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Nasal fractional exhaled nitric oxide analysis with a novel hand-held device*

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SUMMARY

Aim: *To assess the performance of a novel hand-held nitric oxide (NO) analyzer in the measurement of nasal fractional exhaled NO (FE_{NO})*

Methods: *In ten healthy subjects (controls) and ten patients with chronic rhinosinusitis (CRS), oral and nasal FENO were obtained with the NIOX MINO® Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden) on two consecutive days, complying with current standards.*

Results: *Intraclass correlation coefficient (ICC) of oral FENO was 0.91 and of nasal FE_{NO} 0.79. In controls, mean (± SD) nasal FENO (40.3 ± 23.6 ppb) was higher than oral FE_{NO} (15.6 ± 2.7 ppb; p = 0.005). In CRS patients, mean oral FENO (23.9 ± 12.2 ppb) was higher than in controls (15.6 ± 2.7 ppb; p = 0.01). CRS patients with nasal polyps had lower nasal FE_{NO} levels (19.7 ± 5.9) than healthy controls (40.3 ± 23.6 ppb; p = 0.01).*

Conclusions: *The novel hand-held NO analyzer was found suitable for nasal FE_{NO} measurements. It may be useful in differentiating hyperplasic eosinophil rhinosinusitis from chronic unspecific rhinosinusitis. Moreover, nasal FE_{NO} may be used to monitor the clinical course of CRS with polyps.*

Key words: diagnosis, nasal polyps, nitric oxide, respiratory function tests, rhinosinusitis

INTRODUCTION

Nitric oxide (NO) is a biologic messenger produced by mammalian cells serving various functions including regulation of blood flow, platelet function, immunity, and neurotransmission. Measurements of orally fractional exhaled NO (FE_{NO}) allows the monitoring of airway inflammation in the lower airways. In patients with lower airway inflammation, particularly of the eosinophilic type, oral FE_{NO} is higher than in healthy controls. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) recently recommended a standardized procedure for online measurement of oral FE_{NO} [1].

Two major modes to assess upper airway NO are currently recommended [1]. For nasal aspiration/insufflation measurements, referred to as *nasal NO*, flow through the nasal cavities in series is achieved by aspirating or insufflating air with a target airflow rate of 0.25 l/min (~5 ml/s) to 3 l/min (50 ml/s) via one nostril, while the velum is closed during breath hold, so that air circulates around the posterior nasal septum. Aspiration/insufflation flows of approximately 5 ml/s are most frequently reported. During breath hold, an intranasal NO plateau indicating steady state conditions is then reached after approximately 20 s [2]. *Nasal NO* results from nasal mucosal NO exchange with aspirated or insufflated air free of endogenous NO under steady state low flow conditions. For *nasal fractional exhaled NO (nasal FE_{NO})*, the subject exhales nasally through a tight facemask with a fixed flow similar to oral FE_{NO}. Nasal FE_{NO} measurements differ fundamentally from nasal NO measurements. Nasal FE_{NO} represents the fraction of NO, which the nasal cavities in parallel add to exhaled, endogenous NO-contaminated air passing through the nose with a high flow of 50 ml/s during the last 3 seconds of a 10 second exhalation manoeuvre. In this way the oral cavity, which makes a significant contribution to oral FE_{NO} [3,4], is bypassed. An advantage with nasal FE_{NO} measurements is that exhalation can be performed at the flow recommended for orally exhaled NO, which facilitates comparisons between upper and lower airway NO output [1]. However, due to the short mucosal contact time and the high volume of bypassing air, nasal FE_{NO} levels are lower and possibly more variable than nasal NO levels. Silkoff and co-authors compared various methods of assessing nasal NO in healthy volunteers and found nasal NO of up to 1000 ppb employing nasal aspiration measurements and of approximately 50 ppb with nasal FE_{NO} [5].

The results of upper and lower airway NO measurements differ in various respects. Nasal NO levels are considerably higher than lower airway levels [3,4]. In contrast to the lower airways,

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nasal NO levels in patients with upper airway inflammation are rather decreased than increased when compared with healthy controls [6-8]. Particularly low nasal NO levels have been observed in patients with immotile cilia syndrome [9]. For both upper and lower online NO measurements chemiluminescence NO analysers are the current standard equipment. They are fast responding and highly sensitive, but also rather bulky and expensive. Recently a new hand-held NO analyzer has been introduced which works with an NO detecting electrochemical sensor [10]. Comparing this with a standard chemiluminescence device, acceptable accuracy, test-retest reliability, and handling properties have been demonstrated [11]. The hand-held NO analyzer is designed for oral FE_{NO} measurements, but can be adapted to nasal FENO measurements. In this explorative trial, the applicability and test-retest reliability of this novel hand-held NO monitor to measure nasal FE_{NO} was assessed in patients with CRS and healthy volunteers.

MATERIALS AND METHODS

Study subjects

Between May 2006 and July 2006, patients referred to the Department of Otorhinolaryngology & Head and Neck Surgery of the University Hospital of Ulm for treatment of CRS were screened. Male and female patients aged 18 years or older with CRS with and without nasal polyps according to the European Academy of Allergology and Clinical Immunology (EAACI) guidelines were eligible [12]. Exclusion criteria were steroid dependent asthma, acute sinusitis exacerbations or a common cold within the last 4 weeks, use of oral antibiotics, systemic, inhaled or nasal steroids, or nasal decongestants within four weeks prior to the investigation. Healthy controls were recruited by an announcement on the ad board in the hospital cafeteria. Volunteers aged 18 years or older without chronic nasal disease or acute nasal disease within the last four weeks were eligible. In all participants, self-reported asthma and smoking habits were recorded. Skin prick tests to inhalant allergens common in Central Europe were performed according to the EAACI guidelines [13]. Informed consent was obtained from all study participants or their parents, respectively. IRB approval was obtained in a shortened procedure.

Measurements of nitric oxide

Study participants had to refrain from eating and drinking at least for 1 hour before measurements. Online single breath oral FE^{NO} and nasal FE^{NO} measurements were performed using the NIOX MINO® Airway Inflammation Monitor (Aerocrine AB, Solna, Sweden). The subjects first exhaled through the mouth to residual lung volume and then inhaled through the adapter of the analyzer to total lung capacity. Then the subjects exhaled 10 s against an expiratory resistance of 5-20 cm H_2O with a constant flow of 50 ml/s, either through the mouthpiece of the analyzer or through a tightly fitting nasal mask (Respironics, Herrsching, Germany). The nasal mask was connected to the mouthpiece inlet of the NO-monitor by an abacterial/viral filter (Hygrobac "S", Mallinckrodt DAR, Italy) as used in breathing circuits. The patient was able to adapt expiratory flow rates by viewing a display showing flow rate located on the posterior surface of the device through a mirror. Oral and nasal measurements were repeated the following day at the same time.

Data analysis

Test-retest reliability was assessed with intraclass correlation coefficient (ICC). For data description, mean, standard deviation and 95% confidence intervals were calculated. FE_{NO} were compared with the Mann-Whitney-U-test or Wilcoxon paired samples test. Type I error was set to 0.05 (two sided). Calculations were performed with SYSTAT 10.2 (Systat Software, Inc., San Jose, CA, USA).

RESULTS

Study participants

In total, 10 patients with CRS and 10 healthy subjects without nose-related diseases were included. The major reason for exclusion of screened CRS patients from the trial was current use of nasal steroids. Clinical characteristics of the study participants are detailed in the table. Coincidentally, a 6-year-old patient with Kartagener's syndrome visited the clinic and was

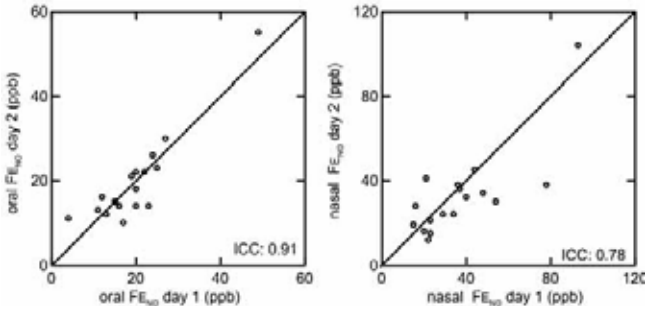

Figure 1. Test-retest reliability of oral (left panel) and nasal (right panel) fractional exhaled nitric oxide (FE_{NO}) levels measured on two consecutive days with a novel hand-held NO analyzer. (ICC: intraclass correlation coefficient, ppb: part per billion).

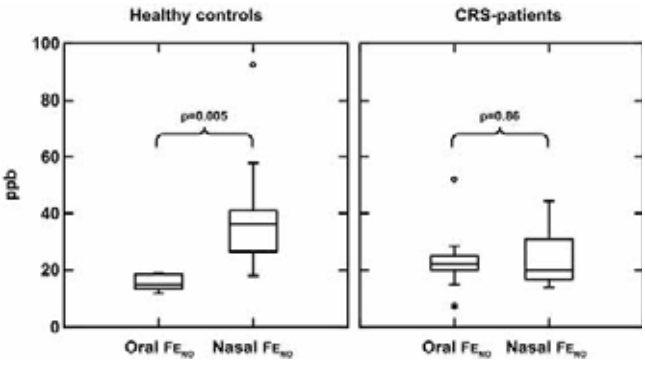

Figure 2. Comparison of oral and nasal FE_{NO} in healthy controls (n=10) and patients with chronic rhinosinusitis (CRS; n=9).

also included. Oral and nasal FE_{NO} values are reported but the data were excluded from further evaluations, reducing the number of included CRS patients to 9.

Test-retest reliability

Oral FE_{NO} was measured in 19 study participants on two consecutive days with identical test parameters (Figure 1). The test-retest reliability was assessed with intraclass correlation coefficient (ICC). The ICC for oral FENO was 0.91 (95% CI 0.79-0.96). The ICC for nasal NO in 17 participants was 0.78 (0.49-0.91). Two participants were not able to comply with the FE_{NO} test requirements on day 2 due to nasal obstruction.

Table 1. Clinical characteristics of patients with chronic rhinosinusitis (CRS) and controls.

	CRS	Control
N =	10 [a)]	10
Age (mean ± SD)	42 ± 14	38 ± 21
Male	7	3
Nasal polyps	6	0
Asthma	5	0
Atopy	2	0
Current smoker	3	0

[a)] including 1 patient with Kartagener's syndrome

Comparison of oral and nasal FE_{NO} within subjects

For the description of oral and nasal FE_{NO} results, the averages of the two measurements obtained on consecutive days from each subject were used (Figure 2). In healthy subjects, mean (± SD) nasal FE_{NO} (40.3 ± 23.6 ppb) were higher than oral FE_{NO} (15.6 ± 2.7 ppb; $p = 0.005$). In patients with CRS, nasal FE_{NO} (25.2 ± 11.3 ppb) and oral FE_{NO} (23.9 ± 12.2 ppb) did not differ significantly ($p = 0.86$). Oral FE_{NO} values and nasal NO levels were not correlated, in either control subjects (ICC 0.27; 95% CI - 0.74 to 0.39) or in CRS-patients (ICC 0.06; 95%CI - 0.54 to 0.64).

Oral and nasal FE_{NO} in healthy individuals and CRS patients

Average oral FE_{NO} was higher in CRS patients (23.9 ± 12.2 ppb) than in controls 15.6 ± 2.7 ppb; $p = 0.01$). To identify asthma as a possible confounder, patients were sub-grouped in CRS-patients with asthma and without asthma (Figure 3). Oral FE_{NO} did not differ relevantly between these subgroups. Nasal FE_{NO} levels were lower in CRS patients (25.2 ± 11.3 ppb) than in controls (40.3 ± 23.6ppb), however this difference was not significant ($p = 0.08$). To identify possible differences in CRS subgroups, CRS-patients were categorized in CRS-patients with and without nasal polyps (Figure 3). Nasal FE_{NO} levels in CRS-patients without polyps (36.2 ± 12.3 ppb) were similar to controls ($p = 0.67$), whereas in CRS-patients with nasal polyps it was significantly lower (19.7 ± 5.9; $p = 0.01$). In the one patient with Kartagener's syndrome, oral FE_{NO} was 12.0 ppb and nasal FE_{NO} was 7.0 ppb.

DISCUSSION

In this preliminary trial, oral and nasal FE_{NO} measurements employing a novel hand-held NO analyzer were performed in 20 subjects on two consecutive days. Ten healthy subjects without nose-related diseases and ten patients with CRS according to EAACI criteria were included. The main results were a) excellent test-retest reliability of oral and b) good test-retest reliability of nasal FE_{NO} measurements, c) higher nasal than oral FE_{NO} levels in healthy participants, d) higher oral FE_{NO} levels in CRS patients, and e) lower nasal FE_{NO} levels in CRS patients with nasal polyps when compared with healthy controls.

Study participants

In addition to the presence of CRS, the two included groups differed in several aspects. On average CRS patients were 4 years older than controls and there were more males among them. It is not assumed, however, that age and sex differences biased the results of this trial [(1)]. Kartagener's syndrome was present in one 6-year-old patient, and is known to be associated with particularly low oral and nasal FE_{NO} levels [(9)]. In fact, FE_{NO} levels were below the lower 95% confidence limits of the study population. In 5 CRS patients, bronchial asthma not requiring inhaled or systemic steroids might have confounded the results. Asthma was associated with lower nasal FE_{NO} ($p = 0.04$; data not shown), while oral FE_{NO} was not affected (Figure 3). All asthma patients suffered from nasal polyps and the lower nasal FE_{NO} levels are attributed to the presence of polyps in these patients. However, due to collinearity, no conclusive interpretation is achievable. Atopy (positive skin prick test to common inhalant allergens) was diagnosed in 2 patients and did not yield relevant differences. Three CRS-patients were current smokers and had lower oral FE_{NO} levels ($p = 0.04$), while nasal NO levels were not altered ($p = 0.36$, data not shown). This is consistent with previous studies [(1)] and may lead to underestimation of increased oral FE_{NO} levels in CRS patients in this trial.

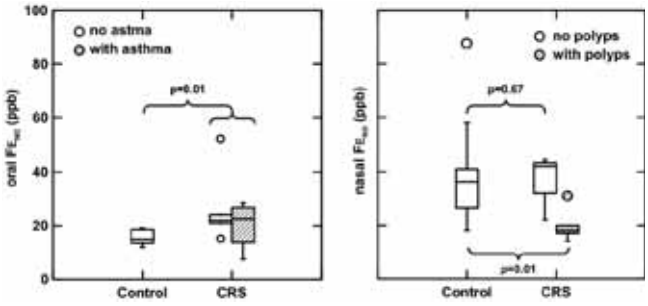

Figure 3. Oral (left panel) and nasal (right panel) FE_{NO} in healthy controls (n=10) and patients with CRS (n=9), grouped by presence of asthma (left panel) or nasal polyps (right panel).

Determination of oral and nasal FE_{NO} with a hand-held NO analyzer

The NIOX MINO® airway inflammation monitor tested in this pilot trial is designed for oral FE_{NO} [1]. NO free air is inhaled through the device rendering ambient air NO measurements dispensable. Oral FE_{NO} levels obtained with the hand-held analyzer were consistent with results obtained with a standard chemiluminescence analyzer [10,11]. Employing standard breathing circuit filters, a tightly fitting nasal mask could be adapted to the analyzer enabling nasal FE_{NO} measurements. The employed filter was compared with the standard filter provided by the manufacturer and did not bias NO measurements (data not shown). For nasal FE_{NO} measurements, the subject exhaled through the nasal mask, otherwise the procedure was identical to the assessment oral FE_{NO}.

Test-retest reliability

Consistent with previous studies [11], an excellent reproducibility of oral FE_{NO} measurements with an ICC of 0.91 was found. For nasal FE_{NO} an ICC of 0.78 indicated good reproducibility. However, due to nasal obstruction, two participants were not able to perform a second measurement. The fact that severe nasal obstruction may render nasal FE_{NO} measurements impracticable might be a relevant shortcoming of the method. It is assumed that lower reproducibility in nasal FE_{NO} measurements is mainly due to the variable physiologic state of the nasal cavities [14]. Moreover, the accuracy of the device decreases with higher NO levels as obtained with nasal FE_{NO} measurements [11].

Comparison of oral and nasal FE_{NO} within subjects

In 10 healthy controls, oral FE_{NO} ranged from 12 to 19 ppb, consistent with data obtained in healthy individuals in recent studies [15,16]. Average nasal FE_{NO} levels were approximately 2.5 times higher (40.3 ppb) ranging between 18 ppb and 98 ppb. Only few data on nasal FE_{NO} in healthy individuals under experimental conditions similar to those used in this trial have been reported. Silkoff and co-authors found a mean nasal FE_{NO} of 50.2 ppb at a constant expiratory flow of 100 ml/s [5]. Palm and co-authors reported nasal FE_{NO} levels ranging between 10 and 37 ppb at a constant expiratory flow of ~3 ml/s [3]. Sanders and co-authors reported nasal FE_{NO} levels ranging between 41 and 349 ppb at a constant expiratory flow of 27 ml/s [17]. Tornberg and co-authors reported nasal FE_{NO} levels of 59 ± 9 ppb in patients tracheotomized due to neurological conditions at a constant flow of 50 ml/s [4]. In conclusion, nasal FE_{NO} levels obtained in healthy subjects with the hand-held analyzer are plausible and consistent with previous reports. As previously reported [3], oral and nasal FE_{NO} levels did not correlate in either the whole study population or in healthy subjects or in CRS-patients only.

Oral and nasal FE_{NO} in healthy individuals and CRS patients

Oral FE_{NO} was higher in CRS patients than in healthy controls. This effect was observed in CRS-patients with and without asthma (Figure 3). Increased oral FENO levels in patients with upper airway inflammation have been reported previously in experimentally induced viral rhinitis [18], in patients with allergic rhinitis [19], and in patients with nasal polyps [20,21]. Possible explanations for this phenomenon include induction of bronchial NO synthase and inflammatory cell recruitment into the lower airways by upper airway inflammation.

The fact that no significant differences between controls and patients with sinusitis were found might be attributed to the relatively low number of patients included. This is especially relevant in terms of the subgroup analysis where patients with asthma and nasal polyposis were analysed separetely. Nasal FE_{NO} levels were lower in CRS patients with polyps than in healthy controls (Figure 3). This observation is consistent with previous reports [6,8,22]. Decreased nasal NO levels have also been reported in acute bacterial rhinosinusitis [7,23,24]. The reasons for decreased nasal NO in rhinosinusitis are not clear, especially since increased inducible nitric oxide synthase (iNOS/NOS2) activity has been observed in CRS [25-27]. It has been assumed that blockage of sinus ostia in rhinosinusitis reduces NO transfer from the paranasal sinuses [22], but low NO concentrations in rhinosinusitis have also been found within the sinus itself in experimental animals [28] and in patients with nosocomial maxillary sinusitis [7,24]. An alternative hypothesis is NO consumption by reactive oxygen species derived from inflammatory cells [29,30]. NO and O_2- rapidly react together leading to their reciprocal inactivation and eventually to peroxynitrite (ONO_2-), which can elicit protein tyrosine nitration. Moreover, inflammatory cell-derived peroxidases can catalyze protein tyrosine nitration, hereby reducing free NO [31]. Nitrotyrosines have been demonstrated in nasal polyp tissues, supporting this hypothesis [25-27,32,33]. However, reduced upper airway NO in rhinosinusitis may just reflect inflammatory cell dysfunction interfering with cNOS catalyzed constitutive epithelial NO production [33].

CONCLUSION

A novel hand-held NO analyzer was found suitable for nasal FE_{NO} measurements. It may be useful in the diagnosis of CRS, particularly in differentiating hyperplasic eosinophil subtype from chronic unspecific rhinosinusitis. It might moreover be used to monitor the course of CRS with polyps, where increasing oral FE_{NO} and decreasing nasal FE_{NO} may indicate deterioration and the need for therapeutic intervention. However, in the meanwhile, there is a need for well-conducted prospective trials confirming the preliminary results obtained in this pilot trial.

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