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The Potential of eNose Technology in Lung Transplantation: a Proof of Principle

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Take home message: 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.

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Abbreviations
Acute cellular rejection ACR
Chronic lung allograft dysfunction CLAD
Electronic nose eNose
Lung transplantation LTx
Partial least squares discriminant analysis PLS-DA
Main body

With each exhaled breath, thousands of molecules are expelled. Every individual has a unique composition of this expelled air, the so-called “breathprint”, representing one’s 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 information results in a breathprint pattern, which can be analysed with artificial intelligence using pattern recognition [1, 2]. Subsequently, real-time measurements of the breathprint by using an eNose has potential as a cheap and fast point-of-care tool in clinical practice. In the past years exhaled breath analysis using eNose technology has gained increasing attention and has demonstrated great potential as a real-time non-invasive 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 bronchialalveolar lavage and trans-bronchial biopsies. Also, 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) [11]. Here, we would like to illustrate its potential by an illustrative clinical case from this ongoing cohort study lung transplantation recipients.

The patient (female, 61 years old, and 2.4 years after bilateral LTx with stable allograft function) was followed at our outpatient clinic between October 2020 and January 2021, with spirometry (Vyntus One Pulmonary function system, Vyaire Medical, Chicago, 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). Exhaled breath of the patient was analysed using a cloud-connected eNose; SpiroNose (Breathomix®, Leiden, the Netherlands). The SpiroNose measurements consist of five tidal breaths, followed by an inspiratory capacity manoeuvre to total lung capacity, a five second 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. A supervised classification of the measurements through partial least squares discriminant analysis (PLS-DA) on 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, while carrying the same information as the complete dataset. These latent variables are subsequently used for supervised classification and discrimination problems, and can be visualized using a scatter plot [12, 13]. It is described that PLS-DA can be effective for both variable reduction and as a classifier for a large number
of variables and it seems that PLS-DA performs better for a large number of variables than for example principal component analysis combined with a linear discriminant analysis model [14].

During the follow-up period, the patient experienced an episode of ACR (pathology from transbronchial biopsy, A2Bx) for which she was treated with methylprednisolone pulse and prednisone tapering scheme with recovery of pulmonary function. Later she developed bacterial pneumonia (bronchialalveolar lavage showed S. aureus) as a complication of the ACR treatment. In Figure 1, a scatter plot of the results of the PLS-DA (each point depicts one measured sample) as well as a time line, pulmonary function, CRP, and peripheral blood eosinophil count [15] at all of the outpatient visits can be seen. The axes represent the new latent variables, obtained by PLS-DA analysis. These latent variables are summary variables formed to contain as much information as possible from the complete dataset. 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, it is notable that the measurement performed after treatment of the ACR is still clustering 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 lung transplantation 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 could 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.
Whereas eNose technology thus holds promise in clinical follow-up after LTx, potential challenges in this particular field also exist. A major challenge is formed by the relatively small number of transplanted patients, combined with large numbers of potential noise factors that are present after lung transplantation such as medication used, the presence of disease in a native long after single lung transplantation and unknown donor factors. Also, 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 lung transplantation, 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 lung transplantation.
Author contributions

Research idea and design, MH, OM and NW; patient inclusion NW; data analysis and interpretation, NW, MH, and OM; drafting and/or critically reviewing of the manuscript, NW, MH, OM, RH, BM, LS, and JA; advise on study design RH, BM, LS, and JA. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

NW: has no conflicts of interest to disclose.
RH: has no conflicts of interest to disclose.
BM: has no conflicts of interest to disclose.
LS: has no conflicts of interest to disclose.
JA: reports personal fees and non-financial support from MSD; personal fees from BMS, Boehringer Ingelheim, Amphera, Eli Lilly, Takeda, Bayer, Roche, Astra Zeneca outside the submitted work. In addition, JA has a patent on allogenic tumor cell lysate licensed to Amphera, a patent combination immunotherapy in cancer pending, and a patent biomarker for immunotherapy pending.
OM: has no conflicts of interest to disclose.
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