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Endothelial damage in young adult e-cigarette users☆

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The use of e-cigarettes has increased exponentially in recent years especially in young adults and teenagers. The US FDA has declared teenager use of e-cigarettes an epidemic, a severe public health problem. It has become evident that e-cigarettes, originally developed as means to help stop smoking, have toxic effects at cellular, organ and whole body levels [1]. In August 2019, e-cigarette, or vaping, product use-associated lung injury (EVALI) outbreak developed, resulting in 2,807 hospitalized cases and 68 deaths as of February 18, 2020 (CDC), among which 80% of the patients were under 35 years old [1]. The patients suffer from shortness of breath, cough, chest pain, and gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal pain, and respiratory failure especially in those deceased. Evidence suggests that tetrahydrocannabinol (THC, active ingredient of marijuana)/Vitamin E acetate (THC-containing e-liquid additive) was detected in approximately 80%/all of the bronchoalveolar lavage samples of the EVALI cases, indicating potential pathophysiological basis of EVALI. A latest report on one-year follow-up of these patients (n = 41, median age 21) indicate that 80% of the patients (33) had a subsequent health-care encounter, with 24% treated at ER or admitted to hospital [2]. The out/in-patients (29/10) had symptoms and respiratory diagnosis, indicating lasting effects from initial development of EVALI [2]. Molecular mechanisms underlying EVALI and potential biomarkers of e-cigarette-related injuries however, have remained unknown.

In the present study, we examined circulating nitrite levels as an indicator of endothelial function in three different cohorts of young adults (n = 33, 21–25 years old) with similar demographics (Fig. 1A) except smoking status: e-cigarette users (n = 13), tobacco cigarette smokers (n = 11) and non-users (n = 9). The e-cigarette participants were e-cigarette users for >1 year without usage of tobacco cigarettes within the last year; and the tobacco smokers were those who smoked for >1 year without usage of e-cigarettes. It is intriguing to observe that circulating levels of nitrite, an indicator of endothelial function in humans [3], were significantly lower in young adult e-cigarette users (Fig. 1B), while this response was absent in tobacco users likely attributed to the fact *these were young adults with limited/reversible endothelial injuries* [4,5] (Fig. 1B). Of note, circulating cotinine levels were similarly elevated in e-cigarette users and tobacco users, indicating that there was no difference in smoking burden to explain this finding. During vaping of e-cigarettes, besides vaporized nicotine, decomposed solvents and flavoring additives are known to have toxic effects in inducing oxidative stress to potentially result in endothelial dysfunction [6]. The fact that young adult e-cigarette users develop severe endothelial injuries might underlie development of EVALI since acute lung injury is characterized by endothelial damage in the lung proceeding inflammation and organising pneumonia as typical pathological features in EVALI cases [7,8] although the subjects studied in the current study were not exposed to THC-containing e-cigarettes, resulting in respiratory failure, which is however not usually observed in young adult tobacco users. Importantly, *this does not imply that tobacco smoking is less toxic*, rather, a possible unique mechanism of injury induced by use of e-cigarettes *even in young adults*, which alerts for more stringent regulations on e-cigarette use. These data for the first time demonstrate endothelial damage in young adult e-cigarette users at the level of endothelial dysfunction, which plays a central role in the pathogenesis of a variety of cardiorespiratory diseases [9]. Therefore, regulations on e-cigarette use should be further enhanced to prevent EVALI and development of other pathological consequences, and that circulating nitrite levels may be used as a novel and effective biomarker for heath damage attributable to e-cigarettes.

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	Non-users	E-cigarette	Tobacco
Age (y), n	9	13	11
Mean ± SD	22.00 ± 1.12	22.38 ± 1.33	23.27 ± 1.19
Sex, n			
Males/Females	6/3	7/6	5/6
Cotinine (ng/mL)			
Mean ± SEM	0.00 ± 0.00	116.31 ± 27.19	97.91 ± 31.95
Nitrite (μM)			
Mean ± SEM	11.06 ±1.80	7.25 ± 0.45	10.13 ± 1.00

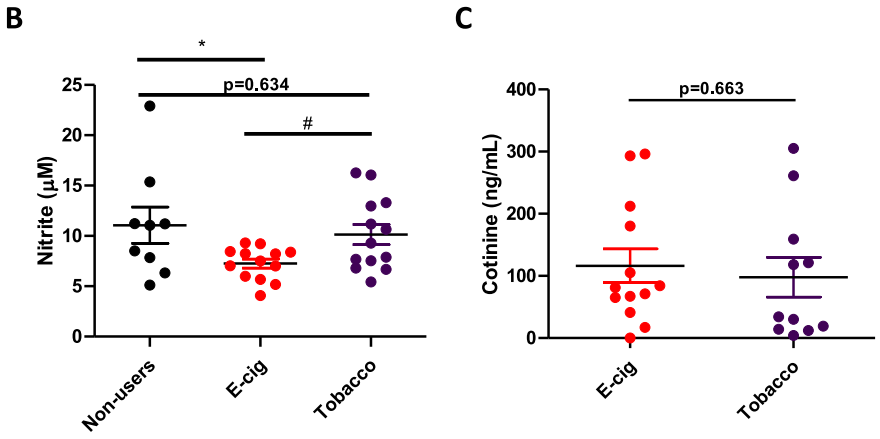

Fig. 1. Endothelial damage in young adult e-cigarette users. **(A)** Demographic information of enrolled subjects by smoking status. **(B)** Circulating nitrite levels in different groups by smoking status. Circulating nitrite levels were determined using freshly collected plasma samples with a Griess assay. Grouped data indicate that circulating nitrite levels, reflective of endothelial function in humans, were significantly lower in young adult e-cigarette users compared to those of non-users. **(C)** Cotinine levels in different groups by smoking status. Grouped data indicate that cotinine levels reflecting smoking burdens were increased similarly in both e-cigarette users and tobacco users. Data are presented as Mean ± SEM (n = 9–13). One-way ANOVA was used for comparison among multiple groups, and unpaired *t*-test was used for comparison between two groups. *p < 0.05, #p < 0.05.

Data availability

Data will be made available on request.

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