Research Square

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Vaping with nicotine causes an acute increase in endothelial-dependent vasodilation

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Abstract

Background

Tobacco smoking remains a leading global cause of premature death and disability, and the tobacco industry has increasingly promoted electronic cigarettes (e-cigarettes) as alternatives. Despite their growing popularity, particularly among adolescents, the long-term health effects of e-cigarettes are not fully understood. Nicotine, a primary component of e-cigarettes, has been implicated in adverse cardiovascular outcomes; however, its acute effects on endothelial function remain poorly characterized.

Objective

This study aimed to investigate the acute effects of inhaled nicotine on endothelial function using venous occlusion plethysmography (VOP), a well-established method for assessing vascular responses.

Methods

Nineteen healthy male sporadic-tobacco-using volunteers participated in a double-blind, randomized, crossover study. Participants were exposed to nicotine-containing or nicotine-free e-cigarette aerosol in two sessions separated by a 7-day washout period. Forearm blood flow (FBF) was measured following intra-arterial infusion of acetylcholine (ACh) and sodium nitroprusside (SNP).

Results

Acute exposure to nicotine-containing e-cigarette aerosol significantly enhanced ACh-mediated vasodilation compared to nicotine-free aerosol ($p = 0.04$), whereas no significant corresponding changes in FBF were observed following SNP exposure.

Conclusions

This study demonstrates that acute nicotine exposure enhances endothelium-dependent vasodilation, likely mediated through activation of nicotinic acetylcholine receptors (nAChRs). This response may represent an early pathological adaptation rather than a protective effect, as chronic nAChR stimulation is linked to adverse cardiovascular outcomes, including endothelial dysfunction and atherosclerosis.

Introduction

Tobacco smoking remains a leading risk factor for premature death and disability worldwide [1]. The World Health Organisation (WHO) estimates that approximately 8.7 million deaths annually are

attributable to smoking [2]. In response, legislative measures have been implemented worldwide to restrict cigarette sales, particularly in industrialized countries. To offset revenue losses, the tobacco industry has shifted focus toward alternative tobacco products (ATPs), with electronic cigarettes (e-cigarettes) being a dominant product category.

E-cigarettes vary in design and generations, however all devices operate by heating a liquid, composed primarily of a mixture of propylene glycol, vegetable glycerine, nicotine and added flavorings, into an inhalable aerosol [3]. Global e-cigarette use has seen a rapid expansion, reaching an estimated market value of $40 billion in 2025[4]. This trend is concerning as e-cigarette use has been found to be an independent risk factor for future cigarette use, equaling or surpassing other known predictors such as parental, sibling and peer smoking [5]. Beyond acting as a potential gateway to conventional cigarettes, the long-term adverse health effects of e-cigarettes themselves are not yet fully understood. Widely cited claims that e-cigarettes are less harmful than combustible cigarettes lack robust evidence, and increasing data indicate that e-cigarettes may themselves cause serious adverse outcomes, such as EVALI (electronic cigarette or vaping product use-associated lung injury), a dangerous and potentially fatal condition [6].

The role of nicotine in the adverse effects seen in e-cigarette use have been contentious, as the industry often claims that nicotine is relatively harmless apart from its addictive potential. However, growing evidence demonstrates that nicotine alone is associated with a wide range of adverse health outcomes[7–9]. A methodological challenge has been isolating the effects of inhaled nicotine from those of the other substances found in tobacco products. One approach we have taken has been to use crossover studies with exposure to e-cigarette vapor with and without nicotine. We have previously shown that e-cigarette vapor containing nicotine caused an increased inflammatory response in the lungs[10], along with signs of increased vascular damage[11] and increased arterial stiffness, as compared to without nicotine[12].

Another way of studying vascular health is venous occlusion plethysmography (VOP), which is considered the “gold standard” for evaluating endothelial function[13]. Through the infusion of endothelial-dependent and independent vasodilatory drugs in the brachial artery, different aspects of endothelial function can be measured. Using this method, we have previously concluded that endothelial-independent vasodilation was impaired in chronic snus (a form of smokeless tobacco) users[14]. Similar impairing effects have been found in conventional cigarette smokers[15].

To our knowledge, no previous study has examined the acute endothelial responses to electronic cigarette aerosol exposure using venous occlusion plethysmography. The aim of the present study was to investigate the acute effects of inhaled nicotine on endothelial function. Based on previous research, we hypothesized that exposure to nicotine-containing e-cigarettes would result in reduced vasodilation. [14].

Methods

2.1 Subjects

Nineteen healthy male volunteers were recruited through public advertisement. Eligible participants were aged 18–45 years, reported sporadic nicotine use (≤ 10 cigarettes or equivalent per month), and had a body mass index (BMI) < 30. Exclusion criteria included any systemic or chronic disease (e.g., metabolic, rheumatologic, pulmonary, or cardiovascular disorders). Participants were instructed to abstain from alcohol and caffeine for 12 hours and from strenuous exercise for 24 hours prior to each study session. Nicotine-containing products (such as cigarettes, e-cigarettes, and Swedish snus) were prohibited for 7 days before participation. All subjects underwent baseline screening, including a physical examination, routine laboratory testing, electrocardiography, blood pressure, and dynamic spirometry.

2.2 Study design

The study was approved by the Swedish Ethical Review Authority and conducted in accordance with the Declaration of Helsinki (1975). Written and verbal informed consent was obtained from all participants. A double-blind, randomized, cross-over design was employed. Randomization determined the order of exposure to nicotine-containing or nicotine-free e-cigarette aerosol. Both participants and investigators performing outcome assessments were blinded to exposure condition. Aerosol solutions were prepared and assigned by a co-worker not involved in data collection.

Each participant attended two exposure sessions, separated by a washout period of at least 7 days to minimize carryover effects. Sessions were conducted under standardized conditions in a well-ventilated controlled laboratory environment.

2.3 Electronic cigarette exposure

Subjects inhaled 30 puffs of e-cigarette aerosol over 30 minutes, at a frequency of one puff per minute, using a variable-mode third-generation electronic cigarette (eVic-VT, Shenzhen Joyetech Co., Ltd., China). The same settings were applied for all exposures: temperature 230°C, effect 32 W and resistance 0,20 – 0,22 Ω. Each puff lasted an average of 3 seconds.

E-liquids were unflavored and either nicotine-free or contained 18 mg/mL nicotine (Valeo Laboratories GmbH, Germany). All e-liquids were purchased premixed, stored in identical containers, and labelled with different letters to maintain blinding.

2.3 Venous occlusion plethysmography

Two hours after e-cigarette exposure, following a light, standardized lunch, subjects were placed in a semi-supine position with inflatable cuffs positioned around the upper arms and wrists. The distal wrist cuff excludes arterio-venous shunts that could otherwise affect measurements. The proximal cuff briefly interrupts venous drainage without affecting arterial inflow, resulting in a linear increase in forearm blood volume proportional to arterial blood flow. Blood volume changes were measured via forearm circumference using a strain gauge [17].

Brachial artery cannulation was performed using a 27-standard wire gauge steel needle. Endothelial-dependent (acetylcholine, ACH) and endothelial-independent (sodium nitroprusside, SNP) vasodilators were administered intra-arterially at doses of 5, 10, and 20 µg/min (ACH) and 2, 4, and 8 µg/min (SNP). Each drug was infused for 3 minutes prior to cuff inflation, and forearm blood flow was recorded for 3 minutes. Distal cuffs remained inflated during measurements, while proximal cuffs were inflated intermittently for 8 seconds, followed by 4 seconds deflation.

The two vasodilators were administered in randomized order, separated by an 18-minute washout period with saline infusion. Blood pressure was repeatedly measured using a validated semi-automatic oscillometric sphygmomanometer (Omron M7, Omron Healthcare Europe B.V., Hoofddorp, NL).

2.4 Statistics

To compare the effects of nicotine-containing and nicotine-free aerosol on forearm blood flow (FBF), separate linear mixed-effects models were fitted for ACh and SNP. The model included fixed effects for exposure condition (nicotine vs. nicotine-free), doses and their interaction term, along with a random intercept for subjects. To account for heterogeneity in variance and within-subject correlation across doses, nested within exposure sessions, an unstructured covariance structure was applied to the error term. Post-hoc analyses to compare exposure conditions at each concentration were performed based on marginal means. Statistical significance was defined as $p < 0.05$. To control the family-wise error rate, p-values were adjusted for multiple comparisons using the Hommel method. Confidence intervals (95%) were calculated for all estimated differences. The statistical analyses and graphs were performed R version 4.3.1 (R Core Team (2023). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. (https://www.R-project.org) and GraphPad Prism version 9.3.1 for Windows (GraphPad Software, San Diego, California USA).

Results

Nineteen male participants were included in the analysis with the base characteristics seen in Table 1. Data from one participant were excluded due to technical difficulties.

Table 1
Subject base characteristics, [1]mean(sd) [2]median (Q1, Q3).

Characteristic	N = 19
Age[1]	26.2 (4.4)
Systolic blood pressure [mmHg] [1]	123 (13)
Diastolic blood pressure [mmHg] [1]	74.7 (6.5)
BMI[1]	23.64 (2.38)
HbA1c[1]	32.4 (3.9)
Leukocyte count [x10^9/L][1]	5.19 (1.23)
Platelet count [x10^9/L] [2]	225 (210, 283)
Creatinine [µmol/L] [1]	81 (14)

Both acetylcholine (ACh) and sodium nitroprusside (SNP) induced dose-dependent increases in forearm blood flow (FBF) following exposure to nicotine-containing and nicotine-free e-cigarette aerosol. ACh caused a significantly greater increase in FBF after vaping nicotine-containing e-cigarettes compared with nicotine-free e-cigarettes. No significant corresponding increases in FBF following SNP exposure could be observed.

Mixed model: ACh 5 µg/ml: p = 0.02, ACh 10 µg/ml: p = 0.04, ACh 20 µg/ml: p = 0.04

Mixed Model: SNP 2µg/ml: p = NS (0.16), SNP 4 µg/ml: p = NS (0.20), SNP 8µg/ml: p = NS (0.20)

Discussion

In the present study, contrary to our hypothesis, acute exposure to nicotine-containing e-cigarette aerosol significantly enhanced ACh-mediated vasodilation in healthy volunteers compared with nicotine-free aerosol. This finding contrasts with the established association between chronic tobacco exposure and impaired endothelial function[16–19]. The discrepancy may reflect fundamental differences between acute and chronic effects of nicotine on endothelial physiology. Endothelial dysfunction in chronic smokers is characterized by attenuated ACh-mediated vasodilation due to reduced NO bioavailability and impaired endothelial signalling[20]. These pathological changes correlate with cumulative tobacco exposure and require prolonged use to develop. Furthermore, the contribution of

individual constituents of cigarette smoke to endothelial damage has not been clearly established. As the subjects in this study had no history of chronic tobacco use, such long-term effects would not yet be expected to manifest.

Acetylcholine (ACh) is a neurotransmitter whose receptors (AChRs) are widely distributed throughout the body and are essential for synaptic transmission in both the central and peripheral nervous systems, as well as in non-neuronal tissues. These receptors are divided into two distinct subtypes based on their structure and mechanism of action: the muscarinic (mAChR) and nicotinic acetylcholine receptors (nAChR). mAChRs mediate slower, longer-lasting effects (seconds to minutes) such as regulation of heart rate, glandular secretion and smooth muscle cell contraction and are therefore predominantly expressed in the heart, smooth muscle and glands[21]. In contrast, nAChRs are responsible for fast synaptic transmission (milliseconds) and skeletal muscle contraction[22]. These receptors are found mainly in the neuromuscular junction, autonomic ganglia and the central nervous system but are also expressed in non-neuronal tissues, including vascular endothelium and immune cells. Nicotine is a selective agonist for nAChRs and, owing to its slower metabolism compared with ACh, leads to prolonged receptor activation[23].

ACh has a constrictive effect on vascular smooth muscle cells through activation of mAChR[24]. However, in healthy blood vessels, its predominant action occurs via endothelial stimulation, resulting in nitric oxide (NO) release and a net vasodilatory effect[25]. Consequently, intra-arterial ACh infusion is frequently used to assess endothelium-dependent vascular function in venous occlusion plethysmography (VOP) studies. Cigarette smoking has been associated with endothelium-dependant vascular dysfunction through several mechanisms [26], including increased production of endothelin-1, a potent vasoconstrictor synthesized by endothelial cells. Elevated circulating endothelin-1 levels have been reported in otherwise healthy smokers[27].

Nicotine exerts acute effects primarily through activation of nAChRs, which can promote transient vasodilation [12, 28]. It is therefore plausible that acute nicotine exposure in non-tobacco users can result in an enhanced vasodilatory response. Our findings in the current study suggest that, in individuals without prior chronic tobacco exposure, acute nicotine exposure may initially augment endothelial-dependent vasodilation. However, this response is likely short-lived and may represent an early pathological adaptation rather than a protective physiological effect. Supporting this interpretation, a previous study using a similar exposure model demonstrated nicotine-induced arterial stiffness that peaked immediately after exposure and diminished after 30 minutes[12], highlighting the temporally dynamic nature of nicotine's vascular effects.

Nicotine and endothelial dysfunction

The vascular endothelium plays a pivotal role in maintaining vascular homeostasis through the production of nitric oxide (NO), a key mediator of vasodilation, anti-inflammatory signalling, and anti-thrombotic effects. Flow-mediated dilation (FMD), a physiological response to shear stress, is critically

dependent on NO bioavailability. Both active smoking and second-hand smoke exposure are associated with impaired FMD, reflecting endothelial dysfunction. Mechanistically, this impairment is largely driven by oxidative stress and chronic inflammation, which reduce NO bioavailability through oxidative inactivation and disrupted synthesis.

Although pharmacological nicotine administration—via localized infusion or nasal spray—has been shown to impair endothelial function, the extent to which nicotine alone contributes to vascular dysfunction relative to other toxic constituents of tobacco smoke remains incompletely understood [29]. In vitro and animal studies have shown that nicotine reduces the expression of GTP cyclohydrolase 1 (GTPCH1), a critical enzyme for NO synthesis, thereby promoting endothelial dysfunction and atherosclerosis [30]. A meta-analysis reported that chronic e-cigarette use was associated with impaired FMD even in the absence of combustion products; however, the number of included studies was limited and the overall findings did not reach statistical significance, despite similar effect sizes when comparing e-cigarette users and smokers with non-users [31].

Cardiovascular disease

Nicotine-mediated activation of vascular nAChRs can contribute to the development and progression of atherosclerotic plaques through multiple mechanisms. Endothelial nAChR activation promotes angiogenic processes, including enhanced endothelial survival, proliferation and migration. However, newly formed micro vessels are typically fragile, increasing the risk of intraplaque hemorrhage and subsequent plaque rupture. Nicotine also induces vascular smooth muscle cell (VSMC) proliferation and migration, contributing to lesion growth [8] and driving inflammation[32], which, together with oxidative stress, is a key driver of endothelial dysfunction.

These mechanisms may help explain the results seen in a recent meta-analysis demonstrating similar odds ratios for risk of cardiovascular disease among conventional cigarette users and e-cigarette users [33]. Although enhanced vasodilation was observed in the present study, this response should be interpreted as an early pathological effect rather than a protective one. Furthermore, *Glantz et al.* also reported that users of both conventional cigarettes and e-cigarettes had a significantly increased cardiovascular disease risk compared with exclusive cigarette smokers. This finding is particularly relevant when considering e-cigarettes as smoking cessation tools, as a substantial proportion of individuals who switch to e-cigarettes remain dual users [34–36].

Cancer

While this study focuses on the acute cardiovascular effects of inhaled nicotine, it is important to recognize that nicotine's activation of nAChRs has been implicated in broader pathological processes. Chronic nicotine exposure, even in the absence of combustion products, may promote angiogenesis, tumor growth, and metastasis, as demonstrated in preclinical models [37, 38]. Additionally, nicotine has been shown to reduce the efficacy of cancer therapies, including chemotherapy and radiotherapy, by

attenuating pro-apoptotic and anti-proliferative effects in malignant cells [39–42]. These findings suggest that nicotine's systemic effects extend beyond cardiovascular health, though further research is needed to elucidate the long-term oncological risks of e-cigarette use. As such, the potential for nicotine to contribute to cancer progression and treatment resistance underscores the need for caution in promoting e-cigarettes as a harmless alternative to conventional smoking.

Strengths and limitations

This present study included only male participants, as hormonal fluctuations in menstruating females can influence vascular function, particularly endothelial responses[43]. Given that electronic cigarettes are used by individuals of both sexes, future studies should include female participants to improve generalizability. Additional factors known to affect endothelial function, such as socioeconomic status, education level and dietary habits, were not assessed. Instead, body mass index was used to partially correlate with these variables. However, the study also has several strengths among them being ample experience using a gold standard methodology assessing vascular response as well as a randomized, double-blinded, cross-over study design.

Conclusions

This study demonstrates that acute exposure to nicotine-containing e-cigarette aerosol enhances acetylcholine-mediated vasodilation in healthy individuals, likely via the activation of nicotinic acetylcholine receptors (nAChRs). Nicotine binds to nAChRs, triggering intracellular signalling pathways that regulate vascular tone, inflammation, and cell proliferation. While this acute response may appear beneficial, it should not be interpreted as protective. Rather, it may represent an early, pathological adaptation. Chronic nAChR activation is associated with adverse cardiovascular outcomes, including endothelial dysfunction, and atherosclerosis.

These findings contribute to the growing body of evidence challenging the perception of e-cigarettes as a harmless alternative to conventional smoking. While acute nicotine exposure may induce transient vasodilation, the long-term consequences of chronic use, including endothelial dysfunction and increased cardiovascular risk, must warrant serious consideration. Public health policies should prioritize evidence-based strategies to regulate e-cigarette marketing, particularly to vulnerable populations such as adolescents, and ensure that claims regarding their safety are rigorously scrutinized.

These findings further highlight the complex and dynamic nature of nicotine's impact on vascular health. Further research is essential to clarify the long-term vascular and systemic consequences of e-cigarette use and to inform effective public health interventions.

Declarations

Author contributions: MK, JaB, ABl and ML were involved in study conception and design; MK, ABr, JaB, ML, LA participated in the acquisition, analysis and interpretation of the data; MK, ABr, ABl, ML, JaB took part in drafting and reviewing the manuscript, all authors were involved in the final approval of the submitted version.

Competing interests

We declare no conflict of interest.

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Data availability

Data and study protocol are available upon request and after a confidentiality evaluation.

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Figures

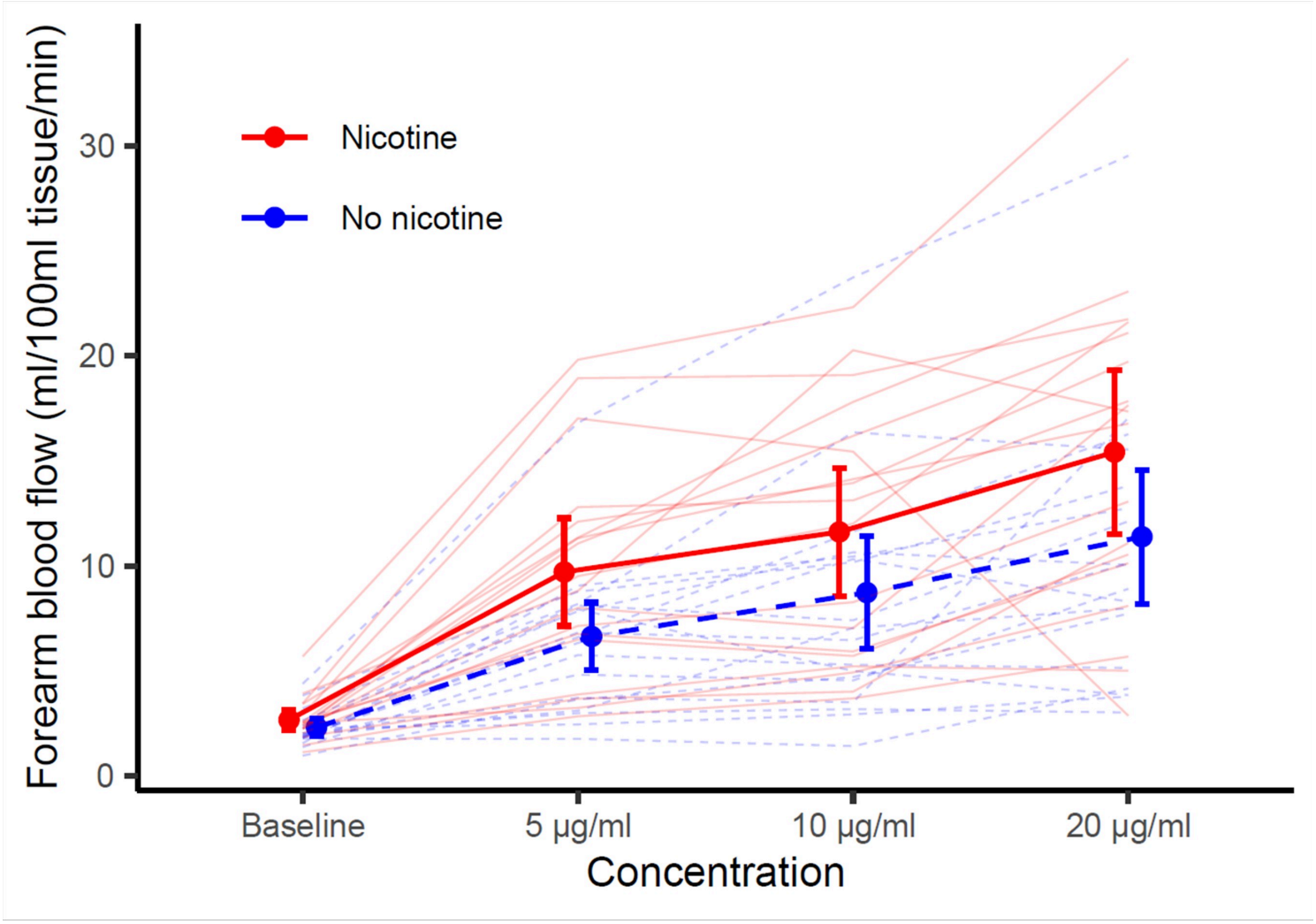


Figure 1

Forearm blood flow was measured following intra-arterial infusion of acetylcholine (ACH) in participants exposed to nicotine-containing and nicotine-free e-cigarette aerosol. Data are shown for three doses of ACh (5, 10, 20 µg/min.
Mixed model: ACh 5 µg/ml: p=0.02, ACh 10 µg/ml: p=0.04, ACh 20 µg/ml: p=0.04

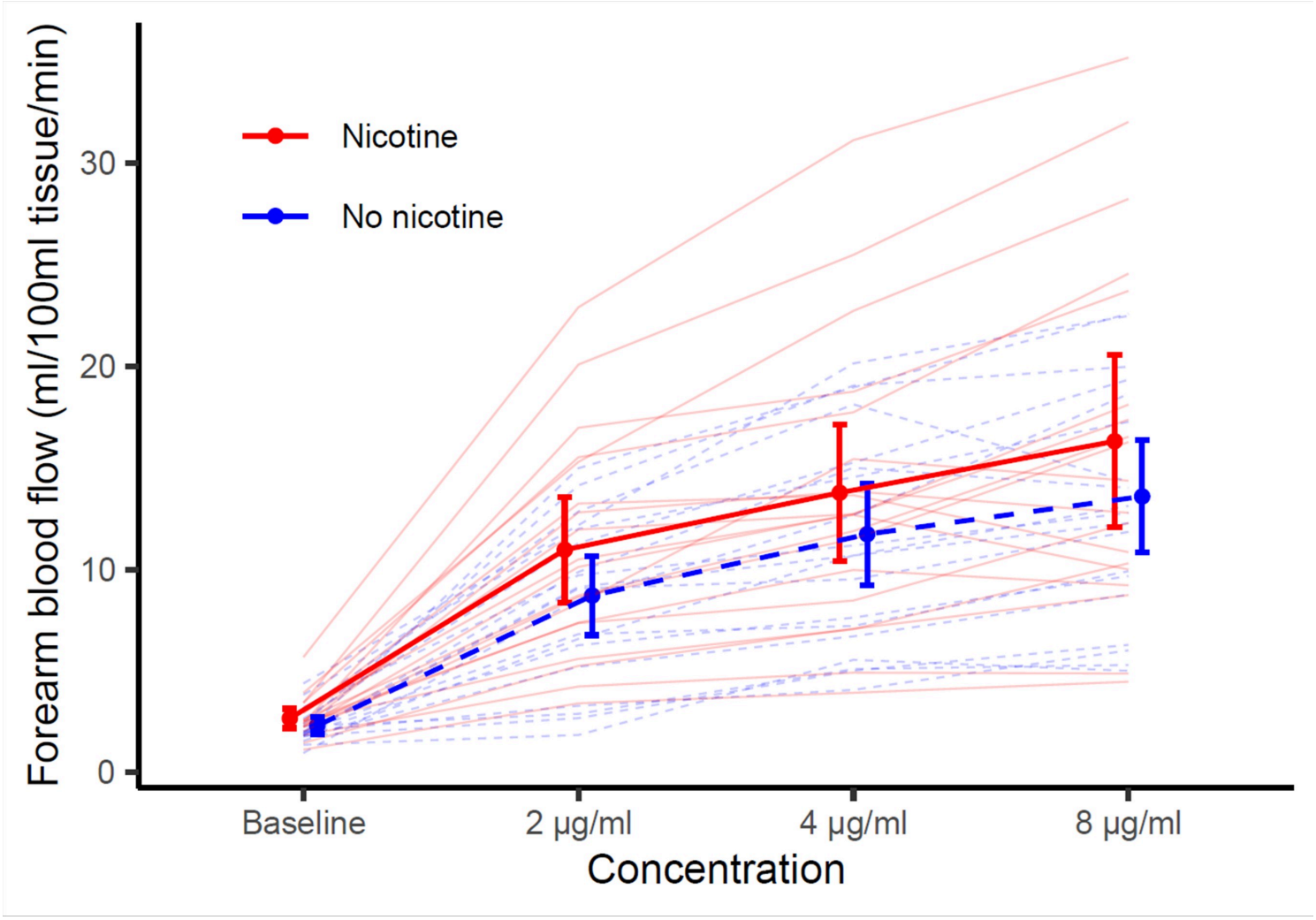


Figure 2

Forearm blood flow was measured following intra-arterial infusion of sodium nitroprusside (SNP) in participants exposed to nicotine-containing and nicotine-free e-cigarette aerosol. Data are shown for three doses of SNP (2, 4, 8 µg/min).
Mixed Model: SNP 2µg/ml: p=NS (0.16), SNP 4 µg/ml: p=NS (0.20), SNP 8µg/ml: p=NS (0.20)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- floatimage1.png