

Nasal nitric oxide in relation to psychiatric status of patients with empty nose syndrome

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ABSTRACT

Background: Although cases of empty nose syndrome (ENS) are not very common, the suffering that ENS causes patient is immense and could be very difficult to imagine. Nasal nitric oxide (nNO) is an airway disease biomarker, and its levels increase after endoscopic sinus surgery. The trend of nNO levels in ENS before and after surgical treatment remains unknown. This study aimed to evaluate the role of nNO in ENS.

Methods: Patients with ENS who received surgical implantation and with chronic hypertrophic rhinitis (CHR) who underwent turbinoplasty and completed at least 1 year of follow-up were prospectively enrolled. nNO measurements and subjective assessments [SinoNasal Outcome Test (SNOT)-22, Beck Depression Inventory (BDI)-II, and Beck Anxiety Inventory (BAI)] were performed preoperatively and at 3, 6, and 12 months post-operatively.

Results: We enrolled 19 ENS and 12 CHR patients. nNO levels were significantly lower in the ENS than in the CHR patients before surgical treatment ($p < 0.001$). nNO levels in the ENS patients significantly increased 3 months after implantation and remained plateaued ($p = 0.015$). BDI-II and BAI scores significantly improved after surgical treatment for the ENS patients but not for the CHR patients; changes in nNO levels correlated well with improvements in BDI-II and BAI scores ($p = 0.025$ and 0.035 , respectively).

Conclusions: nNO significantly increased at third month after surgical treatment and remained plateaued in ENS patients. This increase correlated with improvements in BDI-II and BAI scores. Therefore, nNO may be important in assessing the psychiatric status of empty nose syndrome.

1. Introduction

Nasal nitric oxide (nNO) is synthesized by inducible NO synthase (iNOS) from L-arginine, mainly in the paranasal sinus mucosa; it is used to monitor local immune and inflammatory responses in the sinonasal tract [1,2]. It contributes to non-specific local host defenses against airway pathogens and its levels correlate well with cilia beat frequency [3,4]. Thus, nNO has been used in screening for primary ciliary dyskinesia and cystic fibrosis. It has been even applied in the evaluation of chronic cough [5]. This feasible, non-invasive measurement of nNO revealed that nNO levels are related to paranasal sinus ventilation, radiologic stages, and quality of life improvements after sinus surgery

[6–9]. These correlations make nNO levels a potentially powerful postoperative biomarker after medical or surgical treatment for sinonasal diseases. However, the same trend of nNO cannot be applied to other sinonasal diseases because postoperative elevation patterns of nNO levels vary for different sinonasal diseases [10,11].

Empty nose syndrome (ENS) is characterized by paradoxical nasal obstructions caused by excessive loss of turbinate tissue. Other common symptoms include dyspnea, nasal and pharyngeal dryness, rhinorrhea or post-nasal drip, sleep disorder, concentration problems, chronic fatigue, frustration, irritability, anxiety, and depression [11,12]. Hyperventilation syndrome is reportedly frequent in ENS patients [13]. Further, the mechanism of ENS remains poorly understood. Surgical

Abbreviations: NO, nitric oxide; nNO, nasal nitric oxide; ENS, empty nose syndrome; CHR, chronic hypertrophic rhinitis; SNOT-22, SinoNasal Outcome Test-22; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; cGMP, cyclic guanosine monophosphate

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sensory nerve damages, improper healing, and airflow pattern alterations play major roles in abnormal nasal sensations experienced by ENS patients [14]. ENS diagnosis is difficult owing to a lack of reliable and objective measurements; thus, subjective symptomatology remains the key to ENS diagnosis. Combined information on past turbinectomy history, reported symptoms, and excessively patent nasal cavity found in physical examination is essential for diagnosis. Cotton test is a valid test for assessing ENS, and positive results may indicate eligibility for surgical treatment [15]. Surgical submucosal implantation alleviates rhinological and psychological symptoms [16,17]. This study is the first to evaluate the roles of nNO in ENS patients, postoperative changes of nNO, and parameters potentially associated with nNO levels.

2. Materials and methods

2.1. Study subjects

Patients were enrolled if they were diagnosed with ENS, had operative history of inferior turbinectomy, and passed the cotton test [17]. ENS was diagnosed based on consistent physical examinations and subjective symptoms (paradoxical nasal obstruction, breathing difficulty, and other related discomforts). Sham surgery would not be considered ethical; therefore, patients who received turbinoplasty for nasal obstruction caused by hypertrophic inferior turbinates were enrolled into the chronic hypertrophic rhinitis (CHR) group for comparison. Endoscopy was performed in all patients to examine the nasal cavity and exclude other sinonasal diseases before treatment initiation. Patients with congenital craniofacial anomaly or other sinonasal diseases (rhinosinusitis or nasal polyps) were excluded. Patients who failed to complete subjective assessments or the one-year follow-up were also excluded.

Upon confirming surgical history and diagnosing ENS, the patient received a cotton test without local anesthesia or decongestant. ENS patients who passed the cotton test were considered surgical candidates and enrolled into the study [16]. Enrolled ENS patients then received surgical submucosal implantation, which improved rhinological and psychological symptoms [16–18]. Patients in both groups completed a baseline survey one day before receiving surgical treatment. General demographic data, such as age, sex, and smoking status, were recorded. Routine blood tests, allergy tests, and rhinomanometries were completed before surgical treatment initiation. Written informed consent was obtained from all patients. This study was approved by the institutional review board of Chang Gung Memorial Hospital (IRB No.104–6433A3), Taoyuan, Taiwan.

2.2. Measurement of nNO levels

nNO levels were measured using an electrochemical analyzer (NIOX MINO®; Phadia AB/Aerocrine AB, Sweden) following recommendations from the American Thoracic Society/European Respiratory Society [19]. Automatic measurements lasted 45 s; aspiration flow rate was set at 5 mL/s. Subjects exhaled to tidal volume via a filtered mouthpiece and a NIOX nasal olive through one side of the nostril. They then gently orally inhaled to total lung capacity through the mouthpiece while nNO levels were being continuously measured. After 45 s, the olive was removed from the subject's nostril, and the nNO values were analyzed within 2 min. The nNO level for the other nostril was measured in the same manner. Postoperative nNO levels were measured at the 3, 6, and 12 month follow-ups for both groups.

2.3. Measurement of clinical outcomes

Surgical outcomes were assessed using the SinoNasal Outcome Test-22 (SNOT-22), which scored from 0 (no symptoms) to 5 (severe symptoms) for each item. We used the Beck Depression Inventory-II (BDI-II) and Beck Anxiety Inventory (BAI) to evaluate psychological

status, as previously described [17]. BDI-II and BAI each contained 21 items [rating, 0 (no symptoms) to 3 (severe symptoms)]. These assessments were performed preoperatively and at 3, 6, and 12 months postoperatively.

2.4. Statistical analysis

Demographic between-group differences were analyzed using independent *t*-test and two-sided Fisher's exact test to compare continuous and categorical variables, respectively. The generalized estimating equation model was used to compare repeated measures of outcome variables, including pre- and postoperative symptom scores of the SNOT-22, BDI-II, and BAI questionnaires, and the nNO levels. Pearson correlation was used to assess potential links between different variables. The linear regression model was then used to further investigate the significance of all potential correlations. Data were presented as mean \pm standard deviation. Data were analyzed using IBM SPSS (version 20.0; IBM Corp, Armonk, NY) and GraphPad Prism (version 5; GraphPad Prism Software, Inc., San Diego, CA). All *p*-values were two-tailed, and *p* < 0.05 was considered statistically significant.

3. Results

3.1. Patient demographics and preoperative assessments

One ENS and three CHR patients were excluded for dropouts. Eventually, thirty-one patients who met the inclusion criteria and completed at least one-year of postoperative follow-up were included (19, ENS; 12, CHR; Table 1). All patients completed both the pre- and postoperative assessments. No statistically significant intergroup difference in demographics was found; further, ENS group patients were older than those in the CHR group but the difference did not reach significance (*p* = 0.076). Lab tests results, allergy test results, and smoking status were similar in both groups. Prior to surgical treatment, as expected, the CHR group patients had significantly higher nasal resistance than the ENS group patients (*p* < 0.001). Preoperative SNOT-22 scores were similar for both groups (*p* = 0.156); however, the BDI-II and BAI scores were significantly higher for the ENS than for the CHR patients (*p* = 0.007 and 0.005, respectively). The ENS patients suffered moderate degree of depression and anxiety, which was also observed in our previous study¹⁴, whereas CHR patients revealed normal psychological assessments.

Table 1
Demographic data and clinical parameters of the two groups.

	ENS (n = 19)	CHR (n = 12)	<i>p</i> value
Age, median (range), years	52.0 (22.0–67.0)	40.0 (20.0–66.0)	0.076
Female, No. (%)	6 (31.5)	2 (16.7)	0.433
Smoker, No. (%)	1 (5.2)	1 (8.3)	1.000
Atopy, No. (%)	5 (26.3)	4 (33.3)	0.704
Total IgE, median (range), kU/L	33.2 (4.2–382.0)	169.0 (6.0–830.0)	0.118
Nasal resistance, median (range), Pa	0.5 (0.2–1.2)	1.0 (0.5–3.0)	< 0.001
SNOT-22 score, median (range)	65.0 (14.0–88.0)	51.0 (12.0–74.0)	0.156
BDI-II score, median (range)	15.0 (5.0–52.0)	8.0 (0.0–18.0)	0.007
BAI score, median (range)	21.0 (1.0–42.0)	2.5 (0.0–26.0)	0.005
Pre-op nNO, median (range), ppb	85.5 (5.5–333.0)	231.3 (114.0–426.0)	< 0.001

ENS, empty nose syndrome; CHR, chronic hypertrophic rhinitis; SNOT-22, SinoNasal Outcome Test-22; BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; pre-op, preoperative; nNO, nasal nitric oxide.

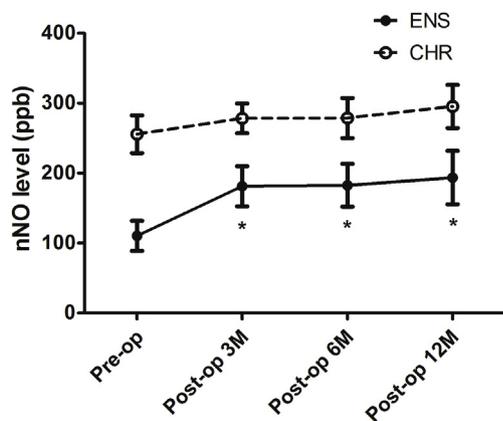


Fig. 1. nNO levels preoperative and 3, 6, and 12 months postoperative in ENS patients and CHR patients. * $p < 0.05$ when compared with preoperative value. Error bars represent 95% confidence interval. ENS, empty nose syndrome; CHR, chronic hypertrophic rhinitis.

3.2. Levels of nasal nitric oxide

The average of nNO levels measured with the same method for healthy adult population was reported 379.6 ± 107.4 ppb to 401.6 ± 207.8 ppb [20]. We enrolled a group of healthy adult volunteers in our institute to obtain the range of normal nNO levels, with similar demographics to the two groups of patients and without any recent sinonasal symptoms reported. The mean nNO level of this healthy group was 396.2 ± 125.6 ppb, identical to the reported range [20]. nNO levels in our patients of the present study were both lower than the reported value. Further, compared with the CHR group patients, the ENS group patients had significantly lower preoperative nNO levels ($p < 0.001$), and their nNO levels significantly increased 3 months after surgery and remained plateaued ($p = 0.015$; Fig. 1). Contrarily, the CHR group patients had higher preoperative nNO levels; however, their postoperative nNO levels remained mostly unchanged until one year postoperatively (Fig. 1). The nNO levels elevated more prominently postoperatively in the ENS group patients than in the CHR group patients; however, the postoperative nNO levels in the ENS group patients remained lower than those in the CHR group patients ($p = 0.001$).

3.3. Subjective assessments

The SNOT-22 scores for the ENS patients improved significantly and plateaued 3 months later ($p < 0.001$; Fig. 2), thus indicating that the surgical treatment was effective in relieving rhinological symptoms for ENS patients and that the therapeutic effects did not rely on nasal resistance recovery. For the CHR group patients, SNOT-22 scores also significantly improved 3 months post surgery ($p < 0.001$) as generally expected (Fig. 2). Postoperative improvement in nasal patency in the CHR group patients provided more satisfying treatment results.

BDI-II and BAI scores for the ENS group patients markedly improved post surgical treatment and both plateaued 3 month later (both $p < 0.001$) (Fig. 3). Similar results were observed in our previous study [17]. Contrarily, the BDI-II and BAI scores were normal for the CHR group patients before surgery, and no further postoperative improvements were observed (Fig. 3).

3.4. Correlation and regression analysis

Univariate analysis was performed to identify medical factors potentially related to preoperative nNO levels of the study subjects. The ENS patient group and positive allergy test results (atopy) were found to affect nNO levels ($p < 0.001$ and $p = 0.036$, respectively). Multiple

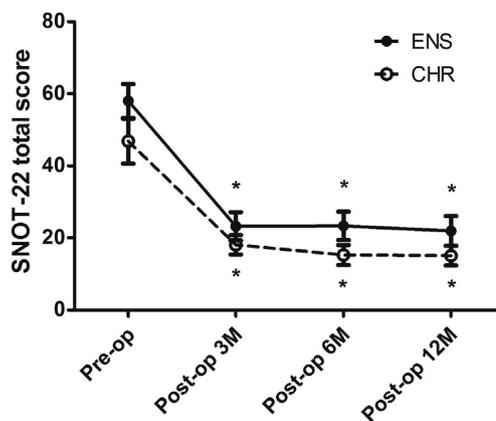


Fig. 2. SNOT-22 scores before and after the surgical treatment in ENS patients and CHR patients. * $p < 0.05$ when compared with preoperative value. Error bars represent 95% confidence interval. SNOT-22, SinoNasal Outcome Test-22; ENS, empty nose syndrome; CHR, chronic hypertrophic rhinitis.

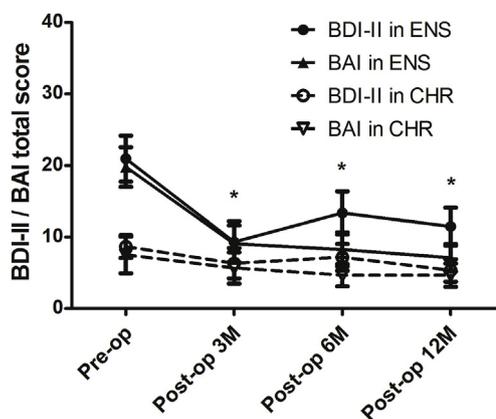


Fig. 3. BDI-II and BAI scores before and after the surgical treatment in ENS patients and CHR patients. * $p < 0.05$ when compared with preoperative value. Error bars represent 95% confidence interval. BDI-II, Beck Depression Inventory-II; BAI, Beck Anxiety Inventory; ENS, empty nose syndrome; CHR, chronic hypertrophic rhinitis.

linear regression analysis was subsequently conducted to adjust for potential confounding factors; it confirmed that the ENS patients group and allergy status correlated with the preoperative nNO levels ($p < 0.001$ and $p = 0.020$, respectively). However, further analysis of the effects of allergy in each group revealed that for the CHR group, the allergic patients had significantly higher preoperative nNO levels when compared when the nonallergic patients ($p = 0.028$), whereas for the ENS group, the preoperative nNO levels were similar between the allergic and nonallergic patients ($p = 0.237$). The correlations between nNO levels and subjective rhinological and psychological assessments for both groups were evaluated using the Pearson correlation and linear regression tests. No significant correlation was found between preoperative nNO levels and the scores of SNOT-22, BDI-II, or BAI for either group. However, for the ENS group, postoperative increases in nNO levels significantly correlated with absolute improvements in the BDI-II and BAI scores after surgical implantation ($p = 0.025$ and 0.035 , respectively) but did not correlate with the improvement in SNOT-22 scores ($p = 0.456$). For the CHR group, the postoperative increase in nNO levels correlated with absolute improvements in the SNOT-22 scores ($p = 0.004$) but not the BDI-II or BAI scores ($p = 0.153$ and 0.086 , respectively). Multiple linear regression analysis revealed that allergy was not associated with postoperative changes in nNO levels for either the ENS or the CHR group ($p = 0.121$ and 0.839 , respectively).

4. Discussion

In the upper airway, NO is mainly synthesized by ciliated cells in paranasal sinuses. nNO is a surrogate biomarker for paranasal sinus inflammation, indicating that nNO levels would decrease during sinusitis and increase again post treatment [2,5].^{2,5} nNO levels in chronic rhinosinusitis (CRS) reportedly increased post surgical treatment and plateaued 3–6 months later [9,10]. Extremely low levels of nNO are expected in patients with primary ciliary dyskinesia; thus, nNO could serve as a screening criterion [3,4]. Two theories were proposed for nNO decrease in CRS, including decreased NO production in the maxillary sinuses and obstruction of sinus ostia caused by secondary changes of sinusitis, local edema, or nasal mucosal swelling [21]. NO can upregulate ciliary motility of nasal mucosa [22]. The number of occluded sinuses determined by computed tomography inversely correlated with nNO levels, and the occluded sinuses might have caused the impaired diffusion of nNO into the nasal cavity [23]. ENS patients with sinus problems were excluded, and nNO levels in the enrolled ENS patients significantly increased after submucosal implantation, which rebuilt the geographic contour inside the nasal cavities (instead of the sinus cavities). Contrarily, nNO levels did not change postoperatively in patients with CHR who received surgical treatment inside their nasal cavities as well for better nasal patency. In ENS patients, nNO was significantly lower, elevated 3 months postoperatively, plateaued, and maintained at 12 months after the surgery, similar to the postoperative trend of nNO in CRS patients [9]. Restoration of nNO in ENS patients after nasal cavity surgery, in a pattern comparable with that of CRS patients after sinus surgery, may have resulted owing to improved ciliary function and increased NO production, rather than increased patency of the sinus ostia. By contrast, the airflow gained after turbidoplasty in CHR patients might not have significantly improved the ciliary function in paranasal sinuses as the nNO levels did not increase post surgery. A direct histological proof for postoperative changes of iNOS in the nasal mucosa is needed to draw appropriate conclusions in future studies. Further, the sinonasal mucociliary function has been reported to recover at least 3 months after surgical treatment [24], thus we made the first measurement of postoperative nNO levels at third month. Further measurements within 3 months would be performed in the future study.

Nitric oxide modulates major neurotransmitters involved in neuropsychiatric disorders, and NO is proposed to play “dual roles” in these disorders. L-arginine and NO metabolite levels decrease in patients with major depression [25]. A national survey revealed that depression is associated with lower fractional levels of exhaled nitric oxide [26]. However, several studies demonstrated a contradictory role of NO in psychiatric disorders. Increased NO levels can activate soluble guanylate cyclase, which converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) and may lead to a depression-like status [27]. Furthermore, significantly higher than normal levels of plasma NO metabolites in depressive patients decrease after a treatment period; hence, the NO levels could serve as a therapeutic indicator [28]. In addition to depression, NO may also have similar two-sided effects on anxiety status modulation [29]. NOS inhibitors can reportedly reduce cGMP signaling and attenuate the anxiolytic-like effects of the benzodiazepine chlordiazepoxide [30]. Recent animal studies revealed that loss of NOS increases anxiety-like behavior and that angiogenesis induced by restraint stress is associated with lowered levels of brain NO metabolites and the anxiolytic effect of morphine, which is modulated by NO [31,32]. However, other animal studies revealed that NO induces anxiety-like responses and may serve as a therapeutic target [32–35].

Here, we found that the psychiatric status of ENS patients significantly improved within the first three months post surgery, whereas nNO levels significantly increased and then plateaued following a similar timeline. The increase in postoperative nNO levels significantly correlated with postoperative improvements of psychiatric status.

Contrarily, patients with CHR exhibited no changes in either their psychiatric status or nNO levels post surgical treatment. Our results indicated that NO levels in the sinonasal tract may be associated with changes in the depression and anxiety status in ENS patients.

Expression of NOS in the nasal mucosa increases in patients with allergic rhinitis, thereby resulting in nNO elevation [36].³⁴ Here, unlike in the case of the CHR group patients, the preoperative nNO levels in the ENS patients did not significantly vary between individuals with and without allergy. Hence, allergy did not seem to be a factor confounding nNO levels in ENS patients. Further, no differences were found between the allergic and nonallergic ENS patients in the preoperative levels and the postoperative trends of nNO. According to regression analysis, nasal allergy is unlikely a factor confounding postoperative changes of nNO levels in both groups.

The main purpose of using surgical treatment for ENS is to reconstruct the geographic contour of the nasal cavities and narrow the nasal airway, thereby increasing resistance and deflecting the airflow from insensitive tissues to unoperated areas [37]. According to the correlation and regression analyses in this study, change in nasal resistance was not associated with postoperative improvements in the SNOT-22, BDI-II, or BAI scores. This may indicate that nasal resistance is not a useful clinical biomarker for assessing ENS severity.

5. Conclusion

Nasal NO increase and psychiatric parameters significantly improved post surgical treatment both elevated at three months post surgery and remained plateaued in ENS patients. The increase in nNO correlated with improvements in psychiatric status. Further, nNO levels were not affected by the atopic status in ENS patients, which means that nNO could be used as a biomarker in patients with or without allergy. Therefore, nNO may be a novel biomarker and the first objective one for assessing improvements post surgical treatment in ENS patients.

Statement of conflict of interest and funding

There are no patents, products in development or marketed products to declare. The authors declare that there is no conflict of interest regarding the publication of this paper, and disclose any existing financial arrangements. This work was supported by the grants from Chang Gung Memorial Hospital (CMRPG1H0031).

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