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Breath profiles by electronic nose correlate with systemic markers but not ozone response[☆]

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Summary

Background: The evaluation of exhaled breath profiles by electronic nose (eNose) is considered as a promising non-invasive diagnostic tool, and the discrimination of breathprints between patients with COPD and asthma has been reported. The aim of this study was to assess, whether exhaled breath profile analysis can detect the inflammatory airway response induced by ozone inhalation. **Methods:** In a randomized double-blind, cross-over study 14 healthy ozone-responsive subjects were exposed to 250 ppb ozone and filtered room air for 3 h with intermittent exercise. Blood biomarkers, exhaled NO, exhaled CO, and breathprints (Cyranose 320[®]) were assessed prior and at 3 time points up to 24 h post exposure. Induced sputum was collected at baseline and 3 h post exposure. Multivariate analysis of eNose data was performed using transformed and normalized datasets.

Results: Significantly increased numbers of sputum and blood neutrophils were observed after ozone, whereas the eNose signals showed no differences between exposures and no correlation with neutrophilic airway inflammation. However, independent of ozone exposure, sensor data correlated with serum SP-D levels and to a smaller extent with blood neutrophil numbers.

Conclusions: Exhaled breath profiles as measured by the Cyranose 320[®] did not reflect airway responses to ozone. This suggests that exhaled volatiles did not change with ozone challenges or that the changes were below the detection limits. Conversely, the correlation of eNose signals with blood neutrophils and serum SP-D, i.e. markers of systemic inflammation and lung permeability, suggested that the Cyranose 320[®] can detect volatile organic compounds of systemic origin.

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Introduction

Both asthma and COPD are inflammatory diseases of the airways.^{1,2} While diagnosis, monitoring and disease management are mainly based on lung function and symptoms, it is believed that an efficient treatment of these diseases should aim at a reduction of inflammation and on drugs with anti-inflammatory action. Based on this, the need for simple non-invasive tools to assess airway inflammation in clinical practice is widely recognized.

The analysis of induced sputum can be considered as the gold standard of the non-invasive methods to assess airway inflammation. It enables the analysis of both cellular composition and of fluid phase biomarkers. There are, however, significant limitations, as due to the need of mucus homogenisation not all fluid phase compounds are readily detectable.³ In addition, the induction process is not without risk for severely ill patients⁴ and can influence sputum composition, which limits the sampling to at most once every 48 h.³ Spontaneous sputum is produced by some but not all patients and generally of lower quality; it is therefore not suited for experimental studies. These restrictions might be circumvented by using indirect measures of inflammation, such as exhaled breath analysis. This has been established for exhaled nitric oxide (FeNO), a valuable tool for the detection of eosinophil-related airway inflammation and an indicator for steroid sensitivity.⁵ Exhaled breath condensate offers the analysis of multiple non-volatile compounds, but is still hampered by methodological difficulties and standardization issues.⁶

The analysis of volatile compounds in exhaled breath using an electronic nose is considered as a promising non-invasive diagnostic tool. Published data already suggest that it is possible to discriminate breathprints of tumour patients from those of healthy subjects⁷ or breathprints of patients with COPD from those of asthma patients.^{8,9} Despite these results, the usefulness of the technique for the identification of specific phenotypes of airway inflammation has not been proven. In this study we addressed the ability of the instrument Cyranose 320® to detect airway responses to ozone inhalation. The ozone challenge model

safely and reproducibly allows to induce transient neutrophilic airway inflammation in healthy subjects. This response is well known from experimental studies on air pollution and has meanwhile been employed in proof-of-concept studies of early drug development.^{10–13}

Therefore the major aim of this study was to determine whether exhaled breath profile assessed by the Cyranose 320® would be altered in response to ozone inhalation in healthy subjects. For the sake of comparison we additionally measured multiple markers in blood and serum at different time points and explored the relationship of these markers with the eNose signals.

Material and methods

Study design

In a randomized, double-blind, two-way cross-over study, subjects were exposed to either ozone (O₃) or filtered room air (RA) in an ozone challenge chamber (Fig. 1). Subjects were randomized to two different sequences (RA-O₃)/(O₃-RA) in a 1:1 ratio. Exposures were performed at least 14 days apart to avoid carry-over effects. Before the start, immediately after, as well as 3 h and 21 h post exposure exhaled air of the subjects was analyzed by eNose. In addition, FeNO and exhaled CO were measured at these time points. Induced sputum was collected during screening and 3 h post exposure. Blood was collected before, 2, 4 and 21 h post exposure.

During a screening visit a physical examination was performed, the subject's history taken, and a baseline sputum induction performed. Subjects capable of producing an adequate sputum sample ($\geq 1 \times 10^6$ total cells, $\geq 50\%$ cell viability, $\leq 20\%$ squamous epithelial cells) underwent a screening ozone challenge and were included into the study, if their response to ozone was a $>10\%$ increase in the percentage of neutrophils. A follow-up visit was scheduled within 7 days after the last exposure to perform a physical examination, spirometry and to assess any adverse events or concomitant medications.

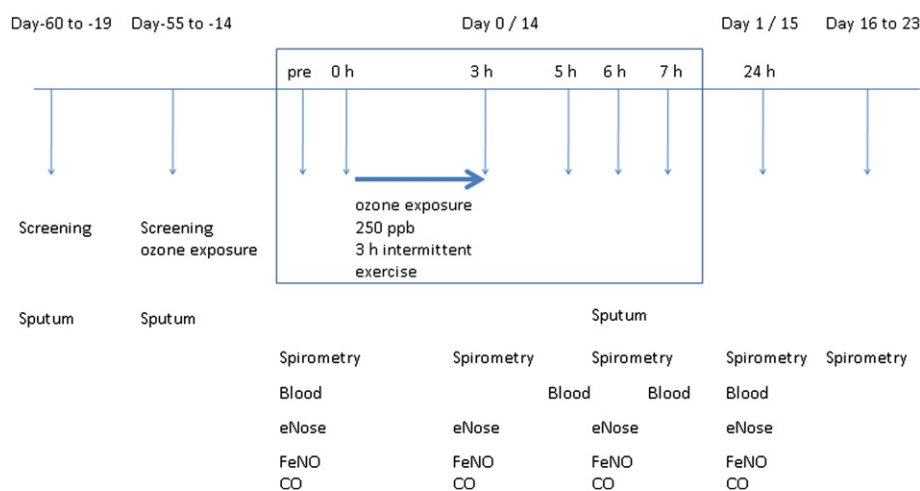


Figure 1 Study design. Ozone exposures were performed at least 14 days apart (eNose: electronic nose, FeNO: exhaled nitric oxide, CO: exhaled carbon monoxide, ppb: parts per billion).

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