The potential of electronic nose technology in lung transplantation: a proof of principle

To the Editor:

With each exhaled breath, thousands of molecules are expelled. Every person has a unique composition of this expelled air, the so-called breathprint, representing their current state of health. Identification of individual volatile organic compounds (VOCs), although specific, is an extremely time-consuming process and hard to implement in routine clinical care. An electronic nose (eNose) can be used to capture the complete mixture of VOCs in exhaled air by several cross-reactive gas sensors. Without identifying individual components in expelled air, the sensor captures information that results in a breathprint pattern which can be analysed with artificial intelligence using pattern recognition [1, 2]. Consequently, using an eNose to collect real-time measurements of the breathprint has potential as a cheap and fast point-of-care tool in clinical practice. In recent years, exhaled breath analysis using eNose technology has gained increasing attention and has demonstrated great potential as a real-time noninvasive diagnostic tool, where different vendors are available [3]. For example, promising results were demonstrated in diagnosis of asthma phenotypes and interstitial lung diseases, with international confirmation studies ongoing to bring this technology to outpatient clinics [3–5].

Within the field of lung transplantation (LTx), eNose technology has barely been explored, despite its numerous potential applications within this particular field. One study was conducted using eNose technology that found a significant association between breathprint and plasma tacrolimus levels [6]. Additionally, a few non-eNose studies were performed measuring the individual VOCs of LTx recipients with allograft dysfunction [7, 8]. Long-term survival after LTx remains hampered by high prevalence of complications, such as acute cellular rejection (ACR), chronic lung allograft dysfunction (CLAD) and infections. Differentiation between various causes of lung function decline can be challenging and often requires extensive invasive diagnostic procedures, such as bronchoalveolar lavage and trans-bronchial biopsies. In addition, given the current diagnostic criteria, the establishment of diagnosis of CLAD takes several months and a reliable biomarker to diagnose CLAD early is lacking [9]. Being able to detect complications such as ACR or CLAD, including its phenotype, in an early or developing stage or with greater accuracy, could enable quicker interventions directed at reversing or slowing the process and could lead to better outcomes [9, 10]. In all of these aspects, eNose technology may be of clinical value during the follow-up of LTx recipients. Therefore, we started a prospective cohort study to assess the diagnostic accuracy of exhaled breath analysis using eNose technology to detect complications after LTx (Netherlands Trials Register identifier NL9251). Here, we would like to illustrate its potential using an illustrative clinical case from this ongoing cohort study in LTx recipients.

The patient (female, 61 years old, and 2.4 years after bilateral LTx with stable allograft function) was followed up at our outpatient clinic between October 2020 and January 2021, with spirometry (Vyntus One Pulmonary function system; Vyaire Medical, Chicago, IL, USA) and eNose measurements at each outpatient clinic visit (nine times in total during this time period). Informed consent was given and the study was approved by the medical ethics committee (MEC-2019-0497). The patient's exhaled breath was analysed using a cloud-connected eNose (SpiroNose; Breathomix, Leiden, the Netherlands). The SpiroNose measurement consists of five tidal breaths, followed by an inspiratory capacity manoeuvre to total lung capacity, a 5-s breath hold and slow expiration to residual volume. eNose sensor responses to both the tidal breathing and the slow vital capacity breath manoeuvre were jointly used for data analysis.

Shareable abstract (@ERSpublications)
Exhaled breath analysis using eNose technology holds promise as a point-of-care indicator of clinical status after lung transplantation. This case study invites further exploration of eNose technology in the field of lung transplantation. https://bit.ly/3wgQ3DE

A supervised classification of the measurements through partial least squares discriminant analysis (PLS-DA) of the eNose data was performed. In short, PLS-DA is a modelling technique for data reduction, creating simplified new explanatory variables (known as latent variables) that carry as much information as possible of the complete dataset. These latent variables are subsequently used for supervised classification and discrimination problems and can be visualised using a scatter plot [11, 12].

During the follow-up period, the patient experienced an episode of ACR (pathology from trans-bronchial biopsy was classified as A2Bx) for which she was treated with methylprednisolone pulse and a prednisone tapering scheme with recovery of pulmonary function. Later, she developed bacterial pneumonia (bronchoalveolar lavage showed *Staphylococcus aureus*) as a complication of the ACR treatment. In figure 1, a scatterplot of the results of the PLS-DA (each point depicts one measured sample) as well as a timeline, pulmonary function, C-reactive protein and peripheral blood eosinophil count [13] at all of the outpatient visits, can be seen. The axes represent the new latent variables, obtained by PLS-DA analysis. It can be appreciated that the eNose was able to separate between the stable measurements, and the measurements where the patient had ACR and bacterial pneumonia (figure 1a). Looking at the timeline (figure 1d), it is notable that the measurement performed after treatment of the ACR still clustered towards the ACR measurement, outside of the other clinical stable measurements.

As this case illustrates, it may be feasible to discriminate between a clinical stable situation after LTx and occurrence of complications such as infection or ACR using eNose pattern recognition. eNose measurements thus, possibly, have substantial added value over pulmonary function alone, as it may help to discriminate between the causes of pulmonary function decline. Furthermore, in centres that perform routine surveillance bronchoscopy, if validated, eNose technology might possibly replace these invasive procedures. Nonetheless, it must be noted that this case is a proof of principle to illustrate the potential of using eNose technology within the field of LTx. Future studies will be directed at further exploring the potential of eNose technology to detect complications after LTx. Additionally, further studies will also be directed at the specificity of the signal to discriminate between different complications or even predict complications before onset of symptoms.
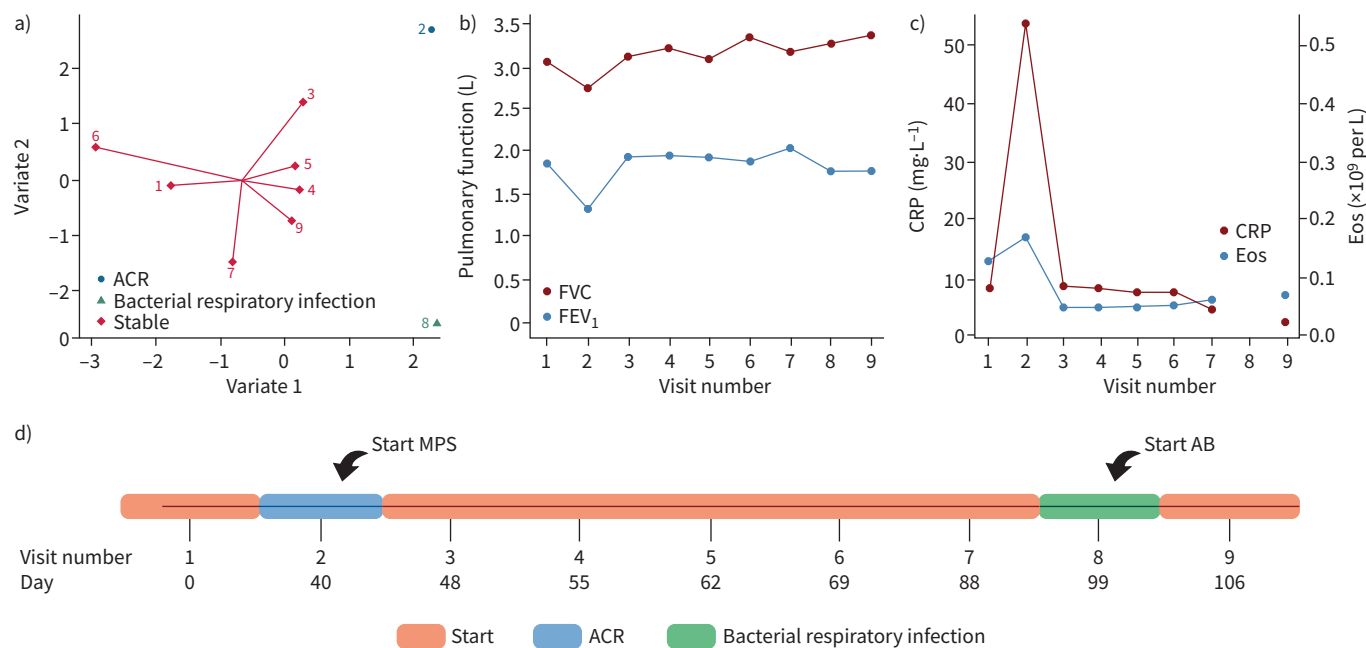

FIGURE 1 Timeline of the case report of a lung transplant recipient. a) Scatterplot of the partial least squares discriminant analysis (PLS-DA) results, using the first two latent variables obtained by the PLS-DA and the corresponding visit numbers. Each point is one measured sample. b) The course of pulmonary function. c) The course of the C-reactive protein (CRP) values and peripheral blood eosinophil counts (Eos). d) Timeline of the patient's treatment. ACR: acute cellular rejection; FVC: forced vital capacity; FEV$_1$: forced expiratory volume in 1 s; MPS: methylprednisolone; AB: antibiotics.

eNose technology thus holds promise in clinical follow-up after LTx, but potential challenges in this particular field also exist. A major challenge is the relatively small number of transplanted patients, combined with large numbers of potential noise factors that are present after LTx, such as medication used, the presence of disease in a native long after single LTx and unknown donor factors. In addition, practice variation between centres and countries might hamper exchange and external validation of eNose application.

All in all, exhaled breath analysis using eNose technology holds promise as a point-of-care indicator of clinical status after LTx, potentially allowing early diagnosis and management of complications, and might improve outcomes after LTx. We feel that findings in this case study, although being a proof of principle, invite further exploration of eNose technology in the field of LTx.

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