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In healthy subjects nasal nitric oxide does not correlate with olfactory sensitivity, trigeminal sensitivity, and nasal airflow

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Abstract

Objective: The aim of the study was to determine the relationship between nasal nitric oxide (nNO) and olfactory sensitivity, trigeminal sensitivity and nasal airflow in healthy subjects.

Study design: This is a correlational study.

Setting: This study was carried out in a tertiary referral centre.

Participants: Forty healthy participants were recruited.

Main outcome measures: nNO was measured using a chemiluminescence analyser (Niox Vero®, Circassia AB, Uppsala, Sweden), olfactory sensitivity was determined using phenyl ethyl alcohol odour thresholds using the 'Sniffin' Sticks', trigeminal sensitivity was assessed with carbon dioxide delivered by an automated device, and nasal airflow was measured using the peak nasal inspiratory flow (PNIF).

Results: The median nNO was 518 ppb (IQR =333) in the right nostril, and it was 567 ppb (IQR = 314) in the left nostril. The median odour threshold was 7.1 (IQR = 4.4), the median CO_2 threshold was 919 ms (IQR = 1297) and the mean PNIF was 108 L/min (SEM = 4.9). nNO did not correlate significantly with odour threshold, CO_2 threshold or PNIF (Spearman's $|\rho| < 0.15$, $p > .18$).

Conclusion: In healthy subjects, nNO does not appear to be associated with olfactory sensitivity, trigeminal sensitivity and PNIF.

KEYWORDS
nasal airflow, nitric oxide, olfaction, trigeminal sensitivity

1 | INTRODUCTION

Nitric oxide (NO) is a molecule implicated in numerous biological processes, including vasodilation, haemostasis, central and peripheral neurotransmission, and inflammation.[1] Airway NO has received growing attention in the last decades. Since its detection in exhaled air in 1991, exhaled NO (eNO) has been abundantly studied, now being formally recommended as a tool for monitoring asthma.[2,3] In studies on eNO, high concentrations of NO in upper airway were reported.[4] Mainly produced in the nasal and sinus mucosa, it improves ventilation perfusion matching after being inhaled and contributes to sinus sterility through antimicrobial effects and increased ciliary motility.[5–7]

Nasal NO (nNO) variations in nasal inflammatory diseases are an active research field. Allergic rhinitis (AR) patients have been shown to present higher nNO levels.[8–10] Chronic rhinosinusitis (CRS) patients show lower nNO levels,[11,12] especially if they present with higher Lund–Mackay scores[13] or polyposis.[14] Nasal NO levels are also low in patients with cystic fibrosis[15] and primary ciliary dyskinesia.[16]

NO is proposed as a surrogate marker in inflammatory airway diseases, and olfactory dysfunction in those conditions is well-established.[17] Given the current interest in NO and nasal disease, one must also consider its behaviour in relation to overall nasal function in healthy subjects. NO has been suggested to play a role in olfactory epithelium neurotransmission and regeneration.[18] Another important yet less explored part of nasal function relates to the trigeminal system, even though it mediates the important sensation of airflow[19] and plays a major role in the pathophysiology of AR. There, inflammation leads to enhanced responsiveness of trigeminal afferents, which, following chemical, mechanical, or thermal stimulation, can initiate neural reflexes that result in mucus secretion, vasodilatation, itching and sneezing.[20] To our knowledge, there are no studies on the relation between nNO and trigeminal sensitivity. Hence, our aim in this study was to determine whether nNO correlates with overall nasal function, determined by olfactory sensitivity, trigeminal sensitivity and nasal airflow, in healthy subjects.

Keypoints

- Nasal nitric oxide (nNO) relates to inflammatory processes.
- Olfactory dysfunction correlates with nasal inflammation.
- We investigated the relation between nNO and chemosensory perception in 40 healthy subjects.
- In healthy subjects, nNO is not related to olfactory/trigeminal sensitivity.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

This correlational study was conducted in a tertiary referral centre, the Smell & Taste Clinic, Department of Otorhinolaryngology of the Technical University of Dresden, Germany.

2.2 | Ethical considerations

All participants gave their written informed consent, and all experiments were conducted according to the Declaration of Helsinki on biomedical research involving human subjects and were approved by the Ethics Committee at the University Clinic of the TU Dresden (EK406102018).

2.3 | Participants

All participants answered a questionnaire to assess their past medical history and to perform a symptom-based screening of active nasal conditions, which led to exclusion from this study in case any pathology was reported. We tested 40 healthy participants, 31 female and 9 male participants, with a median age of 27 years (IQR = 6.0).

2.4 | Main outcome measures

nNO was measured in a well-ventilated room with a NO concentration of less than 5 ppb. We used a chemiluminescence analyser, the Niox Vero® (Circassia AB, Uppsala, Sweden), with the adult nasal kit. Air was aspirated at a 5 ml/s sampling rate through an olive tightly adjusted to one nostril, with the contralateral one open. We used the tidal breathing sampling method by asking subjects to slowly breathe through their mouth for 30 s.[21] The alternative sampling method for this device requires the subject to exhale for 30 s steadily and continuously, which we found to be impractical for most people. Both nostrils were tested at random, and the mean value was used for further analysis. To test for reliability, a second nNO measurement was obtained in 25 subjects, 1–14 days after the first measurement.

Olfactory sensitivity was assessed by obtaining phenyl ethyl alcohol (PEA) odour thresholds using the 'Sniffin' Sticks'.[22] The threshold subtest was selected as it is more strongly related to olfactory function at the level of the olfactory epithelium than suprathreshold olfactory tests[23] (e.g., odour discrimination and odour identification) which depend to a higher degree on individual experience and higher cognitive processes.[22] In addition, in a younger population, odour thresholds exhibit a larger variance than suprathreshold odour identification. Because the present study was, at its core, a correlational study, we chose to use a measure with more granularity. The odour threshold test comprises sixteen triplets of pens, which consist of one pen with a PEA-soaked tampon and two solvent-filled pens. The highest concentration is of 4%, and it is progressively decreased by a factor of 2:1, over 16 concentrations. Following a vocal command, each pen is placed close to the blindfolded subject's nose, alternating between right and left nostrils, for approximately 3 s. In an alternative forced choice paradigm, the subject has to discriminate the one pen with PEA within each triplet. Starting at the lowest concentration, a staircase paradigm is followed using two subsequent correct answers or one incorrect answer as turning points, leading to a decrease or increase, respectively, in the tested concentration. This procedure is repeated seven times, and the olfactory threshold is determined as the average of the last four turning points. All measurements were performed in a well-ventilated room by the same investigator.

Trigeminal sensitivity was assessed using a previously developed method, which is based on the use of carbon dioxide (CO_2) and has been shown to be valid and reliable.[19] CO_2 is a trigeminal stimulant with negligible, if any, olfactory activation. The technique benefits from the fact that changing the duration of a stimulus with constant concentration provides effects similar to the change of stimulus concentration, at least within a certain time window.[19] Pure CO_2 was delivered through a bilateral nasal cannula, starting at 50 ms and increasing by steps of 50 ms, until the subject signalled the presence of a slightly tingling sensation in his/her nose by pushing a button attached to the device. After a positive response, the stimulus

duration was decreased by steps of 50 ms, until the subject stopped reacting. The CO_2 threshold is determined by a microcomputer in the device as the average of the last four turning points. This procedure was repeated three times, and the average of the three obtained thresholds was used.

Nasal airflow was measured using the peak nasal inspiratory flow (PNIF). PNIF is a reproducible objective airway measurement technique with good correlation with subjective nasal congestion.[16] PNIF was obtained with a flow monitor attached to a face mask. Subjects were instructed to sit upright, fully exhale, tightly seal the mask over their nose and mouth and inspire as hard and fast as they could, keeping a closed mouth. The procedure was repeated for three maximal inspirations, and the highest value was used. This method followed the published European recommendations.[16]

2.5 | Statistical analysis

Statistical analysis was performed using software SPSS, version 25.0 for Windows (SPSS Inc.). Non-normally distributed variables were expressed as median and interquartile range (IQR). Normally distributed variables were expressed as mean and standard error of mean (SEM). Differences between groups were examined using the Mann–Whitney U test. For correlation analyses, Spearman's coefficients were computed. The conservative alpha-level was set at 0.01.

3 | RESULTS

At the first measurement, the median nNO in the right nostril was 518.0 ppb (IQR = 333.0) and that in the left nostril was 566.5 ppb (IQR = 314.0). Twenty-five subjects (62.5%) were subjected to a second nNO measurement, with a mean interval between measurements of 6.1 (SEM = 0.8) days. At the second measurement, the median nNO in the right nostril was 455.0 ppb (IQR = 187.0) and in the left nostril it was 422.0 ppb (IQR = 218.0) (Table 1).

There was a strong correlation between nNO values obtained in the right and left nostrils, both at the first measurement (Spearman's $\rho = 0.84$, $p < .001$) (Figure 1A) and at the second one (Spearman's $\rho = 0.75$, $p < .001$). There was no significant sex-related difference in nNO values, both at the first measurement ($U = 93.0$, $p = .13$) and at the second one ($U = 59.0$, $p = .81$). There was no significant difference between nNO values obtained in the morning and in the afternoon, both at the first measurement ($U = 111.5$, $p = .23$) and at the second one ($U = 41.0$, $p = .33$). A median variation of 18.4% (IQR = 17.0%) was found in nNO levels obtained in the same subject at different time points, with a strong positive correlation between them (Spearman's $\rho = 0.75$, $p < .001$) (Figure 1B).

The median odour threshold was 7.1 (IQR =4.4), the median CO_2 threshold was 918.5 ms (IQR =1297.0) and the mean PNIF was 108.4 L/min (SEM = 4.9) (Table 1). nNO did not correlate with odour threshold (Spearman's $\rho = 0.08$, $p = .31$) (Figure 2A), CO_2 threshold (Spearman's $\rho = 0.08$, $p = .32$) (Figure 2B) or PNIF (Spearman's $\rho = -0.14$, $p = .19$) (Figure 2C).

TABLE 1 Obtained overall nasal function data

	Median	IQR
1nNO_Rn (ppb)	518.0	333.0
1nNO_Ln (ppb)	566.5	314.0
1nNO_Av (ppb)	545.0	252.8
2nNO_Rn (ppb)	455.0	187.0
2nNO_Ln (ppb)	422.0	218.0
2nNO_Av (ppb)	438.5	201.5
Odour threshold (dilution steps)	7.1	4.4
CO_2 threshold (ms)	918.5	1297.0
	Mean	SEM
PNIF (L/min)	108.4	4.

Abbreviations: 1nNO_Av, average nasal nitric oxide, first measurement; 1nNO_Ln, nasal nitric oxide, left nostril, first measurement; 1nNO_Rn, nasal nitric oxide, right nostril, first measurement; 2nNO_Av, average nasal nitric oxide, second measurement; 2nNO_Ln, nasal nitric oxide, left nostril, second measurement; 2nNO_Rn, nasal nitric oxide, right nostril, second measurement; CO_2, carbon dioxide; IQR, interquartile range; PNIF, peak nasal inspiratory flow; SEM, standard error of mean.

4 | DISCUSSION

The current results suggest that in healthy subjects, nNO does correlate neither with trigeminal and olfactory sensitivity nor with peak nasal inspiratory flow. Various authors have explored the relationship between nNO and different parameters of nasal function. Takeno et al. did not find any correlation between the nasal fractional exhaled NO and nasal resistance at 100 Pa, both in AR patients and in healthy controls,[10] which is in line with our results. Other authors reported a positive correlation between nNO, nasal resistance at 75 Pa and nasal symptom visual analogue scale scores, and a negative correlation between nNO and nasal volume within 0–7 cm from the anterior nares,[9] but these results were obtained in a heterogenous sample of AR patients and healthy subjects, and the reported correlations were weak. In terms of olfactory function, a study on patients with olfactory loss showed a positive correlation between nNO and olfactory discrimination and identification but not with olfactory thresholds.[17] A previous study also found a positive correlation between nNO and olfactory thresholds in CRS patients but not in healthy subjects.[11] A negative correlation between nNO and smell detection was found in a prospective study on persistent AR patients.[24] These results suggest that nasal inflammatory diseases may influence both nNO and olfaction, but a direct influence between these parameters may be absent, which is also in line with our results. We found no other studies exploring the relation of nNO and trigeminal sensitivity.

Studies on nNO face some limitations regarding the use and interpretation of nNO values as normative values are lacking and different devices and sampling methods are available.[9–11,17,24,25] We obtained median nNO values of 422.0 ppb (IQR 218 ppb) to 566.5 ppb (IQR 314 ppb). Although other authors have reported similar results in healthy subjects, with mean values of 313.4 ± 106.0 ppb,[13] 424.3 ± 63.4 ppb[17] and 685.9 ± 54.6 ppb,[11] a critical comparison

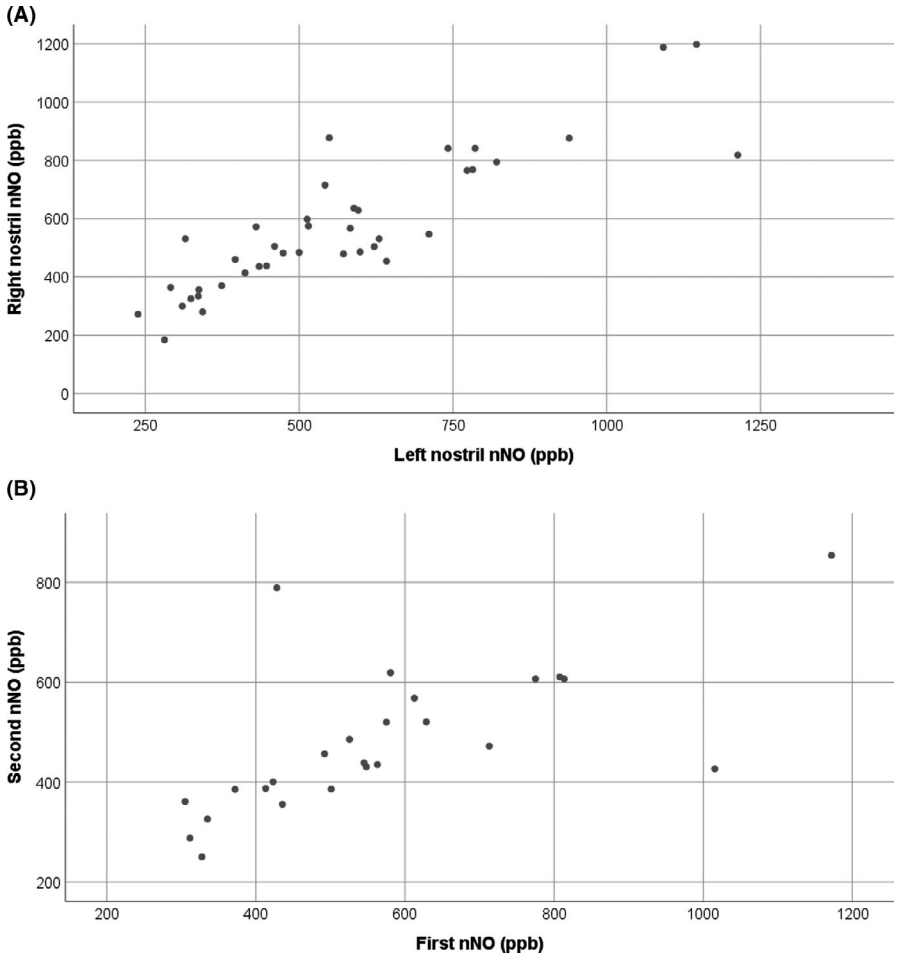

FIGURE 1 (A) Relationship between nNO at first measurement in the right and left nostrils (Spearman's $\rho = 0.84$, $p < .001$), (B) relationship between nNO at the first and second measurements (Spearman's $\rho = 0.75$, $p < .001$)

is needed as different devices and sampling methods were used. A study using the same sampling method and the same device we used obtained mean values of 534 ± 30 ppb in healthy subjects,[21] which overlies our results.

Three sampling methods are usually described: the breath-hold method, the oral exhalation against resistance method and the tidal breathing method. The tidal breathing method has the disadvantage of not providing velopharyngeal closure during sampling, which is recommended in the American Thoracic Society/European Respiratory Society guidelines.[26] Despite using the tidal breathing method, we obtained higher nNO values than those obtained by other authors using a sampling technique with oral exhalation against resistance.[8,13] Given that the result of sample contamination with lower airway air would be a decrease in the nNO values, we believe this did not affect our measurements. Moreover, the strong correlation found between nNO values in samples obtained from different nostrils and at different time points in the same subject suggests that this method is reliable and reproducible.

Regardless of its well-described constant production and important biological functions in healthy subjects, intraindividual variations of 20%–25% over time in nNO values have been described.[9,25] In fact, despite nNO levels obtained in different moments in the same subject highly correlated with our study, we also found a 18% variation, which may be meaningful in a clinical setting. Given its lack of correlation with overall nasal function and this intraindividual variation, nNO levels may have limited clinical importance at this moment. Currently, nNO is a validated screening tool for primary ciliary dyskinesia screening, where very low levels are found.[16] As mentioned before, inflammatory nasal diseases show variable nNO levels, and studies reproducing this protocol in patients with selected nasal conditions may further elucidate on the eventual relation between nNO and overall nasal function.

This study was limited by the limited age range of our participants. However, as previous studies suggested an age-related reduction on nNO, olfactory sensitivity and trigeminal sensitivity,[17,19,22] our participants' young age allowed us to explore the relationship between these parameters without any age-related interference, for example, changes in nasal autonomic innervation.[27] Nevertheless, future studies should engage participants with a wider age range, also aiming at determining potential effects of age in nNO and at establishing normative values. Another limitation of this study was the 75% female distribution of the participants. Female participants outperform men in olfactory tests, but this difference observed in very large samples is relatively small.[22,28] Trigeminal function is also higher in female subjects.[19] Sex-related differences in nNO are not entirely clear as different studies report conflicting results.[9] Despite these potential sex-related differences, one would expect that if a significant relationship between nNO, olfactory sensitivity and trigeminal sensitivity was to exist, it should be apparent both in

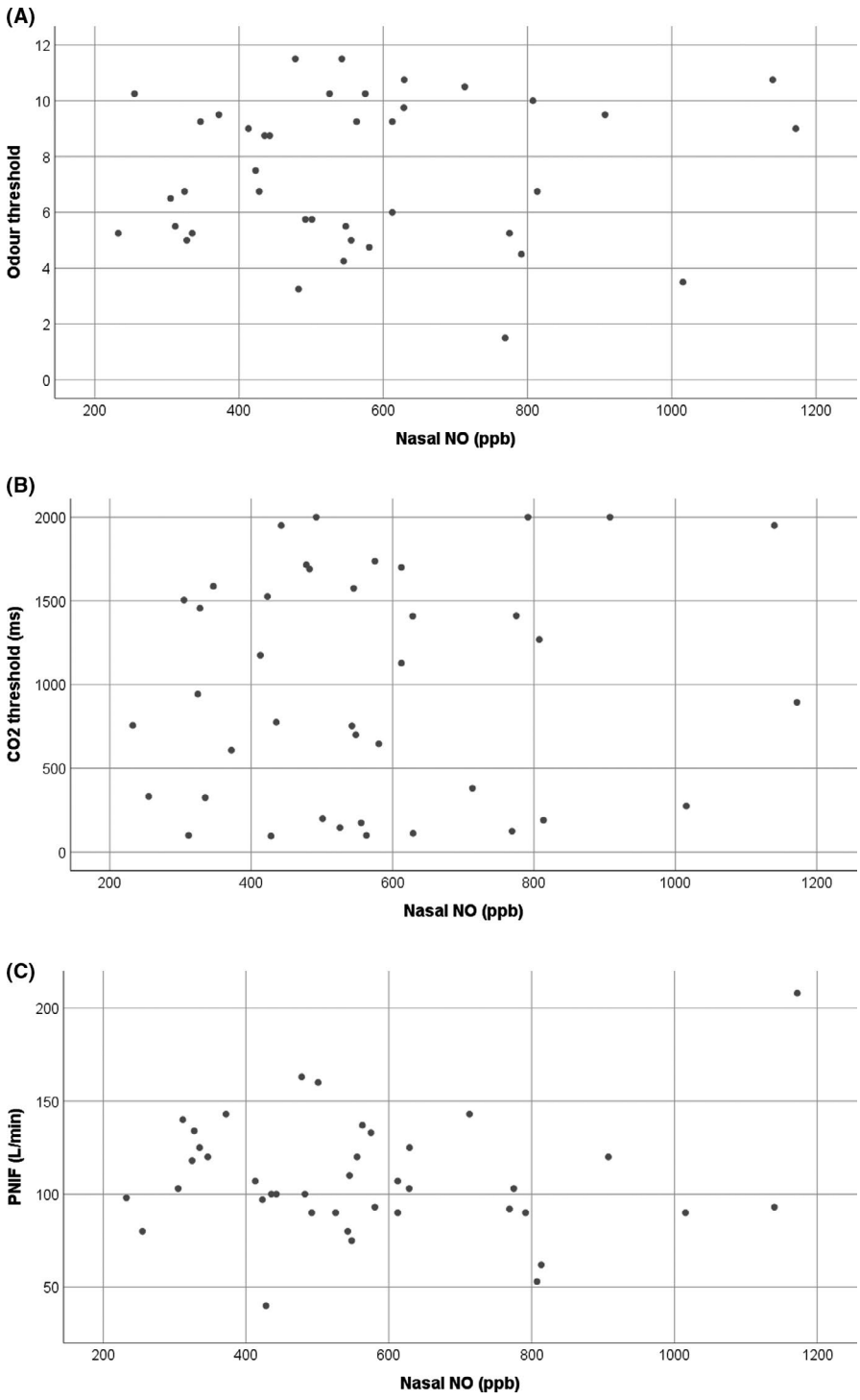

FIGURE 2 Relationship between nNO and (A) odour threshold (Spearman's $\rho = 0.08$, $p = .31$), (B) CO_2 threshold (Spearman's $\rho = 0.08$, $p = .32$) and (C) PNIF (Spearman's $\rho = -0.14$, $p = .19$)

male and female participants, and our results suggest the absence of that relationship. Nonetheless, further research with homogeneous samples for sex or with separate male and female groups is needed to confirm the present results.

In conclusion, our results did not show a correlation between nNO and different parameters of nasal function, namely, olfactory and trigeminal sensitivity and PNIF. nNO is an important nasal mediator and further research on its role in overall nasal function is needed, both in healthy subjects and patients with nasal disorders.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

AUTHOR CONTRIBUTIONS

TH and MM designed the work; MM and TD acquired and analysed the data; MM drafted the manuscript; all authors revised and

approved the final manuscript and agree to be accountable for all aspects of the work.

DATA AVAILABILITY STATEMENT

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

ETHICAL STATEMENT

All participants gave their written informed consent, and all experiments were conducted according to the Declaration of Helsinki on biomedical research involving human subjects and were approved by the Ethics Committee at the University Clinic of the TU Dresden (EK406102018).

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