# Cardiovascular consequences of vaping

*Oscar Echeagaray, Clarissa Savko, Andrea Gallo, and Mark Sussman*

**Purpose of review**
Vaping activity continues to increase worldwide. Promoted as a 'healthier' alternative to traditional smoking, emerging evidence indicates 'healthier' should not be confused with 'harmless'. Direct inhalation exposure of the respiratory tract in experimental research demonstrates pulmonary consequences of vaping. However, cardiovascular consequences of vaping are poorly characterized and are a priority area of research to reveal vaping-induced pathogenesis.

**Recent findings:**
Alterations in cardiovascular homeostasis, inflammation, and molecular changes following vaping exposure demonstrate vaping-related health concerns.

**Summary:**
This review summarizes cardiovascular consequences of vaping from cumulative research findings. Strategic application of emerging technologies to understand the impact of vaping upon the cardiovascular system will be essential for defining the true risks of vaping-associated injury.

**Keywords**
cardiopulmonary, cardiovascular disease, electronic cigarettes, research, vaping, vascular

## INTRODUCTION

Vaping continues to gain popularity over the last decade across a diverse spectrum of users. In 2018 an estimated 14.9% of United States (US) adults over 18 years old reported use of electronic cigarettes (E-cig) [1]. Use among youth has also increased with 19.6% of US high-school students and 4.7% middle school students using E-cigs as of 2020 [2]. Ill-conceived distribution of so called 'Dank Vapes' contributed substantially to hospitalizations with 2807 patients suffering from E-cig or vaping product use-associated lung injury (EVALI) in the United States as of February of 2020 [3,4]. Clinical trials report acute impact of E-cig and nicotine use on cardiac physiology [5,6▪,7] with pathological and economic costs derived from long-term exposure still being delineated [8,9]. Documented smoke-related cardiovascular disease (CVD) [10] and the associated financial burden on healthcare [11,12] foreshadows the future of vaping-associated CVD. Information on the intersection between vaping and cardiovascular health and homeostasis is still in early stages with a clear need for additional research to define susceptibility of cardiac structure and function to vaping.

Systemic biological consequences of vaping are too broad to consider in a short overview of the field. Therefore, this review focuses upon cardiovascular health and vaping with an emphasis upon recent trends and future directions. For detailed information on vaping-related impact on lung, vasculature, and other biological aspects, there are excellent recent reviews covering these subjects in depth [13–16]. Topics addressed here on the consequences of vaping include: cardiovascular health, function, remodeling and homeostasis; cardiac cell and molecular biology; impact from localized and systemic immune responses; and consideration of emerging technologies and experimental approaches. Evaluation of current research is necessary for planning approaches that will ultimately mitigate morbidity and mortality consequential to vaping.

## IMPACT ON CARDIAC STRUCTURE AND FUNCTION

Adverse effects of vaping have been observed in lungs with growing evidence indicating involvement

San Diego Heart Research Institute and Integrated Regenerative Research Institute, San Diego State University, San Diego, California, USA

Correspondence to Mark Sussman, Life Sciences North, Room 426 5500 Campanile Drive, San Diego, CA 92182–4614, USA. E-mail: heartman4ever@icloud.com

**Curr Opin Cardiol** 2022, 37:227–235

DOI:10.1097/HCO.0000000000000952

## KEY POINTS

- Adverse effects of vaping have been observed with growing evidence indicating impact in cardiac structure as well as deleterious impact upon function.
- Current research suggest E-cigs are not innocuous for cardiac endothelium, localized immune cell populations, and overall cardiovascular homeostasis.
- Further research is required to clarify discrepancies in the field and evaluate health and safety consequences of long-term vaping exposure.

of the heart and pulmonary circulation as well as deleterious impact upon function [17▪]. Vaping can lead to acute respiratory distress syndrome (ARDS) in severe cases, which is characterized by pulmonary hypertension and remodeling of the blood vessels of the lung [16,18,19] (Fig. 1). Increased vascular resistance drives right ventricular dysfunction, exacerbating cardiopulmonary damage. Acute cardiomyopathic events are rare and often reversible [20▪]; however, subsequent development of heart failure has also been documented [21]. Potential preventive and therapeutic approaches require insight derived from integrative examination of individual/vaping interactions, which includes chemical makeup and toxicity of vaping liquids, responses in subject's comorbidities and impact on cardiac tissue and cellulome.

Nicotine, propylene glycol/vegetable glycerin (PG/VG), other E-cig components and their byproducts are detrimental to cardiovascular health [22]. Nicotine is a highly addictive sympathoexcitatory drug, increasing heart rate and blood pressure and causing vasospasm during acute administration. Increased sympathetic stimulation can increase risk of arrhythmias and ischemia [23]. Numerous confounding effects, such as sensitization and desensitization responses, individual differences, and unclear dose-response ratios complicate simple interpretation of nicotine effects upon the cardiovascular system [24]. A murine model of high-level nicotine exposure results in both systemic and pulmonary hypertension and subsequent right ventricle remodeling [25]. Systemic hypertension was present only during the first 3 weeks of exposure until development of nicotine tolerance. However, at 8 weeks, right ventricular systolic pressure was increased accompanied by increased right ventricular internal diameter, wall thickness, and Mitogen-Activated Protein Kinase (MAPK) Pathway activation indicative of remodeling. Inhaled nicotine led to right ventricular remodeling mediated by Angiotensin II type 1 receptor by acting upon the renin-angiotensin system [26▪]. Administration of nicotine to young rats induced ROS production, promoting cardiomyocyte death by interfering with mitophagy and the intrinsic apoptotic pathway [27]. E-cig aerosol promotes alterations in a similar manner to tobacco smoke by promoting myocardial oxidative stress and inflammation leading to fibrosis [28]. As with tobacco cigarettes, recent studies found an association between E-cig use and self-reported hypertension in the population [29] and measured systemic hypertension in animal models [30▪], mainly driven by nicotine's effect on vasoconstriction and elevation of systemic vascular resistance. Combustible cigarettes cause a greater increase in sympathetic stimulation compared with E-cigs [23]. Labeling inaccuracies and elevated nicotine concentrations pose novel risks not inherent to combustible cigarettes [31]. Moreover, it is still not known if subsequent increases in adrenaline level have clinically relevant cardiovascular effects among vapers.

Although nonnicotine components and byproducts are more abundant in combustible cigarettes compared with electronic cigarettes, the presence and variety of these components in vape aerosol together with systemic and cardiovascular impact should not be underestimated. Flavoring additives to vaping juice are of particular interest, such as electrophysiological effects of toxic aldehydes, such as vanillin and cinnamaldehyde [32▪]. Flavoring aldehydes increased sympathetic stimulation compared with fruit-flavored e-vapor. Additionally, oxidizing compounds, metals, volatile organic compounds, carbonyls, and other components in E-cig vapor are dangerous for the circulatory system [33]. Further experimental and clinical assessment is needed to determine the impact of heterogeneous byproducts present in vape aerosol.

Vaping is particularly problematic in patients with underlying health conditions because of increased susceptibility to damage from acute and chronic insults. Administration of nicotine to rats increased myocardial infarct size [34]. A high-fat diet and E-cig smoke with nicotine exposure decreased left ventricular contractility with increased apoptosis and structural alteration of the heart in mice [35▪]. Thus, preexisting conditions and comorbidities are likely to contribute significantly to vaping-induced CVD.

## VAPING CONSEQUENCES ON THE VASCULAR ENDOTHELIUM

Cardiac endothelium plays a significant role in the control of vascular relaxation/contraction. The established relationship between smoking-mediated

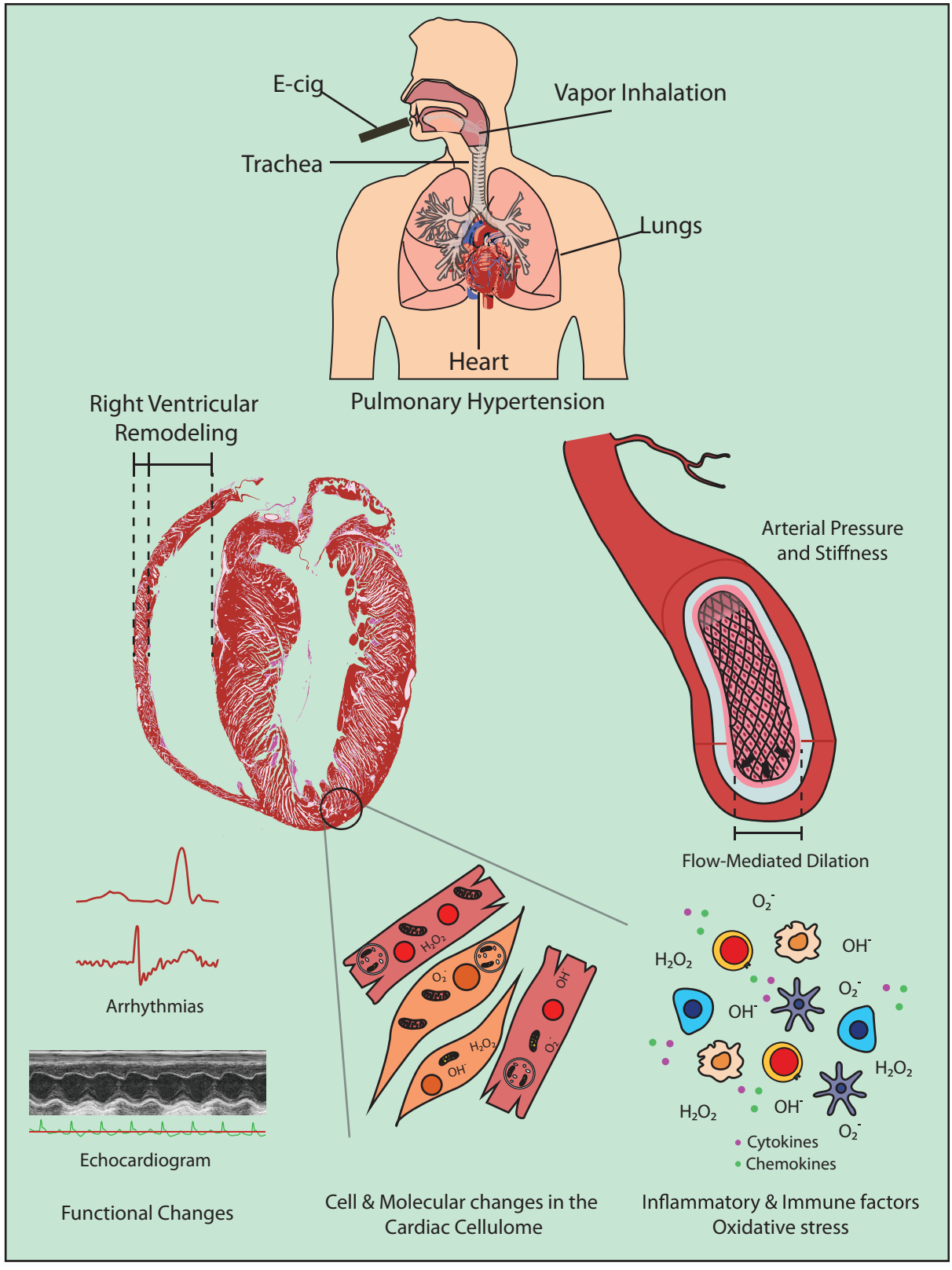


**FIGURE 1.** Summary of reported cardiovascular consequences of vaping.

endothelial dysfunction and cardiovascular disease [36,37] supports the importance of understanding vaping exposure upon endothelial health. A randomized controlled trial showed reduction in endothelial dysfunction on individuals switching from tobacco cigarettes to vaping, independently

of nicotine content of the latter [38]. Impaired flowmediated dilation (FMD), a metric for endothelial dysfunction and a predictor of cardiovascular risk, was reported in acute smokers but not E-cig vapers [39]. In contrast, tobacco cigarettes and JUUL E-cig decreased FMD at comparable levels [40]. Blood biomarkers of inflammation were increased and FMD decreased after a single episode of E-cig inhalation in otherwise healthy adults [41]. These superficially irreconcilable results could be explained because of the diversity of exposure protocols, invivo models, variation in voltage settings, and E-cig brands in each study.

In addition to dysfunction, vascular oxidative stress [42,43], decreased of vascular endothelial growth factor (VEGF) expression, and a reduction of the density of capillaries have been reported [44]. There is significantly increased carotid plaque burden that young adult smokers and vapers exhibit compared with matched nonsmokers [45▪]. Increased atherosclerotic lesions, burden, and risk mediated by TLR9 pathway in response to vaping exposure was demonstrated in a mouse model [46▪]. Increased circulating endothelial progenitor cells, increased acute microvascular endothelial dysfunction, and arterial stiffness are additional factors altered in E-cig studies [47,48]. Evidence for long-term effects of vaping upon the circulatory system is lacking, but available data suggest E-cigs should not be marketed as 'safe' alternatives to cigarettes. However, vaping could mitigate smoking endothelial dysfunction in the short-term when employed as a smoking cessation strategy. However, E-cigs are not innocuous and further research is required to clarifydiscrepancies in the field and evaluate health and safety consequences of long-term vaping exposure.

## CELLULAR AND MOLECULAR RESPONSE TO E-CIGARETTES IN THE CARDIOVASCULAR SYSTEM

Mitigating strategies and therapeutic approaches require identification of pathways driving cardiac disease as well as insight regarding molecular responses to E-cig. Molecular processes, such as inflammation and reactive oxygen species (ROS) contribute significantly to CVD and vaping diseases. Disruption in the balance of prooxidant and antioxidant systems in vasculature is associated with arrhythmias and myocardial remodeling because of pathogenic hypertrophy and apoptotic signaling [49]. E-cig exposure increases ROS in cardiomyocytes and aortic tissue vas detected by dihydroethi-dium (DHE) fluorescence [30▪,42,50]. Increased ROS coincided with decreased endothelial nitric oxide synthase (eNOS) following 3 days of exposure in mice, suggesting that decreased antioxidant nitric oxide is involved in the increase in oxidative stress [42]. The oxidative stress phenotype was alleviated by knocking out the ROS-producing enzyme NADPH Oxidase Subunit 2 (NOX2), confirming that oxidative stress is NOX2-dependent [42]. It is unclear the extent to which ROS accumulation observed in animal E-cig exposure studies translates to chronic users.

The cellular response to E-cig exposure is vital to understand mechanisms of pathogenesis. RNA-sequencing data of iPSC-derived cardiomyocytes exposed to E-cig extract for 2 days *in vitro* altered gene expression signatures for proliferation and apoptosis [50]. Notably, natriuretic peptide B (NPPB) upregu-lation was observed alongside downregulated myosin light chain kinase (MYLK) and troponin I3 (TNNI3). Proper levels of these proteins are essential for healthy heart function and appropriate stress responses. Increased apoptotic nuclei and increased cleaved-caspase 3 protein levels were reported in a high-fat diet/E-cig exposure study [35▪]. Increased apoptosis appears related to dysregulation of the AMPK pathway as apoptosis regulator AMP-activated protein kinase (AMPK) was decreased inE-cigexposed mice with no expression of its downstream target Acetyl-CoA carboxylase (ACC) [35▪]. Cellular and molecular responses to vaping implicate increased oxidative stress and apoptosis but data correlating these risk factors with reported disease is still lacking. Further characterization of the signaling pathways and mechanism for vaping-induced molecular stress and damage, such as vascular dysfunction, inflammation, remodeling, and impaired function are required to inform the public of the risks associated with E-ciguse and will be essential for development of therapeutic interventions.

## INNATE AND ADAPTIVE IMMUNE RESPONSE TO E-CIGARETTES

The innate and adaptive immune response to E-cig exposure has been predominantly examined in the pulmonary system and to a lesser extent in the cardiovascular system [51–56]. Sustained inflammation caused by typical recurring vape exposure could lead to downstream toxicity from oxidative stress and exert compounding effects to increase risk for cardiovascular disease. Additionally, immune response to vaping could exacerbate risk for CVD, such as atherosclerosis and coronary artery disease. Environmental stressors, such as E-cig vapor promote macrophage transition into foam cells, which build up in arteries as atherosclerotic plaques [57].

Ecig exposure for 16 weeks in ApoE—/— mice led to development of atherosclerotic plaques with increased levels of Mac2+ macrophages compared with controls [46▪]. Inhibition of TLR9 ameliorated the phenotype suggesting that TLR9 is mediating the atherosclerotic response. Additionally, macrophage marker CD68 was found to have increased protein levels in the aorta of mice following acute E-cig exposure [42]. Human studies have reported conclusions consistent with animal studies reporting increased levels of lymphocytes, monocytes, and neutrophils in the blood of E-cig users compared with nonusers [58▪].

Increased levels of inflammatory cytokine IL-6 in blood has been reported in both human and mouse models of E-cig exposure following a wide range of exposure time lengths [42,46▪,59▪,60]. Other cytokines including ICAM–1, MCSF, MCP–1, and IL-8 increase following acute exposure times in humans but it is unclear whether this is a transient response to initial E-cig exposure or if the inflammatory response is sustained long enough to be associated with pathogenesis [59▪,60]. Analysis of immune cell populations and signaling in animal studies on a timescale analogous to decades in humans can serve as approximations of future risk for E-cig users. The current SARS-CoV–2 (COVID–19) pandemic [61,62▪] drew attention regarding concerns related to immune system response following infection when combined with E-cig exposure. Alterations of immunocompetency pursuant to vaping are likely to have as yet poorly understood consequences for cardiopulmonary protection and homeostasis.

## EMERGING TECHNOLOGIES AND EXPERIMENTAL APPROACHES

Emerging consequences of vaping on cardiovascular homeostasis will require real-time solutions, creative experimental approaches, and innovative therapeutic approaches. Fortunately, state-of-the-art and high throughput technologies continue to be developed with some already deployed to elucidate the impact of vaping. Single-cell and nuclei RNA sequencing (sc/snRNA-Seq) has proven to be a valuable tool to characterize the lung changes in response to senescence [63], fibrosis [64], and smoking [65]. Exploration of the cardiac transcriptome has yielded a remarkable framework to study the biological diversity, interplay, and plasticity of identified cardiac cell subpopulations. Single-cell transcriptional analysis has revealed the phenotypical diversity and intercommunication within the murine cardiac cellulome at the baseline [66] and under chronic cardiac fibrosis [67▪]. Cardiac topology and chamber-specific transcriptional signatures of the human heart have been contextualized with genes implicated in cardiomyopathies using snRNA-Seq [68]. Dynamic interactions and insight on immune changes following acute injury in mouse models via myocardial infarction [69,70] or ischemia reperfusion [71▪] have been derived from using scRNA-Seq platforms. Vaping effects on cardiac development can be cross-referenced to published datasets of temporal and chamber-specific benchmarks of cardiac development [72,73]. Framework to assess changes on in-vitro phenotypes and protocols of culture-expanded cardiac cell will be critical to evaluate the influence of vaping [74,75]. Organism-wide transcription cell atlas like the Tabula Muris project [76] and the Mouse Cell Atlas [77,78] can be used as baselines for comparison of cardiac and systemic changes derived from vaping exposure. New technologies and approaches in transcriptional analysis are currently underway to determine the impact of vaping upon cardiovascular biology. Paradigm development will benefit from high-throughput technologies targeting the prote-ome and secretome including mass spectrometry and mass cytometry [79], together with epigenomic platforms, and spatial approaches recently adopted to address standing biological questions of intercellular heterogeneity and communication.

## FUTURE CONSIDERATIONS

Vaping popularity and activity continue to evolve with diverse, complex, and dynamic societal pressures advancing E-cig adoption and product development. Cardiopulmonary effects and documentation of pathogenesis continues to benefit from research studies tackling the complex and diverse array of possible exposure regimens (Fig. 2 and Table 1). Acute consequences of vaping exposure include changes in pulmonary hypertension, cardiac remodeling, function, arterial pressure and stiffness, and cell and molecular changes (Figs. 1 and 2, Table 1). Long-term cardiovascular effects of recreational vaping will eventually be revealed in decades ahead, as popularization of the vaping lifestyle is a relatively recent phenomenon, in the near term, implications of acute and chronic vaping for cardio-pulmonary health will be revealed through carefully executed studies that reveal vaping impact.

Datasets [80], research observations, and experimental strategies for assessing vaping pathogenesis can be rooted in the approaches and concepts derived from the decades-long pursuit of biological studies on traditional cigarette smoking. Experimental animal models of chronic exposure with vaping protocols relevant and comparable with

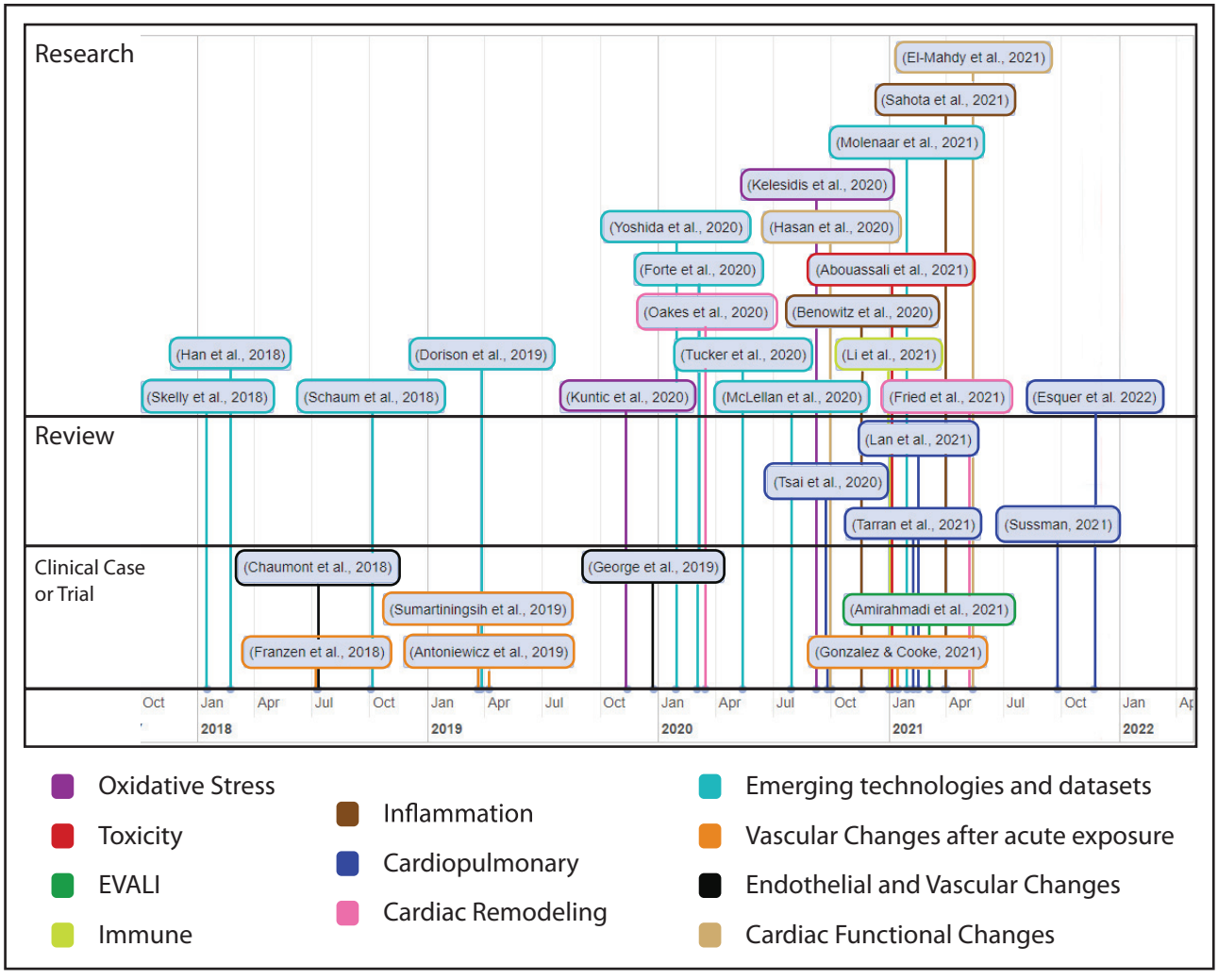


**FIGURE 2.** Cardiovascular consequences of vaping research timeline.

human recreational vaping will be crucial to evaluate long-term progression of cardiovascular health. Experimental approaches should consider cardiac cellular composition, heterogeneity, and topology, together with constraints inherent in handling and preservation of mammalian cardiopulmonary tissues.

## CONCLUSION

In conclusion, there is a profound need for thoughtful and translationally relevant research to address cardiovascular consequences of vaping. New devices, vape juice mixtures, and trends continue to be introduced, increasing variation among previous as well as ongoing studies. A composite strategy incorporating robust longitudinal assessments to investigate vaping-induced pathogenesis will need to account for variability of available products and experimental designs. Clinical evaluations of right ventricular systolic and diastolic function have been centered on ARDS patients [81,82]. However, signs of right ventricular dysfunction, such as chest discomfort and breathlessness manifest only after left ventricular function is compromised, ultimately complicating early assessment of pulmonary involvement [83]. Right ventricular remodeling observed in a mouse vaping model [84▪] implicates cardiopulmonary consequences that can contribute to not only cardiac remodeling but also increased risk for secondary debilitating conditions. Current studies suggest a correlation between vaping and atherosclerosis but additional experimental and clinical data is needed to define causality. Another area worthy of attention is the study of cell and molecular processes potentially affected by vaping, such as mitochondrial metabolism and energetics, stress response, and geno-toxicity.

Collectively, these considerations emphasize the need for promotion and expansion of vaping research. Associations between harm perception and desire to quit vaping have been established

**Table 1.** Selected articles of interest on cardiovascular consequences of vaping

| Authors, year | Reference | Article type | Title | Keywords |
|---|---|---|---|---|
| Esquer *et al.*, 2022 | [84▪] | Research | Fundamentals of vaping-associated pulmonary injury leading to severe respiratory distress | Cardiopulmonary, cardiac remodeling and functional changes |
| Li *et al.*, 2021 | [46▪] | Research | Electronic Cigarettes Induce Mitochondrial DNA Damage and Trigger TLR9 (Toll-Like Receptor 9)-Mediated Atherosclerosis | Immune |
| Benowitz *et al.*, 2020 | [59▪] | Research | Twenty-Four-Hour Cardiovascular Effects of Electronic Cigarettes Compared With Cigarette Smoking in Dual Users | Inflammation |
| Kelesidis *et al.*, 2020 | [58▪] | Research | Elevated Cellular Oxidative Stress in Circulating Immune Cells in Otherwise Healthy Young People Who Use Electronic Cigarettes in a Cross-Sectional Single-Center Study: Implications for Future Cardiovascular Risk | Oxidative stress, inflammation |
| Fried *et al.*, 2021 | [26▪] | Research | Angiotensin II type 1 Receptor Mediates Pulmonary Hypertension and Right Ventricular Remodeling Induced by Inhaled Nicotine. | Cardiac remodeling |
| El-Mahdy *et al.*, 2021 | [30▪] | Research | Long-term Electronic Cigarette Exposure Induces Cardiovascular Dysfunction Similar to Tobacco Cigarettes: Role of Nicotine and Exposure Duration | Cardiac functional changes |
| Raymond *et al.*, 2018 | [31] | Research | The Nicotine Content of a Sample of E-cigarette Liquid Manufactured in the United States | Nicotine content of e-liquid samples |
| Hasan *et al.*, 2020 | [35▪] | Research | Electronic Cigarettes Cause Alteration in Cardiac Structure and Function in Diet-induced Obese Mice | Cardiac Functional Changes |
| Amirahmadi *et al.*, 2021 | [20▪] | Clinical case or Trial | Electric Cigarette-related Lung Injury and Cardiovascular Insult | EVALI |
| Sahota *et al.*, 2021. | [45▪] | Research | Atherosclerosis Inflammation and Burden in Young Adult Smokers and Vapers Measured by PET/MR | Inflammation |
| Abouassali *et al.*, 2021 | [32▪] | Research | In vitro and In-vivo Cardiac Toxicity of Flavored Electronic Nicotine Delivery Systems | Toxicity |
| Lan *et al.*, 2021 | [62▪] | Review | Right Ventricular Damage in COVID-19: Association Between Myocardial Injury and COVID-19 | Cardiopulmonary |
| Tsai *et al.*, 2020 | [17▪] | Review | Effects of e-Cigarettes and Vaping Devices on Cardiac and Pulmonary Physiology | Cardiopulmonary |
| Gonzalez and Cooke, 2021 | [6▪] | Clinical case or Trial | Acute Effects of Electronic Cigarettes on Arterial Pressure and Peripheral Sympathetic Activity in Young Nonsmokers | Vascular changes after acute exposure |
| McLellan *et al.*, 2020 | [67▪] | Research | High-Resolution Transcriptomic Profiling of the Heart During Chronic Stress Reveals Cellular Drivers of Cardiac Fibrosis and Hypertrophy | Emerging technologies and datasets |
| Molenaar *et al.*, 2021 | [71▪] | Research | Single-cell Transcriptomics Following Ischemic Injury Identifies a Role for B2M in Cardiac Repair | Emerging technologies and datasets |

[85], which can be further reinforced by the scientific community contribution of elucidating mechanisms of vaping-induced pathology. Establishing a mechanistic basis of vaping-induced pathogenesis is critical for development of preventive and therapeutic interventional strategies. Efforts to curb the pathologic consequences of vaping are likely to involve multiple and potentially distinct approaches for young versus aged users. Fundamental research at tissue, cellular, molecular, and physiologic levels needs to keep pace with vaping industry initiatives and campaigns. Only through investment and expansion of research efforts on vaping will society be able to implement

interventions designed to mitigate progression of injury and prevent irreversible damage, thereby fostering repair and recovery.

## Acknowledgements

*O.E. acknowledges the support by NIH grants R01HL135661–02. M.S. acknowledges the support by California Tobacco Related Disease Research Program, T31IP1790 and T31IR1585.*

## Financial support and sponsorship

*None.*

## Conflicts of interest

*There are no conflicts of interest.*

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- ■ of special interest
- ■■ of outstanding interest

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