, M., Keaney, J. F., Deanfield, J. E., & Daiber, A. (2020) . Effects of tobacco cigarettes, e-cigarettes, and waterpipe smoking on endothelial function a nd clinical outcomes. European heart journal, 41(41), 4057–4070. https://doi-org.ezproxy.librar y.sydney.edu.au/10.1093/eurheartj/ehaa460

[10] Darville, A., & Hahn, E. (2019). E-cigarettes and Atherosclerotic Cardiovascular Diseas e: What Clinicians and Researchers Need to Know. Current Atherosclerosis Reports, 21(5). ht tps://doi.org/10.1007/s11883-019-0777-7

[11] Zhang, G., Wang, Z., Zhang, K., Hou, R., Xing, C., Yu, Q., & Liu, E. (2018). Safety Assessment of Electronic Cigarettes and Their Relationship with Cardiovascular Disease. Inte rnational journal of environmental research and public health, 15(1), 75. https://doi-org.ezprox y.library.sydney.edu.au/10.3390/ijerph15010075

[12] Balakumar, P., & Kaur, J. (2009). Is nicotine a key player or spectator in the inductio n and progression of cardiovascular disorders? Pharmacological research, 60(5), 361–368. http s://doi-org.ezproxy.library.sydney.edu.au/10.1016/j.phrs.2009.06.005

[13] Farsalinos, K., Tsiapras, D., Kyrzopoulos, S., Savvopoulou, M., & Voudris, V. (2014). Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocar dial function: comparison with the effects of regular cigarettes. BMC Cardiovascular Disorde rs, 14(1). https://doi.org/10.1186/1471-2261-14-78

[14] Centner, A., Bhide, P., & Salazar, G. (2020). Nicotine in Senescence and Atheroscleros is. Cells, 9(4), 1035. https://doi.org/10.3390/cells9041035

[15] Yoshiyama, S., Chen, Z., Okagaki, T., Kohama, K., Nasu-Kawaharada, R., & Izumi, T. et al. (2014). Nicotine exposure alters human vascular smooth muscle cell phenotype from a contractile to a synthetic type. Atherosclerosis, 237(2), 464-470. https://doi.org/10.1016/j.atherosclerosis.2014.10.019

[16] Bals, R., Boyd, J., Esposito, S., Foronjy, R., Hiemstra, P., & Jiménez-Ruiz, C. et al. (2019). Electronic cigarettes: a task force report from the European Respiratory Society. European Respiratory Journal, 53(2), 1801151. https://doi.org/10.1183/13993003.01151-2018

[17] Forrester,S.J.; Booz,G.W.; Sigmund,C.D.; Coffman,T.M.;Kawai,T.;Rizzo,V.; Scalia,R.;Eguchi,S.Angiotensin II Signal Transduction: An Update on Mechanisms of Physiology and Pathophysiology. Physiol. Rev. 2018, 98, 1627–1738.

[18] St.Helen, G., Dempsey, D., Havel, C., Jacob, P., & Benowitz, N. (2017). Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. Drug and Alcohol Dependence, 178, 391-398. https://doi.org/10.1016/j.drugalcdep.2017.05.042

[19] Hurtubise, J., McLellan, K., Durr, K., Onasanya, O., Nwabuko, D., & Ndisang, J. (2016). The Different Facets of Dyslipidemia and Hypertension in Atherosclerosis. Current Atherosclerosis Reports, 18(12). https://doi.org/10.1007/s11883-016-0632-z

[20] Virdis, A., Giannarelli, C., Fritsch Neves, M., Taddei, S., & Ghiadoni, L. (2010). Cigarette Smoking and Hypertension. Current Pharmaceutical Design, 16(23), 2518-2525. https://doi.org/10.2174/138161210792062920

[21] Olfert, I., DeVallance, E., Hoskinson, H., Branyan, K., Clayton, S., & Pitzer, C. et al. (2018). Chronic exposure to electronic cigarettes results in impaired cardiovascular function in mice. Journal of Applied Physiology, 124(3), 573-582. https://doi.org/10.1152/japplphysiol.00713.2017

[22] Martinez-Morata, I., & Navas-Acien, A. (2020). Electronic cigarette use and blood pressure endpoints: a systematic review. ISEE Conference Abstracts, 2020(1). https://doi.org/10.1289/isee.2020.virtual.p-0191

[23] Jatoi, N., Jerrard-Dunne, P., Feely, J., & Mahmud, A. (2007). Impact of Smoking and Smoking Cessation on Arterial Stiffness and Aortic Wave Reflection in Hypertension. Hypertension, 49(5), 981-985. https://doi.org/10.1161/hypertensionaha.107.087338

[24] Middlekauff, H., Park, J., & Moheimani, R. (2014). Adverse Effects of Cigarette and Noncigarette Smoke Exposure on the Autonomic Nervous System. Journal of the American College of Cardiology, 64(16), 1740-1750. https://doi.org/10.1016/j.jacc.2014.06.1201

[25] Moheimani RS, Bhetraratana M, Peters KM, Yang BK, Yin F, Gornbein J, Araujo JA & Middlekauff HR (2017). Sympathomimetic effects of acute e-cigarette use: role of nicotine and non-nicotine constituents. J Am Heart Assoc 6, e006579.

[26] Schulz, E., Gori, T. & Münzel, T. Oxidative stress and endothelial dysfunction in hypertension. Hypertens Res 34, 665–673 (2011). https://doi.org/10.1038/hr.2011.39

[27] Muthumalage, T., Prinz, M., Ansah, K., Gerloff, J., Sundar, I., & Rahman, I. (2018). Inflammatory and Oxidative Responses Induced by Exposure to Commonly Used e-Cigarette Flavoring Chemicals and Flavored e-Liquids without Nicotine. Frontiers in Physiology, 8. https://doi.org/10.3389/fphys.2017.01130.

[28] Beckman, J., & Koppenol, W. (1996). Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. American Journal of Physiology-Cell Physiology, 271(5), C1424-C1437. https://doi.org/10.1152/ajpcell.1996.271.5.c1424

[29] Karr S. (2017). Epidemiology and management of hyperlipidemia. The American journal of managed care, 23(9 Suppl), S139–S148.

[30] Vardavas, C. I., Anagnostopoulos, N., Kougias, M., Evangelopoulou, V., Connolly, G. N., & Behrakis, P. K. (2012). Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. Chest, 141(6), 1 400–1406. https://doi-org.ezproxy.library.sydney.edu.au/10.1378/chest.11-2443

[31] Bhatnagar, A., Whitsel, L., Ribisl, K., Bullen, C., Chaloupka, F., & Piano, M. et al. (2 014). Electronic Cigarettes. Circulation, 130(16), 1418-1436. Https: // doi.org/ 10.1161 / cir. 0000000000000107.

[32] Emery, R., Levine, M., Creswell, K., Wright, A., Marsland, A., & Matthews, K. et al. (2020). Impulsivity and midlife cardiometabolic risk: The role of maladaptive health behavio rs. Health Psychology, 39(8), 642-654. https://doi.org/10.1037/hea0000884

[33] Global tobacco report 2021. Who.int. (2021). Retrieved 6 November 2021, from https: / / www.who.int/teams/health-promotion/tobacco-control/global-tobacco-report-2021.