



# Lung Trauma Promote to Increase Pulmonary Vascular Permeability

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## Abstract

Research subjects were evaluated at the Weill Cornell Medical College Clinical Translational and Science Centre and the Department of Genetic Medicine Clinical Research Facility under IRB-approved protocols.

**Keywords:** Ventilator surface; Lung parenchyma; Bronchiolar narrowing; Respiratory failure; Inflammatory stenosis; Emphysema

## Introduction

Eligibility was determined following a detailed screening visit including medical history, physical exam, complete blood chemistry and coagulation studies, liver function tests, urine analysis, chest X-ray, EKG, and full pulmonary function tests. The smoking phenotype of never-smoker was determined by self-reported history and confirmed by absence of tobacco metabolites in the urine. Upon study enrolment, ten healthy never-smokers with no history of exposure to any tobacco products or EC, were assessed on day 1 with a questionnaire regarding symptoms to be assessed following EC use, vital signs, O<sub>2</sub> saturation, chest X-ray, lung function, plasma EMPs and bronchoscopy with brushings to sample the small airway epithelium and bronchio-alveolar lavage to obtain alveolar macrophages at baseline [1]. Immediately after the 1st and 2nd EC exposures, the questionnaires were administered and vital signs and O<sub>2</sub> saturation were assessed. Within 2 h post the 2nd EC exposure, lung function, plasma EMPs and repeat bronchoscopy with brushing and lavage were obtained. Total cell counts and cell differentials of the SAE and lavage cells were quantified. RNA-sequencing was performed on mRNA from SAE and alveolar macrophages collected at baseline and post-EC exposure. Endothelial micro particles were quantified as previously described. Blood was collected and processed within 1h to prepare platelet-rich plasma. The supernatant was further processed within 5 min to obtain platelet-poor plasma that was stained with 3 antibodies: the constitutive endothelial marker PECAM and the constitutive platelet-specific glycoprotein Ib [2]. To assess the presence of relative contribution of pulmonary capillary endothelium to the elevated EMP levels, CD42b–CD31+ EMPs were co-stained with anti-human angiotensin converting enzyme based on the knowledge that ACE is abundantly expressed on pulmonary capillary endothelium. The optimized condition for each antibody was determined by serial dilution. EMP measurements were performed twice to ensure that the measurements were reproducible. CD42b–CD31+ micro particle levels were normalized to iso-type controls. Small airway epithelium and alveolar macrophages transcriptome SAE was collected from 10th to 12th order bronchi using flexible bronchoscopy as previously described. SAE cells were dislodged from the cytology brush by flicking into 5 ml of ice-cold Bronchial Epithelium Basal Medium and kept on ice until processed. One-fifth of the total volume was removed for cell viability and differential analysis, and the remaining sample was immediately processed and stored in TRIzol reagent at – 80 °C until subsequent RNA purification [3].

## Discussion

Endothelial micro particles are small 0.2–1.5 µm vesicles comprised of plasma membrane and a small amount of cytosol present in circulating blood that are released from activated or injured endothelial

cells. Endothelial micro particles have been demonstrated in active cigarette smokers. To determine if Endothelial micro particles levels are affected following acute EC exposure, blood samples were collected at the pre-exposure baseline visit and then 1 week later at the follow up visit within 30 min following EC exposure [4]. Plasma Endothelial micro particles levels following exposure to EC without nicotine were not significantly changed compared to baseline EMP levels. However, exposure to EC with nicotine resulted in significantly higher levels of total Endothelial micro particles compared to baseline levels of total Endothelial micro particles for the same individuals. These results are not unexpected; since total Endothelial micro particles levels are significantly higher in nicotine-containing cigarette smokers compared to non-smoker Endothelial micro particles levels, but have not yet been reported for initial EC usage. Small airway epithelium transcriptome Genome-wide gene expression profiles were assessed by mRNA-sequencing from small airway epithelium collected by brushing the 10th–12th order bronchi at baseline and again 1 wk. within 2 h of EC exposure. Using significance criteria of  $p < 0.05$  and fold-change  $> \pm 1.5$ , a total of 71 genes were significantly altered in SAE following exposure to EC with nicotine, including 19 up-regulated and 52 down-regulated. Acute aerosol inhalation of EC with nicotine led to global changes in SAE transcriptome profiles as observed by volcano plot and hierarchical clustering [5]. A total of 65 genes were significantly altered in SAE following exposure to EC without nicotine, including 40 up-regulated and 25 down-regulated. Acute aerosol inhalation of EC without nicotine also led to global changes in SAE transcriptome profiles as observed by separation of each study subject by hierarchical clustering of differentially expressed genes. Collectively in the EC users, among the pathways significantly affected were the nicotine receptor pathway and several downstream targets of p53, including up-regulated genes and down-regulated genes, consistent with an altered activation of p53-dependent signalling. While long term studies may eventually demonstrate that smoking EC is safer than smoking traditional cigarettes, this prompts the question: do EC aerosols have an adverse effect on the human lung? To begin to assess this question, we evaluated the biology of lung cells of healthy never smokers before and then after a brief, acute exposure to EC aerosols that is approximately

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equivalent in nicotine delivery to smoking 2 cigarettes. Even in this limited cohort study, we observed that acute exposure of EC aerosols to healthy naïve individuals disorders biology of at least 3 lung cell populations, including: the small airway epithelium, the initial site of cigarette smoking-induced lung abnormalities, alveolar macrophages, the mononuclear phagocyte defender of the lower respiratory tract and, indirectly by assessment of circulating endothelial micro particles, a biomarker for health of the pulmonary capillary endothelium of the alveolar vascular bed [6]. While larger studies will be required to determine if these biologic changes translates into an increased risk for lung disease, the data suggests that EC aerosols are not benign. These observations raise the concern as to whether it is premature for the medical community to proactively recommend EC use as a cigarette smoking alternative until more studies are carried out. Components in EC aerosols possibly relevant to lung health EC aerosols contain nicotine and a variety of other chemicals. Nicotine is capable of evoking extensive cellular changes in cells including proliferation, cell growth and apoptosis via activation of intracellular kinase signalling pathways. Nicotine displaces the local cytotransmitter acetylcholine from nicotinic ACh receptors which are composed of 5 subunits that form hetero- or homomeric pentamer channels made of either 5 identical  $\alpha$  subunits or combinations of  $\alpha$  and  $\beta$  subunits. Nine different types of  $\alpha$  subunits and 3 types of  $\beta$  subunits have been identified [7]. Both the human airway epithelium and AM express multiple nAChR subunits, and it is likely that the effects of nicotine exposure on the epithelium and AM occur, at a minimum, in a nAChR-dependent manner. The finding from our study that EC use significantly altered expression of multiple genes in the nicotine receptor pathway in the small airway epithelium further supports this concept. However, nicotine exposure may have biological effects on the lung independent of nACR-mediated signalling. A recent study by Lee demonstrated that exposure of mice to e-cigarette smoke for 12 wk. induced DNA damage in multiple organs including the lung via the production of DNA damaging agents following nitration and subsequent metabolizing of nicotine [8]. These data suggest that long term exposure to nicotine containing e-cigarettes in humans may have similar consequences. In addition to possible harmful effects of nicotine per se, there is a growing body of literature documenting the presence of harmful chemical constituents in EC aerosols. The liquids used in EC typically contain variable ratios of vegetable glycerin, propylene glycol, and nicotine and flavouring chemicals. Formaldehyde, a known degradation product of PG, reacts with PG and glycerol during vaporization to produce hemiacetals [9]. Assessment of 42 different brands of e-liquids found formaldehyde in all 42 samples at concentrations between 0.02–10.09 mg/L. Other contaminants, such as limonene and various hydrocarbons have been detected in some but not all e-liquids at levels higher than the recommended exposure limits. Emission of aldehydes from EC has also been reported following heating and oxidation of the e-liquid main components, vegetable glycerin and propylene glycol. Our data from EC users without nicotine demonstrates multiple gene expression changes in both the SAE and AM following acute EC exposure. Therefore, these

data suggest that non-nicotine derived chemicals present in EC aerosols can induce molecular changes in cell populations critical to lung health which in the long term may lead to harmful effects. Evidence that EC aerosols modify the biology of lung cells Consistent with the in vivo human data in the present study, there is in vitro and experimental animal evidence that EC aerosols modify lung cell biology. Exposure of cell lines from skin and lung to EC aerosols led to cytotoxic effects [10]. Exposure of human airway epithelial cells in vitro and mice in vivo to EC aerosols led to oxidative stress, low levels of inflammatory cell recruitment, delayed clearance of pathogens and other defects in host response. In addition, EC smoke exposure damages DNA and reduces repair activity in mouse lung and human lung cells in vitro.

## Conclusion

Primary lung micro vascular endothelial cells treated with e-liquid or condensed EC aerosol  $\pm$  nicotine, resulted in increased endothelial permeability, and intra-tracheal administration of e-liquid to mice sensitized to ovalbumin aggravated allergen-induced airway inflammation and hyper-responsiveness.

## Acknowledgement

None

## Conflict of Interest

None

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