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CASE SERIES
Other

Nicotine e-vaping and cardiovascular consequences: a case series and literature review

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Background Cardiovascular toxicity as a consequence of nicotine from conventional tobacco cigarette smoking is well documented. However, little is known about the cardiovascular consequences of nicotine e-vaping. We review the literature and report a case series of three cases of major adverse cardiovascular clinical effects post nicotine e-vaping.

Case summary Three patients with known peripheral arterial disease who switched from heavy cigarette smoking consumption to a high-intensity dose of nicotine e-vaping all developed further arterial complications within 6–30 months.

Discussion With the recent epidemic of e-vaping in young individuals and the national outbreak of e-vaping use-associated lung injury (EVALI), the dangers of e-vaping are now coming to light. The pulmonary effects are now well described, and this paper highlights three new cases of cardiovascular toxicity associated with e-vaping. The potential role of nicotine e-vaping and the risk of coronavirus disease-2019 (COVID-19) will also be discussed.

Keywords Nicotine • e • -Vaping • e-Cigarettes • Electronic nicotine delivery systems • Cardiovascular consequences • Case series • Case report

Learning points

- In this case series, three patients with known peripheral arterial disease who switched from heavy cigarette smoking consumption to a high-intensity dose of nicotine e-vaping all developed further arterial complications.
- Nicotine e-vaping is associated with severe cardiovascular toxicity and should be discouraged as a smoking cessation tool.

Introduction

Detrimental health consequences of tobacco cigarette (TC) smoking have long been established and, consequently, significant public health resources have been allocated to tobacco cessation efforts. In the past two decades, electronic nicotine delivery systems (ENDs) and, most commonly, electronic cigarettes (E-cigs) have emerged as an alternative to tobacco consumption. While END companies and

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smokers claim that ENDs are an effective means for smoking cessation, studies have shown no real-life evidence for this presumed benefit. Additionally, a 2018 systematic review of 29 original articles focusing on the efficacy of ENDs as smoking cessation alternatives found only a modest behavioural and sensory gratification rate in a setting of continued use of E-cigs instead of quitting.[1]

Historically, TC smoking is considered the primary cause of preventable cardiovascular disease (CVD) in the USA. The tobacco/END industry has been citing the lower level of nicotine and particulates in END vapours for advocating ENDs as a 'safe' alternative to smoking. While this may be true, END particulates are different from conventional cigarettes and, given their novelty, their toxicity is unknown.

With the recent epidemic of e-vaping in young individuals and the national outbreak of e-vaping use-associated lung injury (EVALI), the dangers of e-vaping are now coming to light. The pulmonary effects are now well described, and this case series highlights three new cases of cardiovascular toxicity associated with e-vaping. A comprehensive literature review is also presented, and the potential role of nicotine e-vaping and the risk of coronavirus disease-2019 (COVID-19) will be discussed.

Timeline

Case 1	
Initial visit	A 78 year-old female presented with a 1-year history of bilateral intermittent claudication
	Absent femoral pulsation
	ABPI was 0.7 (right leg; toe index of 0.42) and 0.9 (left leg; toe index of 0.5)
	Heavy TC smoker (100 pack-year)
	Best medical therapy
9 months after initial presentation	Patient switched to E-cigs
	Vaped three 10 mg cartridges per week (30 mg/week)
Follow-up visit, 17 months after initial presentation	Presented to the emergency department with confusion, left-sided weakness, abdominal pain, and right leg pain
	Brain CT and brain MRI showed no evidence of stroke
	CT thorax abdomen pelvis (TAP) was performed which showed complete right common iliac occlusion, bilateral renal infarction, and portal vein thrombosis
Revascularization, 19 months after initial presentation	The patient stabilized following retrograde on-table angiography for the right leg and stenting of the right common iliac with a covered stent
Final visit, 21 months after initial presentation	Able to walk for ~1 mile without claudication
	Examination showed normal pulses
	Ceased vaping
Case 2	
Initial visit	A 55-year-old male presented with short distance claudication of the left leg
	Symptoms began 1 year after starting e-vaping
	Best medical therapy (aspirin, clopidogrel, and atorvastatin)
	Former TC smoker (40 pack-year) who had switched to E-cigs 2 years ago
	Vaped three 10 mg cartridges per week (30 mg/week)
Follow-up visit, 12 months after initial presentation	He had symptoms present at ~50 m, worse on going uphill, and interfering with daily life
	Normal capillary refill, no left femoral pulsation, and the left leg was colder than the right leg
	Bilateral ankle brachial pressure index was reduced at 0.8, and his toe pressures were 73 mmHg on the right and 65 mmHg on the left
	CT angiogram revealed complete left iliac occlusion
	Chest CT revealed popcorn appearance (bronchiolitis obliterans) of the lungs
	The patient was advised to stop vaping and successfully stopped for 6 months
Follow-up visit, 18 months after initial presentation	Haemodynamic studies improved, with increase in his toe pressure to 100 mmHg on the right and 88 mmHg on the left
Final visit, 24 months after initial presentation	He subsequently resumed vaping and continues to vape
	Consequently, most recent haemodynamic studies showed a drop in toe pressures again to 81 mmHg bilaterally
Case 3	
Init ial visit	A 55-year-old presented with a 2-year history of bilateral intermittent claudication of <50 yards (increasing on going uphill and more severe in the left leg), interfering with daily activities
	Former TC smoker (30 pack-year)

Continued

	Switched to E-cigs and began vaping three 10 mg cartridges per week (30 mg/week) 6 months before developing lower limb claudication
Follow-up visit, 3 months after initial presentation	Normal capillary refill in a setting of bilateral weak femoral pulsation and bilateral cold legs No pulsation detected on either lower limb at the popliteal artery, or more distally Bilateral ankle brachial pressure index was reduced at 0.5 Right leg digital pressure was 80 mmHg and left leg digital pressure was 75 mmHg CT angiography showed aortoiliac occlusive disease, and thoracic CT was significant for bronchiolitis obliterans Asked to stop vaping Treated with antiplatelet medications with no improvement and is currently awaiting aortoiliac endarterectomy
Final visit, 6 months after initial presentation	Patient stopped vaping for 3 months since her last visit and demonstrated significant improvement and was able to walk for 150 m Digital pressure improved to 80 mmHg bilaterally

Case presentation

Case 1

A 78-year old-female with a past medical history of peripheral vascular disease, atrial fibrillation, ischaemic heart disease, ulcerative colitis, and arthritis presented with a 1-year history of bilateral intermittent claudication (more on the right side) at ~50 yards.

The patient was a former heavy TC smoker (100 pack-year). On examination there was no tissue loss or pain at rest. Absent femoral pulsation was observed on the right leg and there was weak femoral pulsation on the left leg. The ABPI (ankle–brachial pulse index) at this visit was 0.7 (right leg; toe index of 0.42) and 0.9 (left leg; toe index of 0.5). The patient was treated with best medical therapy.

The patient switched to E-cigs after she was gifted a vaping device by her daughter in January 2019. She vaped three 10 mg cartridges per week (30 mg/week) and the approximate nicotine concentration was 12 mg/cartridge. In August 2019, the patient presented to the emergency department with confusion, left-sided weakness, abdominal pain, and right leg pain. A brain computed tomography (CT) and brain magnetic resonance imaging (MRI) showed no evidence of stroke. A CT thorax abdomen pelvis (TAP) was performed which showed complete right common iliac occlusion, bilateral renal infarction, and portal vein thrombosis (*Figure 1A*). Axial cuts showing bilateral renal infarction (*Figure 1B*). The patient was admitted to the intensive care unit (ICU). She desaturated (SO_2: 89 on room air) and she was disoriented to time, place, and person (she could not recognize her family members). On examination, her left leg was warm with normal capillary refill time. No pulses could be palpated in her right leg. There was no motor or sensory deficit. She was treated conservatively in the ICU with anticoagulation and antibiotics for sepsis. Thrombophilia screen was negative.

After the patient stabilized in October 2019, she had a retrograde on-table angiography for the right leg and stenting of the right common iliac with a covered stent (*Figure 1C*). The patient was discharged the day following surgery. Leg digital pressures were 35 mmHg for her right leg (ABPI: 0.48) and 73 mmHg for the left leg (ABPI: 0.7).

Figure 1 (A) CT thorax abdomen pelvis (TAP) showed complete right common iliac occlusion, bilateral renal infarction, and portal vein thrombosis. (*B*) Axial cuts showed bilateral renal infarction. (C) Retrograde on-table angiography for the right leg and stenting of the right common iliac with a covered stent were performed.

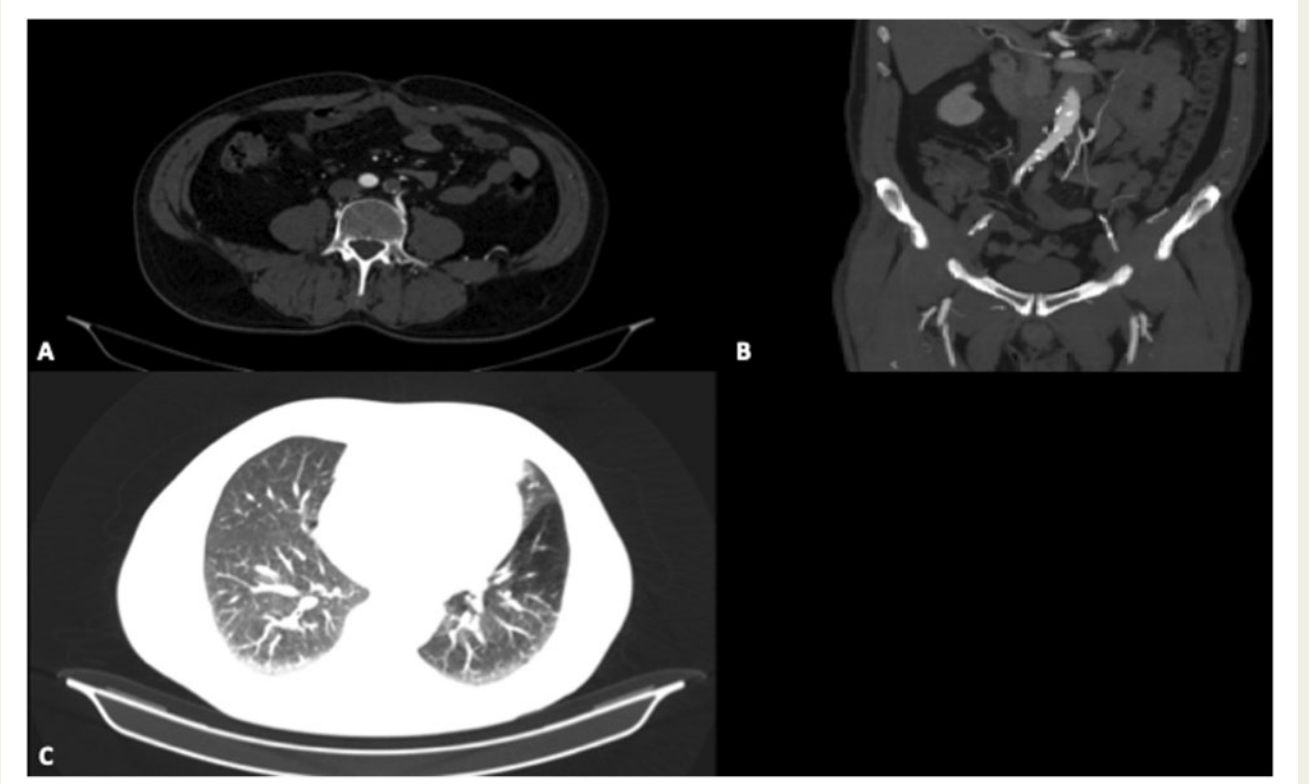

Figure 2 (A) CT angio periphery axial section showing complete left iliac occlusion. (B) CT angio periphery coronal section showing complete left common iliac occlusion. (C) CT of thorax showing popcorn appearance of the lung.

She was able to walk for ~1 mile without claudication. Her examination showed normal pulses and she ceased vaping.

Case 2

A 55-year-old male with ischaemic heart disease, managed conservatively with medical therapy and an exercise programme for the past 3 years (no stent placement), presented with short distance claudication of the left leg. Of note, the patient was a former TC smoker (40 pack-year) who had switched to E-cigs 2 years ago. He vaped three 10 mg cartridges per week (30 mg/week) and the approximate nicotine concentration was 12 mg/cartridge.

He had a past medical history of ischaemic heart disease for which a coronoray angiogram was performed in September 2015 due to ongoing chest pain that radiated to his left arm. In addition, he had dyspnoea during exertion. No flow-limiting lesion was found and no stents were inserted. Thus, he was only given best medical therapy (aspirin, clopidogrel, and atorvastatin).

On his most recent presentation to our clinic in 2019, he had symptoms present at ~50 m, worse on going uphill, and interfering with daily life. Upon examination, there was normal capillary refill, no left femoral pulsation, and the left leg was colder than the right leg. No ulcers or tissue loss were present. Bilateral ABPI was reduced at 0.8, and his toe pressures were 73 mmHg on the right and 65 mmHg on the left. CT angiogram revealed complete left iliac occlusion (*Figure 2A and B*), and chest CT revealed a popcorn appearance (bronchiolitis obliterans) of the lungs (*Figure 2C*).

The patient was advised to stop vaping and successfully stopped for 6 months. Following this, his haemodynamic studies improved, with increase in his toe pressure to 100 mmHg on the right and 88 mmHg on the left. However, he subsequently resumed vaping and continues to vape. Consequently his most recent haemodynamic studies revealed a drop in toe pressures again to 81 mmHg bilaterally.

Case 3

A 55-year-old female with a past medical history of type 2 diabetes mellitus (controlled with oral hypoglycaemics) and ischaemic heart disease (cardiac stent placement 14 years previously) presented with a 2-year history of bilateral intermittent claudication of <50 yards (increasing on going uphill and more severe in the left leg), interfering with daily activities. She is a former TC smoker (30 pack-year). She switched to E-cigs and vaped three 10 mg cartridges per week (30 mg/week), and the approximate nicotine concentration was 12 mg/cartridge. Of note, the patient's symptoms developed ~6 months after she switched to E-cigs.

Upon examination, there was normal capillary refill in a setting of bilateral weak femoral pulsation, and bilateral cold legs. In addition, no pulsation could be felt at the popliteal or more distally, bilaterally. Bilateral ABPI was reduced at 0.5. Right leg digital pressure was 80 mmHg and the leg digital pressure was 75 mmHg. A three-dimensional (3D) reconstruction of a CT angiography showed

Figure 3 (A) 3D reconstruction showing aortoiliac occlusive disease. (B) CT angio showing aortoiliac occlusive disease. (C) Axial section of thoracic CT showing popcorn appearance.

aortoiliac occlusive disease, and thoracic CT was significant for bronchiolitis obliterans (*Figure 3A–C*).

The patient was treated with antiplatelet medications with no improvement and is currently awaiting aortoiliac endarterectomy. She was asked to stop vaping and, during a recent visit (August 2019), she demonstrated significant improvement and was able to walk for 150 m. Her improvement continued and at her most recent visit (October 2019) her digital pressure improved to 80 mmHg bilaterally.

Discussion

In response to a congressional mandate, the National Academies of Science, Engineering and Medicine (NASEM) convened an ad-hoc committee of experts that appraised >800 studies to report on public health consequences of E-cigs. In January 2018, NASEM released a report which, above all else, elucidated the gaps in our current knowledge and identified research priorities as they pertain to the benefits and harms of E-cigs.[2]

ENDs are highly variable in design and delivery, and consequently their health effects are heatedly debated. The potential cardiovascular side effects of ENDs have been generally attributed to (i) nicotine and (ii) oxidizing chemicals, particulates, and acrolein. While the former activates the sympathetic nervous system, and causes vasoconstriction and arrythmogenesis, the latter influence CVD through inducing inflammation in endothelial cells and platelet activation.[3] Despite different pathways, the unfortunate end result of both pathways may be an increased risk of developing myocardial infarction and sudden death.[1]

In pre-clinical studies of ENDs, cell culture or animal models are exposed to high concentrations of END aerosols which do not reflect dose or duration of real-life exposure. Sassano *et al.* developed a high-throughput screening assay to evaluate the toxicity of e-liquids, and found the presence of vanillin and a higher number of chemicals in e-liquids to be positively associated with higher toxicity.[4] Depending on make and model, ENDs produce variable amounts of toxic aldehydes, namely acetaldehyde, acrolein, and formaldehyde, which are also present in cigarette smoke. Exposure to these low molecular weight aldehydes may result in acute lung injury, chronic obstructive pulmonary disease (COPD), asthma exacerbation, and lung cancer, as well as CVD.[5] Although it is difficult to prove direct causation, it is suspected that exposure to aldehydes may have contributed to significant cardiovascular toxicity in already predisposed individuals at high risk for cardiovascular disease, as exemplified in the above three cases.

Studies have shown that the vapour produced by E-cigs reduces immune and alveolar function, with a decrease in surfactant within the air sacs. This leads to failure of gas exchange within the lung tissue. Some flavourings in E-cigs have been associated with depression of respiratory cilia.[6] Impaired ciliary function may in turn predispose the individual to an increased risk of viral infection such as SARS-CoV-2.

Chronic exposure to ENDs has also been reported to down-regulate the innate immunity against viral pathogens. Furthermore, independent of nicotine, END-exposed mice infected with influenza virus demonstrated enhanced lung inflammation and tissue damage.[7] Chronic exposure to E-cig vapour aberrantly alters the physiology of lung epithelial cells and resident immune cells, and promotes poor response to infectious challenge.[7] As of yet, there is no direct evidence of the link between ENDs and COVID-19; however, the aforementioned negative effects of ENDs on immune and alveolar function raise serious concerns about the potential increased risk of developing COVID-19. Moreover, it is known that TC smoke can up-regulate the angiotensin-converting enzyme 2 (ACE2) receptor which is the receptor involved in SARS-CoV-2 viral uptake into host cells.[8] Importantly, second-hand vapour generated by ENDs could enhance the dissemination of SARS-CoV-2 among non-infected individuals in close proximity to SARS-CoV-2-infected vapers.[9]

Given the higher concentration of formaldehyde in high-voltage E-cigs, Jensen *et al.* considered high-voltage E-cig users to be 15 times more at risk of developing upper aerodigestive tract cancer.[10] However, others argue that the tested devices may have overheated, a phenomenon commonly referred to as 'dry puff'.[11] Sultan *et al.* reviewed the existing ENDs and cautioned practitioners against considering and promoting nicotine e-vaping as safe devices for smoking cessation until further evidence regarding their long-term use and health complications is available.[12]

Although replacement of conventional TC with E-cigs has been associated with reduction in central and brachial systolic blood pressure, arterial wave reflection, and oxidative stress, both conventional TC smoking and E-cigs negatively disturb arterial elasticity and increase oxidative stress.[13] An important consideration in replacing conventional TC with E-cigs is the fact that the role of nicotine in CVD development is non-linear, and small amounts of nicotine may suffice to cause CVD and accelerated atherogenesis.[3,14] E-cig use is correlated with 2- to 3-fold higher odds of stroke, myocardial infarction, angina, and coronary heart disease, and induces atherosclerotic states in otherwise normal healthy individuals with an increased risk of subsequent CVD.[15–17] Additionally, greater concentrations of biomarkers of nicotine, tobacco-specific nitrosamines, volatile organic compounds, and metals compared with never TC users have been reported in sole E-cig users.[18] Therefore, it is likely that new exposure to these various components of E-cigs in the three cases described above contributed to disruptions in arterial elasticity, an increase in oxidative stress, and ultimately worsening CVD. Furthermore, the significant amelioration of physical findings after cessation of E-cigs provides indirect supporting evidence that E-cigs have damaging effects on the cardiovascular system and their removal promotes cardiovascular recovery.

The most recent clinical practice guidelines on primary prevention from the American College of Cardiology/American Heart Association Task Force state that ENDs can increase the risk of arrhythmias and hypertension, and can also increase oxidative stress and sympathetic stimulation in young healthy individuals.[19] A randomized crossover study by Franzen *et al.* in 2018 demonstrated the impact of ENDs on worsening peripheral arterial function.[20] In particular, they recorded an increase in peripheral systolic pressure which was sustained for three times longer in those using ENDs compared with TCs. The adverse impact of ENDs on arterial stiffnes was further demonstrated by an increase in pulse wave velocities which were independent of mean arterial pressure. In 2019, Osei *et al.* analysed 449 092 participants from the Behavioral Risk Factor Surveillance System (BRFSS) and found that there was significantly higher odds of CVD among dual users of E-cigs and TCs compared with TC users.[21]

While one hopes that all research is conducted in good faith, the influence of the tobacco/END industry cannot be ignored. Pisinger *et al.* analysed the contradictory outcomes of studies on potential side effects of E-cigs due to investigator's financial conflict of interest (COI).[22] While 95% of published work without COI found potentially harmful effects and substances, only 8% of tobacco industry-funded studies found potential harm.[22] This equated to a 66-fold increase in odds of finding of no harm in industry-funded studies.

A limitation of our study was the small sample size and that no objective quantification of nicotine levels was measured for any of the three cases. Importantly, the Centers for Disease Control and Prevention (CDC) reported >2800 hospitalized EVALI cases in the USA as of February 2020. The recent exponential rise in EVALI cases and their potential negative effects on the cardiovascular system, coupled with the data in the published literature and the case series described above, all add to the evidence that ENDs as smoking cessation alternatives should not be recommended.

Lead author biography

Professor Sherif Sultan obtained his medical degree from the Ain Shams University in 1987. Following completion of a master degree in surgery in 1991, he then finished his MD degree, and moved to Ireland and was awarded his FRCS in Dublin 1995. He completed a fellowship from Arizona Heart Institute in 1997, followed by a Diploma in Endovascular Surgery from University of Paris XII in 1998. He attained his Intercollegiate FRCS in vascular surgery in March 2001 in London and was certified with the European Board of Vascular Surgery in September 2001 in Lucerne Switzerland. Professor Sultan was awarded an honorary PhD from the University of Sibiu, in 2015. He is a senior vascular surgeon at West Northwest Hospital group of the National HSE, Ireland.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing these case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patients in line with COPE guidance.

Conflict of interest: none declared.

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