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Investigation of the abnormal nasal aerodynamics and trigeminal functions among empty nose syndrome patients

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Abstract

Objective—Abnormal nasal aerodynamics or trigeminal functions have been frequently implicated in the symptomology of empty nose syndrome (ENS), yet with limited evidence.

Methods—Individual CT based computational fluid dynamics (CFD) was applied to 27 ENS patients to simulate their nasal aerodynamics and compared with 42 healthy controls. Patients' symptoms were confirmed with ENS6Q, SNOT-22 and NOSE scores. Nasal trigeminal sensitivity was measured with menthol lateralization detection thresholds (LDT).

Results—ENS patients had significantly lower (~25.7%) nasal resistance and higher (~2.8 times) cross-sectional areas compared to healthy controls (both $p < .001$). Despite inferior turbinate reductions, CFD analysis demonstrated that ENS patients had increased airflow concentrated in the middle meatus region ($66.5 \pm 18.3\%$) compared to healthy controls ($49.9 \pm 15.1\%$, $p < .0001$). Significantly less airflow ($25.8 \pm 17.6\%$) and lower peak wall-shear-stress (WSS) (0.58 ± 0.24 Pa) were found in the inferior meatus (vs. healthy: $36.5 \pm 15.9\%$; 1.18 ± 0.81 Pa, both $p < .05$), with the latter significantly correlated with the symptom scores of ENS6Q ($r = -.398$, $p = .003$). Item-wise, complaints of “suffocation” and “nose feels too open” were also found to be significantly correlated with peak WSS around the inferior turbinate ($r = -.295$, $p = .031$; $r = -.388$, $p = .004$). These correlations were all negative, indicating that less air-mucosal stimulations resulted in worse symptom scores. ENS patients ($n = 12$) also had impaired menthol LDT when compared to healthy controls ($p < .0001$).

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Conclusion—This is the first CFD examination of nasal aerodynamics among a large cohort of ENS patients. The results indicated that a combination of loss of neural sensitivity and poorer inferior air-mucosal stimulation may potentially lead to ENS symptomology.

Keywords

Empty nose syndrome; computational fluid dynamics; nasal airflow dynamics

INTRODUCTION

Empty nose syndrome (ENS) was originally coined by Eugene Kern and Monika Stenkvist in 1994 as a rare but debilitating clinical syndrome that typically occurred after surgical therapy¹. The most common symptom is a paradoxical sensation of nasal obstruction, despite an open nasal airway². ENS patients also suffer from varying degrees of nasal crusting, dryness, nasal discharge, and facial pain. In some severe cases, ENS patients complain about sleeping difficulty, disrupted concentration, elevated anxiety, and a constant feeling of suffocation³.

Due to the lack of reliable objective tests to quantify these symptoms, the diagnosis of ENS mainly relies on subjectively reported symptomology. The Empty Nose Syndrome 6-item Questionnaire (ENS6Q) has been recently validated to identify patients suspected of developing ENS⁴. A score of 11 out of a possible total of 30 was determined as the cut-off criterion to predict ENS. In addition, the cotton test has also been used to aid in the diagnosis of ENS^{5, 6}.

The precise pathogenesis of ENS still remains unclear. Alterations in normal airflow due to excessive turbinate resection and the loss of neural sensitivity are suspected as key contributing factors. Computational fluid dynamics (CFD) simulations can quantify nasal aerodynamics in detail and thus have the potential to enhance our understanding of ENS. Most of previous CFD studies were based on virtual turbinectomies simulated on healthy nasal airways and had limited sample size^{7, 8}. However, the presence or absence of a significant portion of the turbinates does not uniformly predict ENS development. Most post-turbinectomy patients will not go on to develop ENS⁷. Thus, it is important to focus on the small subset of patients who unfortunately develop ENS in order to accurately investigate the pathogenesis. We conducted the first CFD analysis to investigate the nasal airflow of six ENS patients⁹. The results indicated that the inferior turbinate (IT) reduction did not draw more airflow to the airway surrounding the ITs, but rather resulted in a distorted airflow jet toward the middle meatus region. Although careful numerical simulations have been designed, the observations were limited to a small cohort of patients and no direct correlations have been reported between the distorted nasal airflow pattern and symptomology of ENS patients.

In this study, we extended our previous study⁹ to 27 ENS patients, utilized CFD analysis to investigate nasal airflow characteristics and compared them to that of 42 healthy controls. Assessment of nasal trigeminal sensitivity was also performed on a subset of ENS patients. The collection of the largest such dataset to date aims to provide more insights into the pathogenesis of ENS.

MATERIALS AND METHODS

Subjects

A total of 27 patients diagnosed with ENS were enrolled in the current study, out of which 12 patients visited our clinics (9 to The Ohio State University and 3 to Thomas Jefferson University), while the rest were recruited through email correspondence around the world. Their ages ranged from 25 to 67 years, with a median of 47. The group included 8 females and 19 males. Their symptoms were confirmed through a combination of ENS6Q, SNOT22, NOSE Score, and the evaluation of medical and surgical history. All patients had a history of inferior turbinate surgeries with CT evidence, and 2 of them had a total inferior turbinectomy while the rest had either a partial turbinectomy or mucosal preserving reduction. Out of 27 ENS patients, 7 patients also had a history of middle turbinate (MT) surgeries (5 with partial MT resection and 2 with total MT turbinectomy), while the rest had relatively intact MTs. Fifteen patients developed ENS after their first nasal surgical procedure, while the remaining patients had a number of past surgical interventions ranging from 1 to 4. The time period between surgery and the appearance of symptoms was within one month for the majority of patients (20 out of 27). All patients, except one, presented bilateral symptoms. The duration of symptoms ranged from 11 to 552 months until the time of this study, with a median of 66 months.

A total number of 42 healthy subjects were used for comparison with ENS patients. Twenty-two of the healthy controls were acquired from our previously published normative data^{10, 11}, and 20 additional healthy controls were recruited through local advertisements. These healthy volunteers were not patients visiting our clinics or hospitals. The ages of individuals in the healthy cohort ranged from 21 to 60 years, with a median of 27. All of the healthy subjects underwent medical history screening to exclude preexisting nasal sinus disease, nasal sinus complaints, prior head trauma, and prior nasal surgery. The SNOT22 and NOSE questionnaires were also filled out by the healthy controls. The comparison of age, gender, race, and SNOT22 and NOSE scores between ENS patients and healthy controls are summarized in Table 1.

Twelve of the total 27 ENS patients that visited our clinics also completed menthol lateralization detection thresholds (LDT) test and were compared with the normative data of 14 healthy controls that were published in a previous study⁹. The current study was approved by The Ohio State University and Thomas Jefferson University Institutional Review Boards.

Questionnaire

All patients were asked to fill out questionnaires documenting their medical history, SNOT-22, NOSE score, and ENS6Q (Table 1). The Sino-nasal Outcome Test (SNOT-22)¹² and Nasal Obstruction Symptom Evaluation (NOSE)¹³ are two commonly used validated outcome questionnaires for nasal sinus patients. ENS patients had significantly elevated SNOT-22 (58.22 ± 15.85) and NOSE scores (69.35 ± 17.1). ENS6Q⁴ is a recently validated specific 6-item questionnaire as an adjunct to the standard SNOT-22 questionnaire to

discriminate patients with suspicion of ENS. A score of ENS6Q >11 is indicative of ENS. All patients fit this criterion with a mean score of 19.78 ± 5.42 .

CT scan and CFD model

All ENS patients had postoperative CT scans following the diagnosis of their symptomology. The newly recruited healthy controls also received a research CT scan (not for any clinical purpose) using a cone beam in-office CT scanner (3D Accuitomo 170, J. Morita USA, Inc., Irvine, CA, USA). These CT scans enabled the construction of CFD nasal airway models for each subject using methods described previously^{14, 15}.

Briefly, the CT scans were imported into a commercial software AMIRA (Visualization Sciences Group, Hillsboro, OR, USA), which is capable of extracting the 3D nasal volume from different 2D images (coronal, lateral, and axial views). After necessary smoothing and artifact correction, a three-dimensional surface geometry of the nasal airway was generated. A second commercial software package ICEM CFD (Ansys, Inc., Canonsburg, PA, USA) was then applied to generate tetrahedral volume elements inside the nasal geometry. A four-layer prism mesh was adopted at the boundary with a total height of 0.2 mm near the mucosal surface (Figure 1) to more accurately model the rapidly changing near-wall air velocity. The final nasal cavity mesh used for the simulations ranged from 1.1 million to 3.6 million hybrid finite elements.

Next, ANSYS Fluent 16.2 (Ansys, Inc., Canonsburg, PA, USA) was employed to solve the steady incompressible Navier-Stokes equations, which are the governing equations for the nasal airflow. Along the nasal mucosal walls, the no-slip boundary conditions were applied, and the walls were assumed to be rigid. A physiologically realistic pressure drop of 15 Pa was applied between the nostrils and the nasopharynx¹⁶. This pressure drop of 15 Pa was chosen to simulate restful breathing¹⁰, a state that is most relevant to patients' symptoms during routine daily life. The numerical solutions of the continuity and momentum equations were determined using the finite-volume method. The continuous pressure and velocity fields were discretized using a second-order upwind scheme for numerical simulations. The SIMPLEC algorithm was used for pressure-velocity coupling. The converged simulation results were determined once the residual of each variable was less than 10^{-5} . The numerical method applied in the current study has been validated by comparing with experimental measurements¹⁷.

Menthol Lateralization Detection Thresholds

Measurement of LDT is a common assessment of nasal trigeminal sensitivity and was performed on 12 ENS patients that visited our clinics. Similar to other trigeminal agonists, menthol produces both an odor (via olfaction) and a cooling sensation (via the TRPM8 trigeminal pathway). The mechanism of this test is based on the fact that non-irritating odorants cannot be lateralized, and thus the lateralization threshold is a measure of nasal trigeminal sensitivity to volatile compounds that are independent of the chemical's effect on the olfactory system. Our procedure was previously reported⁹ and adapted from the literature¹⁸. In brief, menthol was diluted into mineral oil in a 20-step binary dilution series in clear glass bottles, starting at a concentration of 0.125 g/ml (5g/40mL), with each step

diluting the previous solution to half. The final dilution step (#20) had a dilution of $1/2^{19}$ times of the starting concentration, or 2.38×10^{-7} g/ml. All materials were purchased from Sigma-Aldrich ®: Menthol (M2772) 99% in solid, and mineral oil (M8410, CAS Number: 8042-47-5) BioReagent grade. In each trial, the subject simultaneously sniffed from a pair of bottles, one in each nostril. One bottle had Menthol and the other bottle was blank with only mineral oil. The subject was forced to identify which side contained Menthol (which was termed: lateralization). The trials were conducted based on a force-choice ascending method of limits¹⁹. Each stimulus concentration was presented at most once, in ascending concentration. Testing ended when the subject: (1) had responded correctly in four consecutive trials and (2) were confident that the last response was correct (equal or above 7 on a confidence rating of 0-10). The latter criterion represented an attempt to reduce the chances of false positive, as four consecutive “lucky guesses” was not a rare event (6.25%). The threshold was determined as the first of the four consecutive correct trials and reported in dilution step or bottle number. The dilution bottles were numbered 1-20 accordingly. The consecutive correctness of left and right sides were tracked separately, while the presentation order to either side was random. The consecutive correct trials on the left or right side only depended on the previous correct identifications on the same side in order to obtain unilateral thresholds.

RESULTS

ENS patients had significantly lower (~25.7%) nasal resistance and higher (~2.8 times) cross-sectional areas compared to healthy controls (both $p < .001$). This was not surprising since all ENS patients had different degrees of nasal surgeries and was in line with recent CT based measurements of ENS patients²⁰.

To quantify local airflow distribution, a coronal cross section at relative distance $d = 0.6$ (from nostril to pharynx) was split into 3 regions: inferior, middle, and superior on the coronal plane (Figure 2 (a-b)). The comparison between ENS patients and healthy controls (Figure 2 (c-d)) demonstrated a significantly increased airway cross section in all regions, but a paradoxical reduction of flow rate percentage through the inferior region (ENS: $25.8 \pm 17.6\%$ vs. Normal: $36.5 \pm 15.9\%$, $p = .0003$). An increase of flow rate percentage also occurred in the middle region (ENS: $66.5 \pm 18.3\%$ vs. Normal: $49.9 \pm 15.1\%$, $p < .0001$).

We further quantified the locations of the primary and secondary airflow peaks on the coronal plane. The secondary peak was defined as a lesser flow peak that was away from the primary peak (Figure 3 (a-b)). The locations of these peaks were then color-coded (red circle: primary peak; green triangle: secondary peak) on to a generic coronal plane. For the healthy subjects (Figure 3 (c)), the airflow peaks were widely spread out in the inferior meatus, middle meatus, and lower/upper common meatus (between the turbinates and septum). For the ENS patients, the airflow peaks shifted more upward (Figure 3 (d-e)), and a majority of the peaks appeared above the inferior turbinate (Figure 3 (f)).

In addition, streamlines were used to visualize the flow patterns inside the nasal cavity for both healthy subjects and ENS patients. For each individual, 100 buoyant seeds were uniformly released on the nostril plane to track their streamlines. Although various features

of the airflow streamline patterns across the subjects were found, the most striking variation between the healthy subjects and ENS patients was the distorted airflow jet towards the middle meatus among the ENS patients. Figure 4 showed examples of two healthy controls (Fig. 4 (a-b)) and two ENS patients (Fig. 4 (c-d)). For the healthy controls, streamlines were uniformly distributed throughout both inferior and middle turbinate regions. For the ENS patients, however, the airflow formed a very narrow jet towards the middle turbinate region, and left the majority of the inferior region without air movement. This observation was consistent with the flow pattern shown previously on the coronal plane.

Wall shear stress (WSS) is an important variable to identify the level of shear force exerted onto a unit area of nasal mucosa by airflow. In Figure 5 (a-b), we divided the nasal airway into 3 regions: anterior, inferior turbinate (IT), and middle turbinate (MT) regions. The superior region was not included in the analysis due to lack of functional relevance. We calculated both the peak WSS and integration of WSS within each region. As shown in Figure 5 (c), ENS patients had significantly lower peak WSS in both inferior turbinate (ENS: 0.58 ± 0.24 Pa vs. healthy: 1.18 ± 0.81 Pa, $p = .014$) and middle turbinate (ENS: 0.70 ± 0.31 Pa vs. healthy: 1.20 ± 0.82 Pa, $p = .038$) regions. In Figure 5 (d), ENS patients also had significantly lower integration of WSS (5.59 ± 1.52 Pa·cm²) compared to healthy subjects (7.47 ± 1.92 Pa·cm²), especially around the inferior turbinate region (ENS: 1.84 ± 0.93 Pa·cm² vs. Normal 3.79 ± 1.40 Pa·cm², $p < .0001$).

Next, we found that peak WSS in the inferior turbinate region significantly correlated (Spearman correlation, $r = -.398$, $p = .003$) with ENS6Q total score (Table 2). Among the 6 items in ENS6Q, complaints of “suffocation” and “nose feels too open” were significantly correlated with peak WSS in the inferior turbinate region ($r = -.295$, $p = .031$; $r = -.388$, $p = .004$). Additionally, “Nose feels too open” correlated with peak WSS in the middle turbinate ($r = -.322$, $p = .018$); “suffocation” correlated with integration of WSS in the inferior turbinate ($r = -.268$, $p = .050$) region. These correlations were all negative, indicating that less air-mucosal stimulations resulted in worse symptom scores. As aforementioned, ENS patients had lower peak and integration of turbinate WSS compared to healthy controls. Nasal resistance did not correlate with ENS6Q or any other symptom score.

Figure 6 compared the Menthol LDT between ENS patients and healthy controls. The y-axis indicated the first of the four consecutive correct trials reported in the dilution step. The higher dilution step number meant better nasal trigeminal sensitivity. Our data illustrated that ENS patients had significantly lower (or worse) Menthol LDT (10.3 ± 3.9) as compared to healthy controls (14.0 ± 1.8 , $t = 4.51$, $p < .0001$).

DISCUSSION

The underlying pathogenesis of ENS has been attributed to possible radical surgery (especially historically when mucosal and bone resection were more common), poor mucosal wound healing, altered nasal aerodynamics, and impaired nasal sensory functions²¹. For the ENS patients, a smaller inferior turbinate volume has been found significantly associated with their syndrome scores²². The inferior turbinate is essential in providing resistance to airflow and regulating airflow distribution. It has been documented that patients

with ENS showed clinical improvements by receiving endonasal submucosal implantation^{23, 24}.

However, a daunting question in the controversy surrounding ENS is why most post-turbinate surgery or even post-turbinectomy patients will not go on to develop ENS. Millions of turbinate surgeries were performed world-wide with a vast majority of patients having good outcomes – why would a very small subset of patients unfortunately develop ENS? Interestingly, our data also demonstrated that ENS may not necessarily result from the most radical resection of turbinates. Only 4 out of 27 of this ENS patient cohort had total turbinectomies (2 middle turbinectomy and 2 inferior turbinectomy). Previous CFD studies^{7, 8} have tried to simulate ENS by virtual resection of the inferior or middle turbinates on healthy controls or on patients with turbinate hypertrophy. For the reasons stated above, these approaches cannot reveal the true causal factors of ENS. These virtual turbinectomy studies often showed that airflow increases in the region where you cut: e.g. Fig. 4 (C) in Ref⁷, middle turbinectomy resulted in more flow to the middle turbinate region, inferior turbinectomy resulted in more flow inferiorly, and etc. However, our previous study based on patients with confirmed ENS diagnosis showed that surprisingly, ENS patients' inferior turbinate reduction did not draw more airflow to the inferior nasal airway, but rather resulted in a reduction of airflow intensity and wall shear stress surrounding the inferior turbinate, with more airflow toward the middle meatus. We suspected that this paradoxical airflow profile in real ENS patients could be one of the underlying etiologies of ENS.

In the current study, we expanded CFD analysis to 27 confirmed ENS patients (the largest to date) and compared their nasal aerodynamic characteristics with a large cohort of healthy subjects (n=42). The results confirmed that despite undergoing inferior turbinate surgeries, ENS patients had a majority of their nasal airflow shooting through their middle meatus region. This left their inferior region with much lower flow rates compared to healthy controls (Figure 2, 3 and 4). Such a paradoxical airflow pattern significantly reduced the air-mucosa interaction (WSS) in the inferior turbinate region (~2 times lower than normal subjects, Figure 5 (d)), even though ENS patients had more total flow rate, due to lower resistance. Presumably if everything is the same, the shear stress of ENS patients would have either higher peak values or higher total integration, which as we found out is not the case. Furthermore, such reduced inferior turbinate air-mucosa interactions were found to significantly correlate with their ENS6Q symptom score, as well as specific symptoms of “suffocation” and “nose feels too open” (Table 2). These are the two most defining symptoms among the ENS6Q. These results shed new light on the role of altered nasal aerodynamics in the symptomology of ENS.

Why did this distorted nasal aerodynamic profile occur?

There are no definite answers, but we speculated several causes. First, a predisposing anatomical configuration: the pre-surgery nasal airflow of the 3 ENS patients in our previous study⁹ predominantly had airflow in the middle meatus. This potentially predisposed them to prevailing middle meatus airflow after inferior turbinate surgery. We cannot further test this hypothesis in this study, as we lack the pre-surgery CT scans of all the patients enrolled in this study.

Second, the inferior turbinate surgery was not isolated. All our ENS patients had a septoplasty (n=20), FESS (n=9) or middle turbinate resection (n=7, 5 partial and 2 total turbinectomy) accompanying the inferior turbinate surgery. These adjuvant procedures potentially opened up the middle nasal airway as well. It is well known that airflow is not only driven by the path of least resistance, but also by its momentum. Septoplasty, FESS, or middle turbinate resection in combination with the inferior turbinate reduction may have the risk of reducing the nasal resistance too excessively. Human nostrils are pointed downwards, so that nasal airflow would enter the nostrils in an upright direction. As air traverses the nasal cavity, it must then turn 180 degrees to go down into the lungs. Therefore, the nasal airflow has a natural tendency of shooting upwards through the middle meatus region if the proper structures are not in place to distribute the airflow. Individuals with pre-disposing middle meatus flow may compound this phenomenon.

We hypothesized that IT reduction may be more safe and effective if it was done solely. Without competing resistance reduction elsewhere, the expanded inferior airway may distribute airflow more effectively and increase air movement around the inferior turbinate, with a potentially better outcome. Obviously, this hypothesis needs to be further validated. However, we should also emphasize that the above observation was not merely skewed by the 7 patients with middle turbinate partial or total reduction. We repeated the analysis of Figures 2 and 5 while excluding these 7 patients and it did not change the overall findings and its significance (See Figure S1). So, middle turbinectomy or reduction was not the only contributing factor.

Functional Consequences of the Distorted Aerodynamics

Healthy nasal turbinates play critical roles in partitioning the nasal airflow to better facilitate normal nasal physiology. Among healthy subjects, the nasal airflow is more uniformly distributed (e.g. Figure 3 (a-b)), which theoretically improves efficiency. This results in a better capability to warm, humidify and filter the inspired airflow, while preventing unwanted desiccation of the mucosa. The more widely distributed airflow could also improve the capacity of the nasal mucosal to detect airflow.

Over-congregated nasal airflow may reduce the contact of airflow to mucosa. Our results provided the first evidence that both the lower peak and integration of wall shear stress around the inferior turbinate of ENS patients were significantly and negatively correlated with their symptom score of ENS6Q (Table 2). These results indicated that poorer regional air-mucosal stimulation potentially led to worse symptomology. Many ENS patients respond well to the cotton test when the cotton was placed along the inferolateral nasal wall^{5, 6}. The cotton plug in this site may potentially redirect the nasal airflow to create new flow patterns and/or stimulate the mucosa regions with normal sensory function and thus improve the symptoms for ENS patients.

Mucosal sparing turbinate surgery technique has now become the mainstay to preserve mucosa and prevent complications; but we also need to find ways to preserve a healthy air-mucosal stimulation. Without the airflow stimulation, even healthy mucosal may not be sufficient to function properly.

Nasal Neurosensory Losses

The compromised wound healing or loss of sensory nerve fibers may be another contributing factor to ENS. Another key finding in this study was the confirmation of nasal neurosensory impairment among ENS patients. We found that ENS patients had significantly lower Menthol LDT (10.3 ± 3.9) as compared to healthy controls (14.0 ± 1.8), which corroborated previous studies^{9, 25, 26}. The consistency and low variability in Menthol LDTs among healthy controls is a demonstration of the validity of this test. Menthol as well as other TRPM8 ligands (e.g. eucalyptol) have high lipid solubility and thus have strong accumulation and desensitizing effects. Our menthol protocol is applied in ascending order starting at very low concentrations (below detection thresholds). This potentially better mitigates the desensitizing effects comparing to other protocols²⁵ which apply menthol or eucalyptol constantly at close to saturate concentration^{25, 26}.

There is evidence that the perception of nasal airflow involves activation of nasal trigeminal cool receptors when cool ambient air is inspired^{18, 27}. Supporting evidence also comes from menthol, which when topically applied will produce the illusion of improved nasal airflow without actually altering nasal morphology²⁸. Menthol activates TRPM8 trigeminal cool receptors²⁹, thus impaired Menthol LDT may contribute to patients' lack of sensation of airflow in addition to the reduction in airflow stimulation^{7, 11, 18}.

The exact causes of the sensory loss remain unknown. The distorted aerodynamics may have an impact on mucosal sensory recovery, with either too little or too high stresses. There is evidence that nasal trigeminal senses do undergo adaptive processes during disease processes³⁰⁻³² and that mucosal detection sensitivity among a normal population had significant regional variability^{33, 34}, and potentially more so among ENS patients. How to promote mucosal neurosensory recovery at key regions could be a future area of novel treatment options for ENS.

CONCLUSION

In this study, the largest CFD dataset to date of ENS patients (n=27) was collected and their nasal aerodynamic characteristics were compared with a large cohort of healthy subjects (n=42). Our results demonstrated that ENS patients had predominant airflow through their middle meatus region which left the inferior region with much lower flow rate compared to healthy controls. Such a paradoxical distorted airflow pattern of ENS patients significantly reduced the air-mucosa interactions along the inferior turbinate region (approximately 2 times lower than healthy subjects) and were found significantly correlated with symptom score of ENS6Q, including "suffocation" and "nose feels too open". The trigeminal sensory examinations also illustrated that ENS patients had significantly impaired menthol LDT compared to healthy subjects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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BIBLIOGRAPHY

1. Scheithauer MO. Surgery of the turbinates and “empty nose” syndrome. *GMS current topics in otorhinolaryngology. head and neck surgery*. 2010; 9
2. Tam Y-Y, Lee T-J, Wu C-C, et al. Clinical analysis of submucosal Medpor implantation for empty nose syndrome. *Rhinology*. 2014; 52:35–40. [PubMed: 24618626]
3. Lee TJ, Fu CH, Wu CL, et al. Evaluation of depression and anxiety in empty nose syndrome after surgical treatment. *The Laryngoscope*. 2016; 126:1284–1289. [PubMed: 26667794]
4. Velasquez N, Thamboo A, Habib ARR, et al. The Empty Nose Syndrome 6-Item Questionnaire (ENS6Q): a validated 6-item questionnaire as a diagnostic aid for empty nose syndrome patients. *International forum of allergy & rhinology*. 2017; 7:64–71. [PubMed: 27557473]
5. Thamboo A, Velasquez N, Habib ARR, et al. Defining surgical criteria for empty nose syndrome: Validation of the office-based cotton test and clinical interpretability of the validated Empty Nose Syndrome 6-Item Questionnaire. *The Laryngoscope*. 2017; 127:1746–1752. [PubMed: 28349563]
6. Houser SM. Surgical treatment for empty nose syndrome. *Archives of Otolaryngology–Head & Neck Surgery*. 2007; 133:858–863. [PubMed: 17875850]
7. Dayal A, Rhee JS, Garcia GJ. Impact of middle versus inferior total turbinectomy on nasal aerodynamics. *Otolaryngology–Head and Neck Surgery*. 2016; 155:518–525. [PubMed: 27165673]
8. Di M-Y, Jiang Z, Gao Z-Q, et al. Numerical simulation of airflow fields in two typical nasal structures of empty nose syndrome: a computational fluid dynamics study. *PloS one*. 2013; 8:e84243. [PubMed: 24367645]
9. Li C, Farag AA, Leach J, et al. Computational fluid dynamics and trigeminal sensory examinations of empty nose syndrome patients. *The Laryngoscope*. 2017; 127:E176–E184. [PubMed: 28278356]
10. Zhao K, Jiang J. What is normal nasal airflow? A computational study of 22 healthy adults. *International forum of allergy & rhinology*. 2014; 4:435–446. [PubMed: 24664528]
11. Zhao K, Jiang J, Blacker K, et al. Regional peak mucosal cooling predicts the perception of nasal patency. *The Laryngoscope*. 2014; 124:589–595. [PubMed: 23775640]
12. Hopkins C, Gillett S, Slack R, et al. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clinical otolaryngology*. 2009; 34:447–454. [PubMed: 19793277]
13. Stewart MG, Witsell DL, Smith TL, et al. Development and validation of the Nasal Obstruction Symptom Evaluation (NOSE) scale. *Otolaryngology—Head and Neck Surgery*. 2004; 130:157–163. [PubMed: 14990910]
14. Zhao K, Scherer PW, Hajiloo SA, et al. Effect of anatomy on human nasal air flow and odorant transport patterns: implications for olfaction. *Chemical senses*. 2004; 29:365–379. [PubMed: 15201204]
15. Otto BA, Li C, Farag AA, et al. Computational fluid dynamics evaluation of posterior septectomy as a viable treatment option for large septal perforations. *International Forum of Allergy & Rhinology*. 2017; 7:718–725. [PubMed: 28544511]
16. Keyhani K, Scherer P, Mozell M. Numerical simulation of airflow in the human nasal cavity. *Journal of Biomechanical Engineering*. 1995; 117:429–441. [PubMed: 8748525]
17. Li C, Jiang J, Dong H, et al. Computational modeling and validation of human nasal airflow under various breathing conditions. *Journal of Biomechanics*. 2017
18. Zhao K, Blacker K, Luo Y, et al. Perceiving nasal patency through mucosal cooling rather than air temperature or nasal resistance. *PLoS One*. 2011; 6:e24618. [PubMed: 22022361]

19. ASTM. Standard Practice for Determination of Odor and Taste Thresholds By a Forced-Choice Ascending Concentration Series Method of Limits. Philadelphia, PA: American Society for Testing and Materials; 2011.
20. Thamboo A, Velasquez N, Ayoub N, et al. Distinguishing computed tomography findings in patients with empty nose syndrome. *International Forum of Allergy & Rhinology*. 2016; 6:1075–1082. [PubMed: 27409044]
21. Sozansky J, Houser SM. Pathophysiology of empty nose syndrome. *The Laryngoscope*. 2015; 125:70–74. [PubMed: 24978195]
22. Hong HR, Jang YJ. Correlation between remnant inferior turbinate volume and symptom severity of empty nose syndrome. *The Laryngoscope*. 2016; 126:1290–1295. [PubMed: 26692010]
23. Leong SC. The clinical efficacy of surgical interventions for empty nose syndrome: a systematic review. *The Laryngoscope*. 2015; 125:1557–1562. [PubMed: 25647010]
24. Lee TJ, Fu CH, Wu CL, et al. Surgical outcome for empty nose syndrome: Impact of implantation site. *The Laryngoscope*. 2017
25. Konstantinidis I, Tsakiroulopoulou E, Chatziavramidis A, et al. Intranasal trigeminal function in patients with empty nose syndrome. *The Laryngoscope*. 2017; 127:1263–1267. [PubMed: 28224626]
26. Saliba J, Fnais N, Tomaszewski M, et al. The role of trigeminal function in the sensation of nasal obstruction in chronic rhinosinusitis. *The Laryngoscope*. 2016; 126
27. Eccles R. Nasal airflow in health and disease. *Acta oto-laryngologica*. 2000; 120:580–595. [PubMed: 11039867]
28. Eccles R, Jones A. The effect of menthol on nasal resistance to air flow. *The Journal of laryngology and otology*. 1983; 97:705–709. [PubMed: 6886530]
29. Bautista DM, Siemens J, Glazer JM, et al. The menthol receptor TRPM8 is the principal detector of environmental cold. *Nature*. 2007; 448:204. [PubMed: 17538622]
30. Shusterman D, Murphy M. Nasal hyperreactivity in allergic and non-allergic rhinitis: a potential risk factor for non-specific building-related illness. *Indoor Air*. 2007; 17:328–333. [PubMed: 17661929]
31. Benoliel R, Biron A, Quek SY, et al. Trigeminal neurosensory changes following acute and chronic paranasal sinusitis. *Quintessence international*. 2006; 37
32. Dalton P, Dilks D, Hummel T. Effects of long-term exposure to volatile irritants on sensory thresholds, negative mucosal potentials, and event-related potentials. *Behavioral neuroscience*. 2006; 120:180. [PubMed: 16492128]
33. Clarke R, Jones A. The distribution of nasal airflow sensitivity in normal subjects. *The Journal of Laryngology & Otology*. 1994; 108:1045–1047. [PubMed: 7861078]
34. Wrobel BB, Bien AG, Holbrook EH, et al. Decreased nasal mucosal sensitivity in older subjects. *American journal of rhinology*. 2006; 20:364–368. [PubMed: 16871945]

Figure 1.

A Coronal section of the nasal model (left) and its corresponding CT image (right bottom). In a close-up view (right top), layers of small and fine elements along the wall can capture the rapid near wall changes of air velocity.

Figure 2.

(a) Three-dimensional nasal cavity model. (b) Air velocity contour at coronal section $d = 0.6$ from nostril to pharynx. The regions of inferior, middle, and superior airway were defined.

(c) Regional cross-sectional area and (d) Regional flow rate percentage between ENS patients and healthy controls.

Figure 3.

Examples of airflow distribution peaks for 2 healthy subjects (a-b) and ENS patients (d-e). The locations of all primary and secondary peaks of normal subjects (c) and ENS patients (f) are then color-coded onto a generic cross-sectional plane: red circles for the primary airflow peaks and green triangles for secondary peaks, respectively. For the healthy subjects, the airflow peaks were widely spread out in the inferior meatus, middle meatus, and lower/upper common meatus (between the turbinates and septum). For the ENS patients, the airflow peaks shifted upwards, congregated above the inferior turbinate.

Figure 4.

Examples of streamline patterns of two healthy controls (a-b) and two ENS patients (c-d).

The streamlines were color coded by the velocity magnitude. For the healthy controls, streamlines were uniformly distributed throughout both inferior and middle turbinate regions. For the ENS patients, however, the airflow formed a narrow jet towards the middle turbinate region, and leaves the majority of inferior region with little or no airflow movement.

Figure 5.

(a) Wall shear stress (WSS) distributions along the nasal cavity are divided into 3 regions: anterior, inferior turbinate and middle turbinate. (b) Example of WSS distribution for an ENS patient. The overlapping of airflow streamline and the WSS on the lateral turbinate wall with septum removed from the view. (c) Comparison of peak WSS in each region between ENS and healthy controls. (d) Comparison of wall shear force (calculated by integration of WSS) in each region between ENS patients and healthy controls.

Figure 6.

Comparison of Menthol lateralization detection thresholds (LDT) threshold between ENS patients and healthy controls. The y-axis indicated the first of the four consecutive correct trials reported in dilution steps. The higher dilution number means better nasal trigeminal sensitivity. Our data illustrated that ENS patients had significantly lower (or worse) Menthol LDT (10.3 ± 3.9) as compared to healthy controls (14.0 ± 1.8 , $t=4.51$, $p<.0001$).

Table 1

Comparison of age, gender, race, nasal resistance, and symptoms scores between ENS patients and healthy controls.

Characteristic	ENS n = 27	Healthy n = 42
Age, mean yr, [SD]	43.59 [11.24]	31.69 [11.20]
Gender, No. [%]		
Male	19 [70.4]	15 [35.7]
Female	8 [29.6]	27 [64.3]
Race, No. [%]		
White	22 [81.5]	37 [88.1]
Hispanic	3 [11.1]	0
African American	2 [7.4]	3 [7.1]
Asian	0	2 [4.8]
Nasal Resistance, Pa · s/ml, [SD]	0.052 [0.015]	0.070 [0.021]
ENS6Q Scores (0-30)	19.78 [5.42]	–
Dryness (0-5)	3.70 [1.17]	–
Lack of air sensation (0-5)	3.96 [1.09]	–
Suffocation (0-5)	3.52 [1.22]	–
Nose feels too open (0-5)	3.41 [1.78]	–
Nasal crusting (0-5)	2.78 [1.78]	–
Nasal burning (0-5)	2.41 [1.91]	–
NOSE (0-100)	69.35 [17.1]	11.90 [12.90]
SNOT 22 (0-110)	58.22 [15.85]	13.17 [14.85]

Table 2

Spearman correlation matrix between CFD results and ENS-6Q scores (n=27), with only significant correlations presented.

		Suffocation	Nose feels too open	ENS6Q total
Peak WSS (Pa)	Anterior			
	IT	-.295 *	-.388 **	-.398 **
	MT		-.322 *	
Integration of WSS (Pa·cm ²)	Anterior			
	IT	-.268 *		
	MT			

* $p < 0.05$.

** $p < 0.01$.