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RESEARCH ARTICLE

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Identifying chronic rhinosinusitis without nasal polyps by analyzing aspirated nasal air with an electronic nose based on differential mobility spectrometry

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ABSTRACT

Background: The diagnosis of chronic rhinosinusitis (CRS) is a complicated procedure. An electronic nose (eNose) is a novel method that detects disease from gas-phase mixtures, such as human breath.
Aims/Objectives: To determine whether an eNose based on differential mobility spectrometry (DMS) can detect chronic rhinosinusitis without nasal polyps (CRSsNP) by analyzing aspirated nasal air.
Materials and methods: Adult patients with CRSsNP were examined. The control group consisted of patients with septal deviation. Nasal air was aspirated into a collection bag and analyzed with DMS. The DMS data were classified using regularized linear discriminant analysis (LDA) models with 10-fold cross-validation.
Results: The accuracy of the DMS to distinguish CRSsNP from patients with septal deviation was 69%. Sensitivity and specificity were 67 and 70%, respectively. Bonferroni-corrected statistical differences were clearly noted. When a subgroup with more severe inflammatory disease was compared to controls, the classification accuracy increased to 82%.
Conclusions: The results of this feasibility study demonstrate that CRSsNP can potentially be differentiated distinguished from patients with similar nasal symptoms by analyzing the aspirated nasal air using DMS. Further research is warranted to evaluate the ability of this novel method in the differential diagnostics of CRS.

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Chronic rhinosinusitis; differential mobility spectrometry; electronic nose; nasal air

Introduction

The diagnosis of chronic rhinosinusitis (CRS) is a complicated procedure that is based on patient history and clinical findings. It is therefore difficult to estimate the true prevalence of CRS. In Europe, a prevalence of 11% was obtained in a symptom-based questionnaire study [1]. Symptoms alone, however, tend to overestimate the prevalence and are therefore not sufficient for the diagnosis of CRS [2]. The endoscopic visualization of purulence or mucosal inflammation in the middle meatus or the presence of polyps improves the specificity of the symptom criteria. Computed tomography (CT) is the gold standard in the diagnostics of CRS and is recommended for symptomatic, endoscopy-negative patients [3]. New innovative and non-invasive methods are, however, needed to help identify patients with CRS.

The analysis of human breath is an interesting field of research. The measurement of exhaled nitric oxide (NO), for example, can be used in the diagnostics of asthma. In addition to specific molecules, the non-targeted analysis of gas-phase compounds can also be used in disease diagnostics. The electronic nose (eNose) attempts to mimic mammalian olfaction. The device consists of an array of gas sensors combined with pattern recognition software and performs a qualitative analysis of gas-phase mixtures. The result is a measurement signature of the volatile organic compounds (VOCs) contained in the sample, which could represent the VOC pattern of a certain disease. Thus, different diseases could potentially be differentiated by comparing their VOC patterns and, as a result, eNose technology has gained interest in research. In many previous studies, exhaled breath has been used as a sample material [4]. Furthermore, studies have shown that a 'breathomics'-based approach can be used to diagnose and even determine the phenotype of asthma [5]. To date, only a few studies have examined the diagnostics of rhinosinusitis using an eNose. However, the accuracy reported in these studies has varied between 60 and 85% [6–8].

Although differential mobility spectrometry (DMS) is not an eNose in the strictest sense, it provides comparable information on the samples. In DMS, ionized molecules are separated from each other using an alternating electrical field. An *in vitro* study revealed that DMS can distinguish five

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Table 1. Demographics of the patients and comparison of the groups.

	CRSsNP ($n = 27$)	DS ($n = 27$)	p Values
Gender male/female	13/14	22/5	.021*
Age, median (range)	51 (24–71)	43 (23–69)	.140**
BMI, median (range)	28.4 (22.0–39.1)	27.1 (19–39.8)	.169***
SNOT-22 score, median (range)	38 (9–57)	29 (9–67)	.345***
Lund–Mackay score, median (range)	8 (4–19)	–	–

BMI: body mass index; CRSsNP: chronic rhinosinusitis without nasal polyps; DS: deviated septum; SNOT-22: Sino-Nasal Outcome Test.
*Fisher's exact test.
**Independent samples *t* Test.
***Mann–Whitney *U* test.

common rhinosinusitis bacteria from each other with an accuracy of 79% [9].

The aim of this feasibility study was to investigate whether patients with chronic rhinosinusitis without nasal polyps (CRSsNP) could be distinguished from patients with nasal symptoms due to deviated septum (DS) by analyzing the aspirated nasal air of these patients using DMS.

Materials and methods

Participants

In this prospective study, we consecutively recruited eligible patients into two groups: the CRSsNP group and the control group.

The following inclusion criteria were used for the CRSsNP group: age $\geq$ 18 years, symptoms meeting European Position Paper on Rhinosinusitis and Nasal Polyps criteria for CRSsNP [2], and paranasal mucosal changes visible in cone beam tomography or multislice CT. As incidental mucosal changes are possible in CT scans, Lund–Mackay (LM) scores were calculated and only those patients with LM scores of four or more were included. Nasal endoscopy was not performed.

Patients were recruited to the control group if they were aged $\geq$ 18 years, had experienced nasal congestion, and DS was diagnosed based on anterior rhinoscopy, but no evidence of purulence or polyps was observed. Again, nasal endoscopy was not performed.

The exclusion criteria for both groups were pregnancy or lactation, smoking during the past month, nasal polyps, prior paranasal surgery, acute upper respiratory tract infection during the past two weeks, severe immunodeficiency, or malignant disease treated in the previous five years.

All patients were examined and recruited by a single ENT specialist. After giving written informed consent to participate, patients filled out the 22-item Sino-Nasal Outcome Test (SNOT-22). The test is validated in the Finnish language and has revealed that healthy controls have a mean score of 8.9 [10]. Therefore, patients were included if they had a score of nine or more. No prior reparations, such as fasting and no exercise, were required. Information about the patient's current medication, allergies, height, weight, and any drinking or eating during the past two hours was obtained during an interview.

In total, 58 patients were asked to participate and two declined. Of the two patients who declined to participate, one had CRSsNP and the other had DS. Furthermore, two patients (one with CRSsNP and one with DS) were excluded because they had used nasal sprays within the past 24 h. Thus, 54 patients were enrolled in the study. The demographics of the patients are presented in Table 1. All the procedures performed in this study were in accordance with the Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Tampere University Hospital (R16103). The study was conducted according to medical device trial regulations and was approved by National Supervisory Authority for Welfare and Health. All patients provided written informed consent.

Collection of nasal air

We collected nasal air into a collection bag by aspiration in the same manner as described earlier [11]. This resembles the standardized method for the collection of nasal air for the measurement of NO [12]. In brief, nasal air was aspirated using a suction pump SP 625 EC-LC-DU (Spiggle & Theis Medizintechnik GmbH, Overath, Germany). A Teflon tube with a metal Politzer nasal olive was inserted into the patient's nostril while the other end was attached to the suction pump. The collection bag was a metalized polyester 750 ml GaSampler Single-Patient Collection Bag (Quintron Instrument Company Inc., Milwaukee, WI), which was connected *via* a Teflon tube to the outlet port of the pump. The patient blew against resistance of 15 cmH_2O to close the soft palate, allowing only the aspiration of nasal air. This was simply performed by measuring 15 cm of tap water into a plastic bottle and then asking the patient to blow bubbles in the water. Less than ten seconds is required to fill the bag. The contents of the bag were then analyzed with the DMS device within 6 h. The set up for the collection of nasal air (without the plastic bottle) and attachment of the full bag to the DMS device is shown in Figure 1.

DMS device

The DMS device used in this study is a differential mobility spectrometer (Ionvision, Olfactomics Ltd, Tampere,

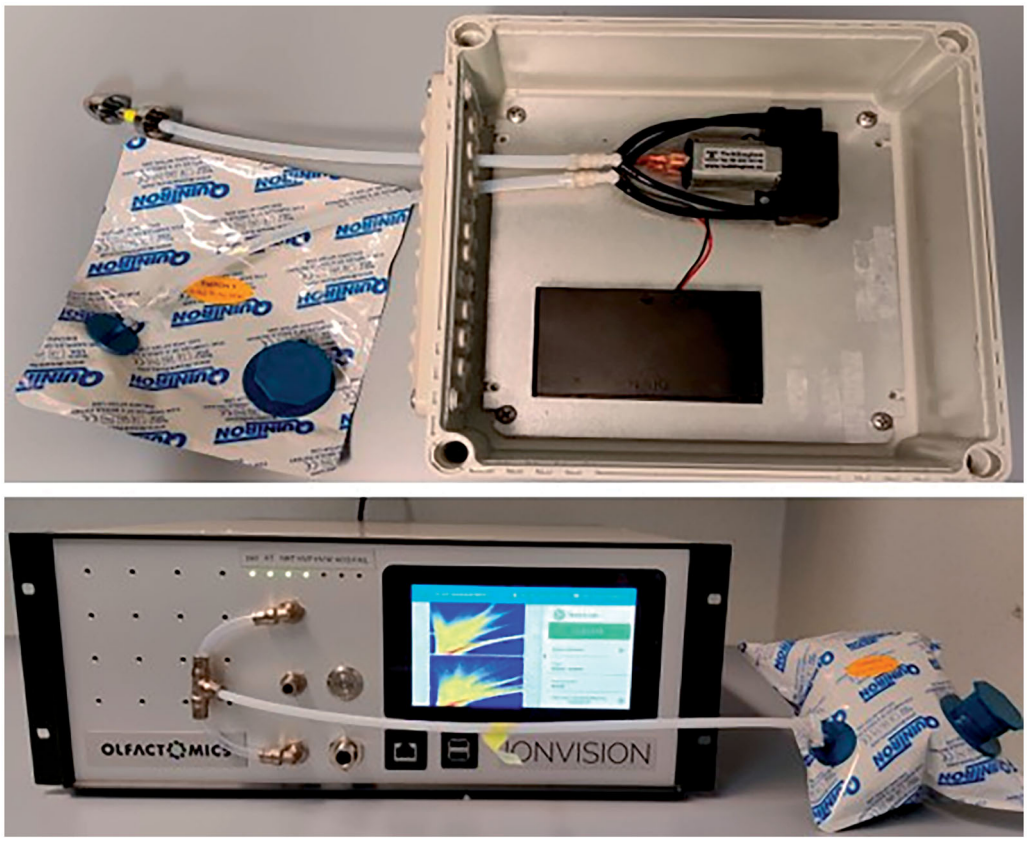

Figure 1. Above: the pump used to aspirate nasal air. A collection bag at the end of Teflon tube and a nasal olive at the end of another Teflon tube. Below: the DMS device attached to the full collection bag and ready for a measurement.

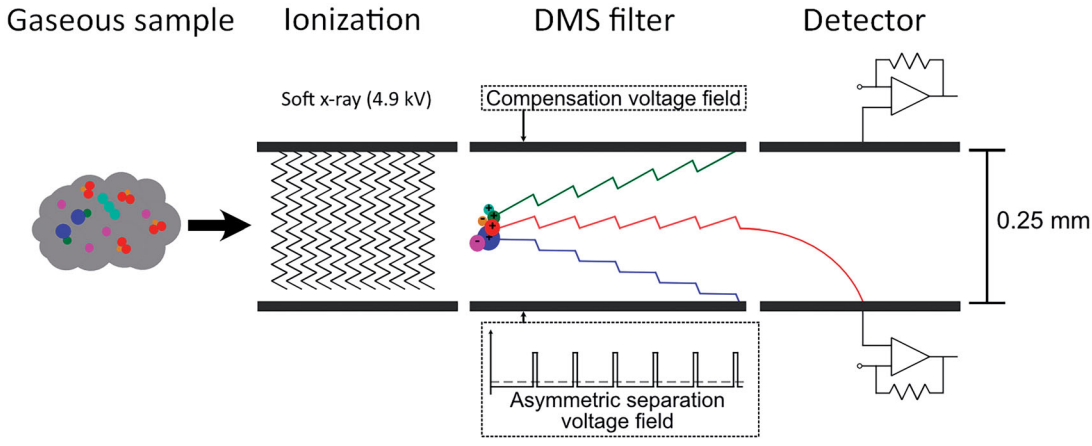

Figure 2. A schematic representation of the differential mobility spectrometer (DMS) used in this study. kV: kilovolts; mm: millimeters.

Finland). In DMS, gas phase molecules are ionized and driven into a drift chamber formed by two electrodes (Figure 2). These electrodes create an oscillating electric field that is perpendicular to the ions' motion in the carrier gas. The separation field of DMS alternates between high and low voltages asymmetrically. This causes ion swarms to travel in a saw-like motion that separates ion clusters based on their mobility characteristics. An additional compensation voltage field is applied to selectively prevent certain ions from colliding with the chamber electrodes. At the end of the chamber is a detector into which ions collide, creating an electric current signal. When different electric fields and compensation voltage values are scanned, the result is a measurement signature called a dispersion plot. The measurement is conducted simultaneously for both positive and negative ions.

Analysis of the samples

Samples were collected and analyzed within 28 separate days. Each sample bag was analyzed three times while connected to the DMS device. The dispersion plots were

measured using separation voltages (U_{SV}) of 200–800 V with 60 increments and compensation voltages (U_{CV}) of −1–8 V with 100 increments, resulting in a 6000-dimensional dispersion plot for positive and negative ions. The baseline of the device was evaluated by inspection of the dispersion plot using an analysis of the room air aspirated through the device between each patient sample at the beginning and the end of the measurement session. Further, bags of room air were collected with the pump and analyzed at least once during a measurement session. However, if significant carry-over was observed in the dispersion plots, the bags of room air were analyzed more often.

Data analysis

The baseline characteristics (age, gender, body mass index (BMI), SNOT-22 scores) were compared to evaluate whether there were any statistical differences between the two groups. Analyses were performed using IBM® SPSS® Statistics for Windows version 27 (IBM, Armonk, NY). First, we evaluated whether the data were normally distributed by visual inspection of the histograms and by Shapiro–Wilk test. For normally distributed variables (age), the comparison was made with independent samples *t* test and for non-normally distributed variables (BMI, SNOT-22) with Mann–Whitney *U* test. Gender was compared with Fisher's exact test.

The DMS data were classified using regularized linear discriminant analysis (LDA) models with 10-fold cross-validation. Regularized LDA has been used in the classification of DMS data in previous studies [11]. The classification models were created in MATLAB version 2019a (MathWorks, Natick, MA). The differentiation of the nasal air samples from the room air samples was first conducted using every available measurement to ensure that there was no methodological problem with the sampling. For the classification of the sample types, the average spectrum of the three DMS measurements from each patient was utilized. Each separation voltage row was normalized to values of 0–1 to further accentuate the differences in the spectra in the higher separation voltages, where the absolute signal intensities are lower.

Spectral archetypes were created by averaging each measurement into a single spectrum for CRSsNP and DS. The statistical differences between the features of the archetype spectra were studied with the Kolmogorov–Smirnov test. The statistical significance was determined by the Bonferroni-corrected *p* value for each feature ($p < .05/6000$). To study the similarity of the measurements within and between classes, the Euclidean distance from the CRSsNP and DS archetype was also calculated for each measurement.

In addition to distance analysis, a subset of patients that had an LM score of at least 10 ($n = 11$) was classified separately against 11 randomly selected patients with DS to assess the effect of the severity of CRSsNP on the classification results.

The performance of the classification models was evaluated using the accuracy, sensitivity, specificity, negative, and positive predictive values. The Wilson score interval method was used to calculate 95% confidence intervals (CIs).

Results

Both groups consisted of 27 patients. There were 13 males and 14 females in the CRSsNP group and 22 males and five females in the DS group. Comparison of the groups shows that only gender was statistically significantly different ($p = .021$) but others (age, BMI, and SNOT-22 score) were not ($p > .05$) (Table 1).

Nasal air vs. room air

Nasal air samples were differentiated from room air samples with a classification accuracy of 94% (CI 91–96%), and visual comparison of the Euclidean distances (Figure 3) revealed that they are clearly distinguishable from the sample archetypes.

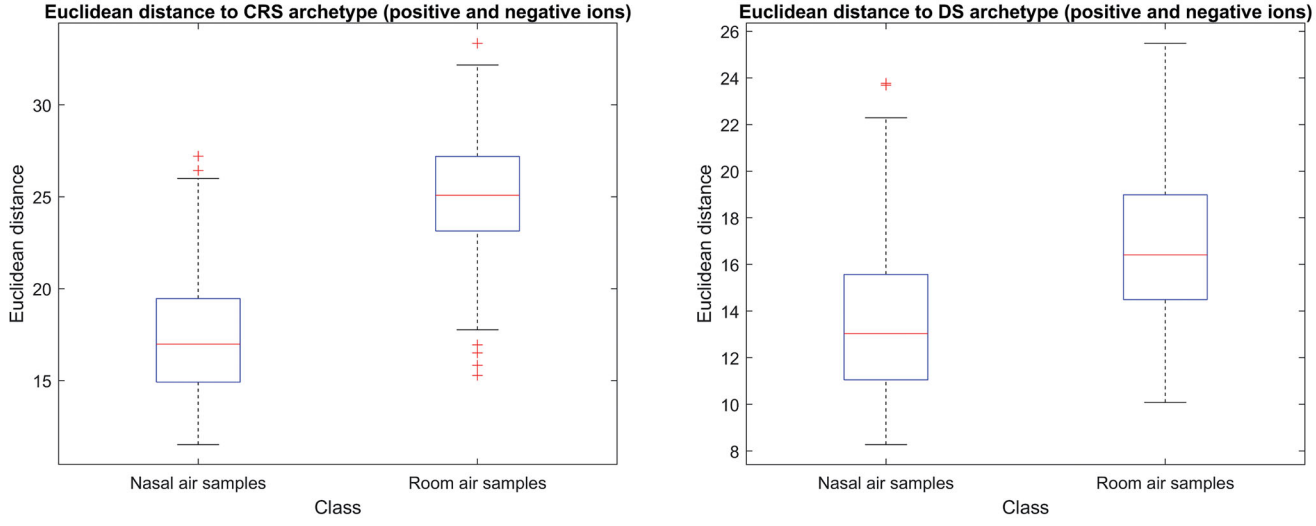

Figure 3. Euclidean distances of each measured sample type from sample archetypes. CRSsNP: chronic rhinosinusitis without nasal polyps; DS: deviated septum.

Table 2. A confusion matrix presenting the classification results of differential mobility spectrometry between chronic rhinosinusitis without nasal polyps (CRSsNP) and deviated septum (DS).

		Predicted class: CRSsNP	Predicted class: DS	
Actual class	CRSsNP	18 True positives (TP)	9 False negatives (FN)	Sensitivity = TP/(TP + FN) = 67%
	DS	8 False positives (FP)	19 True negatives (TN)	Specificity = TN/(TN + FP) = 70%
		PPV = TP/(TP + FP) = 69%	NPV = TN/(TN + FN) = 68%	

NPV: negative predictive value; PPV: positive predictive value.

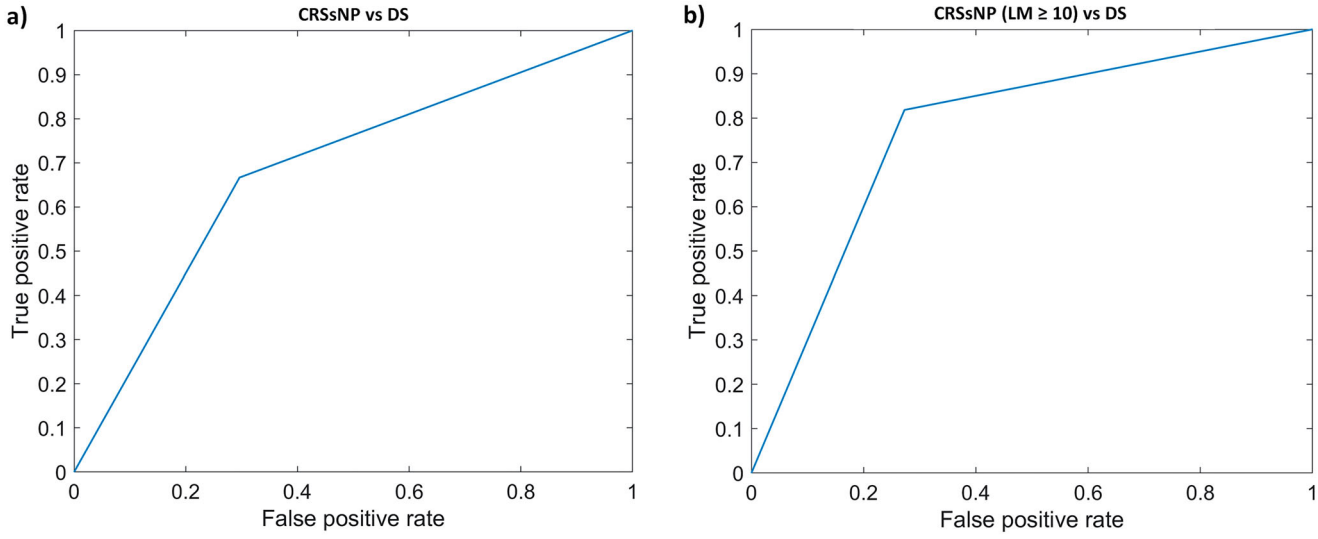

Figure 4. Receiver operating characteristic curves for the classification of CRSsNP and DS; a) for all patients and b) for patients with LM-score of at least 10. CRSsNP: chronic rhinosinusitis without nasal polyps; DS: deviated septum; LM: Lund–Mackay.

CRSsNP vs. DS

After row-normalization and 10-fold cross-validation, the accuracy of the DMS to distinguish CRSsNP from DS patients was 69% (CI 55–79%). Sensitivity and specificity were 67% (48–81%) and 70% (52–84%), respectively. The confusion matrix is presented in Table 2 and the receiver operating characteristics (ROC) curves in Figure 4. The archetype spectra for CRSsNP and DS are shown in Figure 5 and visual comparison of these reveal differences, especially with negative ions. Furthermore, the differences are visible with Bonferroni-corrected statistical differences in the spectra (Figure 6).

In subgroup analysis between CRSsNP patients with LM score $\geq$ 10 ($n = 11$) and randomly chosen DS patients ($n = 11$), the accuracy, sensitivity, and specificity were 82% (52–95%), 82% (52–95%), and 82% (52–95%), respectively.

Male vs. female

As there were statistical differences between males and females in the groups ($p < .05$), we performed a classification between genders. When comparing the samples from men ($n = 35$, labeled as negatives) and females ($n = 19$, labeled as positives), the DMS had an accuracy of 46%, a sensitivity of 26% (5/19), and a specificity of 57% (20/35), showing that classification is not biased due to gender.

Discussion

Our results show that by analyzing aspirated nasal air, DMS can distinguish CRSsNP with a sensitivity of 67% and a specificity of 70%. Moreover, the classification accuracy increases to 82% when a subgroup with more severe inflammatory disease is compared to controls. These findings are suggestive of a distinct VOC profile being associated with CRSsNP.

The previous literature on the eNose in a CRS context is heterogenous. Mohamed et al. examined five CRS patients and five controls. In their study, the eNose developed for research purposes had an accuracy of 60% after leave-one-out cross validation [6]. Thaler and Hanson performed a case-control study and examined rhinosinusitis patients and sampled breath air exhaled through the nose with a modified nasal continuous positive airway pressure (CPAP) mask. After leave-one-out cross validation, the eNose had an accuracy of 72%. However, in their study, most of the patients had acute exacerbation of CRS [7], and the acute infection could have affected the VOC profile. A more recent study by Broza et al. employed an array of

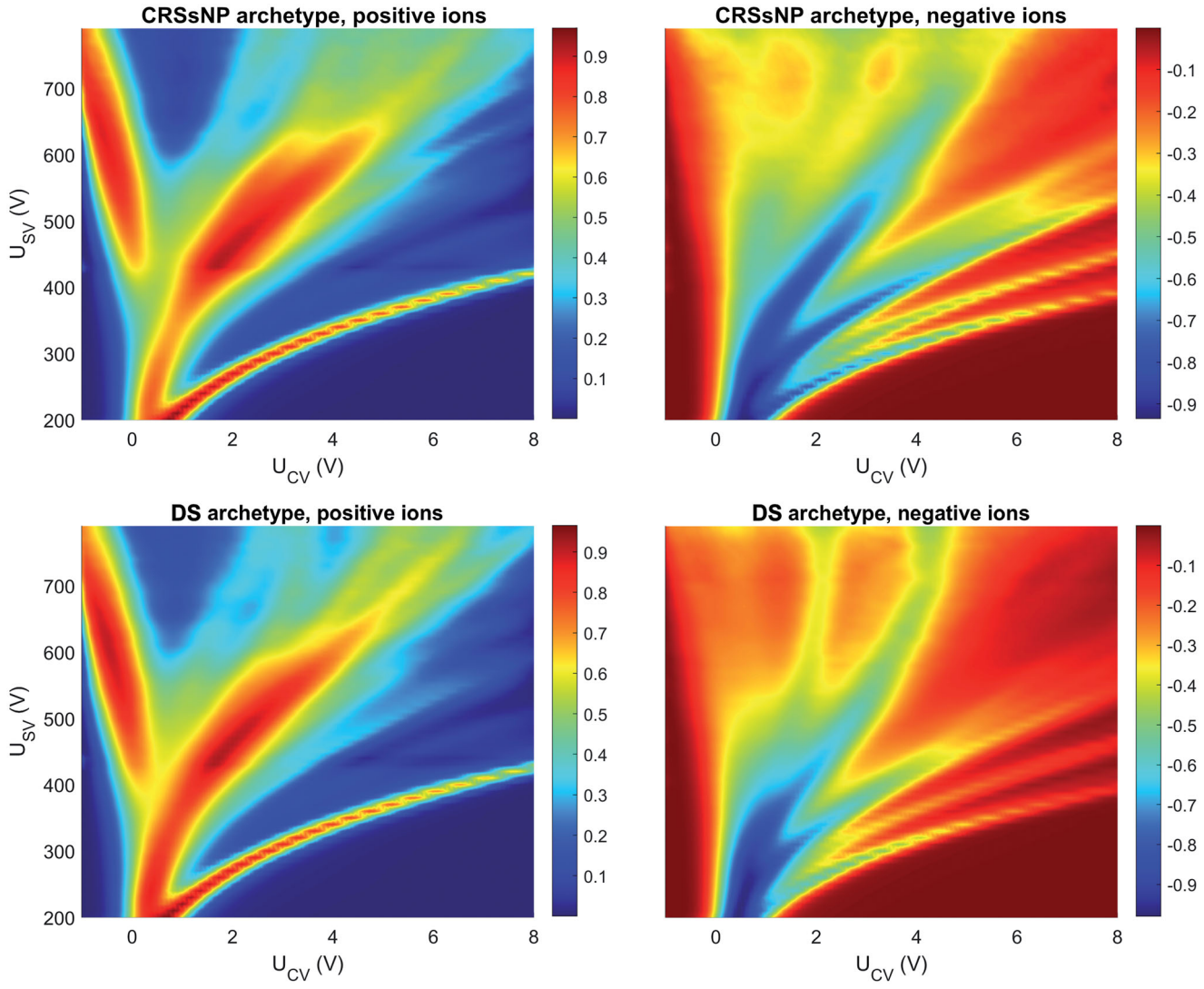

Figure 5. The row-wise normalized archetype spectra for chronic rhinosinusitis without nasal polyps (CRSsNP) and deviated septum (DS). U_{SV}: separation voltage; U_{CV}: compensation voltage; V: volt.

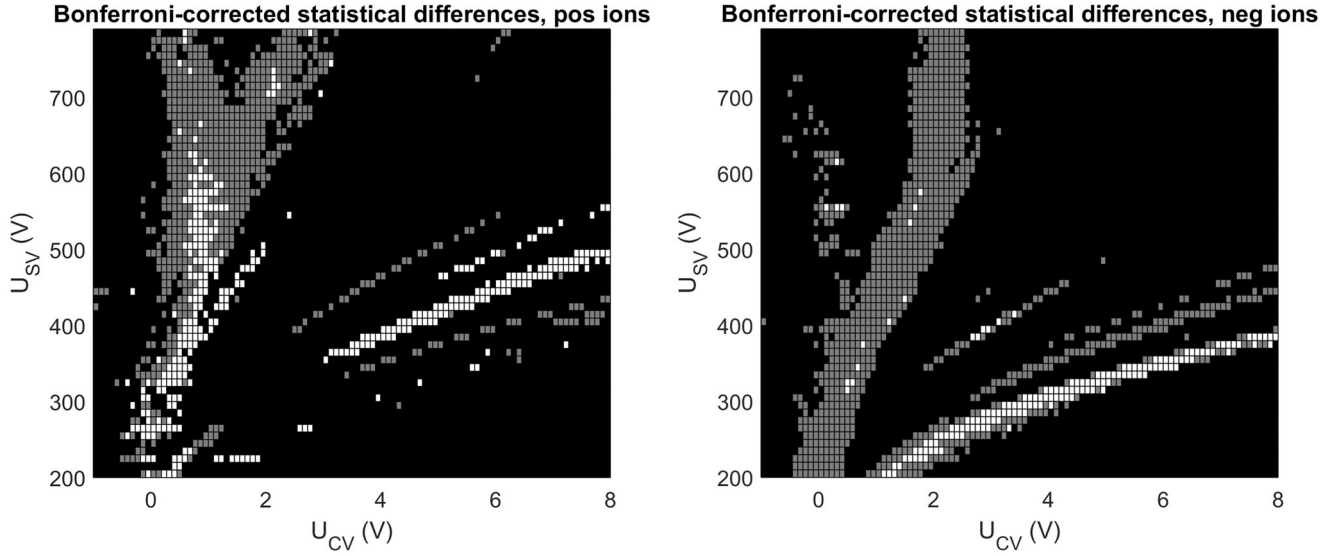

Figure 6. Features with Bonferroni-corrected statistical differences between the classes highlighted with grey for the complete dataset (54 patients) and with white for the subset of patients with Lund–Mackay score of more than 10.

nanomaterials-based sensors to examine exhaled breath through the mouth from CRS patients with polyps ($n = 24$) and CRSsNP ($n = 17$), and healthy controls ($n = 30$). After external validation, patients with CRSsNP were distinguished from healthy controls with a sensitivity of 80% and a specificity of 89% [8].

In all the above studies [6–8], patients with CRS were compared to healthy volunteers, which might have overestimated the diagnostic accuracy. Therefore, in this study, we aimed to distinguish two groups of patients with similar symptoms but with different etiology. In our control group, patients were symptomatic due to anatomical factors rather than inflammatory ones, although DS may predispose to chronic mucosal inflammation [13]. Though unproven, this may alter the measurement signature of the DMS and influence the accuracy. However, as the patients with DS did not undergo CT examination, some of the patients could have had mucosal changes in the paranasal sinuses, which may have also affected the DMS analysis. In addition, the exclusion of nasal polyps in the control group was conducted by anterior rhinoscopy which can, in some cases, result in false negative findings. Other paranasal diseases could also be confounding factors.

Our subgroup analysis revealed that patients with LM scores of 10 or more were more effectively distinguished from DS patients, which may have been due to a more severe inflammatory disease leading to a more prominent VOC profile. The sample size, however, was small and limits the drawing of any further conclusions. Furthermore, the results are limited to only CRSsNP. CRS has different endotypes and phenotypes and the signal patterns of the eNose could differ between them.

Although most eNose studies sample exhaled breath [4], few concentrate on nasal air. In this study, we collected nasal air using a similar method to the one validated for the measurement of nasal NO [12]. The method minimizes the confusing effects in the collected sample for evaluating rhinologic diseases with DMS. Previous studies have shown that exhaled nasal air contains less ammonia, ethanol, and hydrogen cyanide than breath exhaled through the mouth [14]. These compounds could therefore serve as confounding factors, since ion mobility spectrometry is sensitive to them [15,16]. Although collecting exhaled breath is simpler than collecting aspirated air through the nose, VOCs differ in terms of expiratory flow rate, breath hold, and the portion of exhaled breath analyzed [17]. These factors do not, however, affect aspirated nasal air, although targeted airflow during aspiration, such as in the measurements of nasal NO, would be preferable [12].

The comparison of room air samples to nasal air samples was distinguishable (accuracy of 94%) and shows that the measurement protocol works and day-to-day variation or baseline drift of the DMS do not exist to a significant degree. However, nasal air samples were not as well discriminated between patient groups, as the accuracy was 69%. Still, Bonferroni corrected statistical differences reveal that there were differences between patients with CRSsNP and patients with DS.

Patient-related factors can have an impact on breath sampling. For example, age, gender, and smoking, can interfere with the measurement signature of the samples, but it is unclear which of these factors should be adjusted in breath analysis [8,18]. In this study, we excluded some of the potential confounding factors, such as smoking. The groups were similar regarding age and BMI. Furthermore, our analysis showed that the classification was not based on gender. The differences in SNOT-22 scores were not statistically significant, but patients with CRSsNP had higher scores (the median values 38 *vs.* 29). Therefore, the severity of symptoms was not identical even though falling into the category of moderate disease in both groups [19]. Although higher LM scores improved classification accuracy in this study, they do not correlate with SNOT-22 scores [20]. Therefore, the impact of symptom severity on VOC profiles between groups is unclear. Furthermore, it remains unknown whether there are specific symptoms that affect the VOC profile in the spectra of the dispersion plots. Further studies are required to evaluate which covariates and symptoms can affect the VOC patterns.

In addition, the limitations of the data analysis need to be addressed. Even though cross-validation was used in this study to alleviate overfitting, the generalizability of the results could have been improved by using a completely independent set of patients for validation of the model. Furthermore, the sample size is limited, as demonstrated by the wide CI, and reduces the power of the study. Therefore, the results should only be interpreted as preliminary.

The potential use of a breathomics-based approach in addition to the instruments currently used to identify CRS is intriguing. However, it cannot replace clinical examination, such as observing intranasal findings. As phenotyping asthma from exhaled breath is already possible [5], the same could perhaps be done for CRS phenotyping by analyzing nasal air. At present, however, eNose technology is not ready for use in the diagnostics of CRS. Therefore, to evaluate the ability of DMS or other eNoses to diagnose CRS further, a larger study containing a control group of patients who have symptoms positive for CRS, according to established criteria, but negative CT findings should be undertaken. This would lead to a diverse etiology of symptoms, such as allergic and non-allergic rhinitis, DS, and hypertrophy of the inferior turbinates. These etiologies could have an impact on the nasal air profile and would require a larger number of samples to build a trustworthy classifier. Furthermore, patients with different endotypes and phenotypes of CRS should be evaluated as their VOC profile could differ from each other. Preliminary findings show that CRSsNP was distinguished from CRS patients with polyps with an accuracy of 67% [8]. In addition, the impact of disease severity based on symptoms and objective findings to the VOC profile should be further evaluated.

Conclusion

The results of this feasibility study demonstrate that CRSsNP can potentially be differentiated from patients with

similar nasal symptoms by analyzing aspirated nasal air using an eNose based on DMS. Further research is warranted to evaluate the ability of this novel method in the differential diagnostics of CRS.

Acknowledgments

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Disclosure statement

Anton Kontunen, Niku Oksala, and Antti Roine are shareholders in Olfactomics Ltd, which is about to commercialize proprietary technology for the detection of diseases using ion mobility spectrometry. The remaining authors have no conflict of interest to declare.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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