

EDITORIAL

Clinical & Experimental Allergy

Sniffing out steroid responsiveness in asthma using an electronic nose

This editorial discusses the findings of the paper in this issue by M. P. van der Schee et al. [5] pp. 1217–1225.

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What method would you use to identify asthma in a symptomatic patient, and how would you attempt to predict treatment response?

This question is perhaps not so easy to answer. It is becoming increasingly evident that asthma is a complicated disease with different phenotype characteristics and different responses to common asthma medications [1, 2], and there is clearly a need to more efficiently characterize patients in the clinical setting. In traditional clinical practice, a combination of patient history and clinical findings, often recorded during repeated assessments, is commonly used. And albeit time-consuming, this approach is often successful. During the last decade, promising biomarkers such as fractional exhaled nitric oxide (FeNO) and sputum cell counts have emerged as additions to more traditional examinations such as lung function measurements and bronchodilator responses [3, 4]. In the featured study by van der Schee et al., [5] these methods were pitted against – and outmatched by – a novel device for exhaled breath analysis, the eNose.

The eNose or 'electronic nose' [6] belongs to a growing family of technologies for 'smell' analysis with applications ranging from the detection of infections or malignant disease to identifying spoiled red wine [7–9]. The device used by van der Schee et al. analyses exhaled breath for gases and volatile liquids using semiconductor technology combined with pattern recognition software, yielding a breath profile or 'breathprint'

of the examined subject. The eNose has previously been shown to successfully discriminate both mild and severe persistent asthma from healthy controls [10].

In the study by van der Schee et al., 25 adults with physician-diagnosed asthma were taken off inhaled steroids until loss of asthma control occurred or for a maximum of 28 days. Seven patients were excluded for safety reasons, and the remaining 18 patients underwent a 2-week open-label course of oral steroids. Twenty non-atopic non-asthmatics without airway hyperresponsiveness or bronchodilator reversibility were used as controls. The ability to discriminate asthmatic subjects from controls was compared between the eNose, FeNO and sputum eosinophils. Their respective ability to predict loss of control and subsequent steroid responsiveness in asthmatic subjects was also tested against that of airway hyperresponsiveness to hypertonic saline.

The eNose, FeNO and sputum eosinophils were all successful in differentiating subjects with asthma from healthy controls, with levels of sensitivity/specificity of 80/65%, 80/90% and 83/84%, respectively. Interestingly, a course of oral steroids in the asthmatic subjects increased the specificity of the eNose while decreasing that of FeNO. This as well as the very high pre-steroid specificity of FeNO could well be related to the control group being 'supernormal'. Low FeNO levels have very high negative predictive values for asthma and are typically seen in non-smoking non-atopics [11].

In the 25 subjects with asthma the eNose ($P = 0.008$) and sputum eosinophils ($P = 0.002$) were also successful in predicting loss of asthma control after withdrawal of inhaled steroids, which FeNO was not ($P = 0.142$). Most importantly, the eNose was also highly successful in predicting responsiveness to oral steroids, with a sensitivity of 91% and specificity of 71%, while FeNO, sputum eosinophils and airway hyperresponsiveness were all unsuccessful.

As is often the case with clinical trials, and especially pilot studies, it could be argued that this study used

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methods optimized to differentiate between asthma and non-asthma, and to maximize the proportions of subjects with asthma who would experience loss of control and be steroid responsive [12]. It should, however, be noted that the selection of subjects with asthma with predominantly eosinophilic asthma and their controls would not favour the eNose over the other assessment methods. Both FeNO and sputum eosinophils, which are interrelated, are able to identify eosinophilic inflammation also in more mixed asthma populations [11, 13]. To date, the eNose has mainly been used in studies of eosinophilic asthma, but the technology itself does not preclude the study of other endotypes of asthma [1], with the proper configuration of the device.

The high internal validity of the study comes at the cost of lower generalizability. A more heterogeneous study population with various levels of asthma severity and several asthma phenotypes would probably have affected the results and would be necessary for generalized recommendations regarding the use of this technology [2]. Moreover, physicians are rarely concerned with ruling out asthma in subjects such as were used as control group in the study. The eNose has previously proven successful in differentiating asthma with fixed airway obstruction from COPD [14], and such differential diagnostic questions is one of the fields where the eNose and similar novel technologies could be deployed.

One problem with complex measures and pattern recognition is the vast grey scale between disease and healthy, as well as that within the spectrum of disease. The

eNose performed moderately at distinguishing severe persistent from mild asthma in a previous study [10]. However, similar to FeNO [15], electronic nose hardware and software and their optimal detection thresholds have not yet been established. In addition to this lack of consensus, systematic studies of single biomarkers are more feasible and offer better repeatability. In the study by van der Schee et al., principal component analysis (PCA) was used to reduce the number of factors recorded by the eNose into a set of principal components. This approach is eligible for analysing eNose data, however, again at the possible cost of robustness as PCA is subject to variance from, for example, how many and which components are analysed. Data recorded by a novel device and analysed by powerful yet less robust statistics are a caveat of the study, and however interesting, it will require repetition in other well-characterized populations using rigorous methodology.

Conversely, it could be argued that the simultaneous assessment of numerous exhaled components into a compound breath profile is a strength of the eNose compared to analysis of single biomarkers such as FeNO. Asthma is known for its complexity with regard to aetiology, pathophysiology and clinical expression [1]. So far, no single indicator has been identified as definitive of asthma, and pattern recognition approaches have promising properties. Following larger population studies and further technological advances, the eNose certainly has the potential to become a good tracker of asthma, initially in the hands of researchers and perhaps in the longer term also in clinical practice.

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