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Computational fluid dynamics and trigeminal sensory examinations of empty nose syndrome patients

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Abstract

Objective—The precise pathogenesis of empty nose syndrome (ENS) remains unclear. Various factors such as nasal aerodynamics and sensorineural dysfunction have been suspected, yet, evidence is limited. This study reported the first examination of both nasal aerodynamics and trigeminal sensory factors in actual ENS patients.

Study Design—Prospective case control.

Methods—We enrolled 6 patients diagnosed with ENS. Three patients had pre- and post-inferior turbinate (IT) reduction computed tomography (CT) scans, which allowed comparison of their nasal aerodynamics changes through Computational Fluid Dynamic (CFD) simulation. Their symptoms were confirmed through SNOT-22, ENS6Q, acoustic rhinometry and rhinomanometry findings. Nasal trigeminal sensitivity that potentially mediates their perception of airflow, was assessed via menthol lateralization detection thresholds (LDT) and compared with 14 healthy controls.

Results—Post-surgical reductions in nasal resistance were observed and significantly lower than normal ($p < 0.05$). CFD analysis showed that, paradoxically for all ENS patients, IT reduction did not draw more airflow to the airway surrounding the ITs, but rather resulted in nasal airflow forming into a narrow jet towards the middle meatus region, leaving the airway surrounding the inferior turbinate with significantly reduced airflow intensity and air-mucosal interactions (inferior region flow percentage reduced from $35.7\% \pm 15.9\%$ to post-surgery $17.7\% \pm 15.7$, $p < 0.05$; inferior wall-shear-stress, reduced from $7.5 \pm 4.2 \times 10^{-2}$ Pa to $3.4 \pm 3.1 \times 10^{-2}$ Pa, $p < 0.01$). ENS patients also had significantly impaired menthol LDT compared to healthy controls ($p < 0.005$).

Conclusion—The results indicated that a combinatory of factors, including paradoxically distorted nasal aerodynamic, impaired sensorineural sensitivity, and potential pre-disposing conditions, may contribute to the development of ENS.

Keywords

Empty nose syndrome; computational fluid dynamics; nasal airflow dynamics; TRPM8

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INTRODUCTION

Empty nose syndrome (ENS), is a rare but debilitating disease that can occur after surgical therapy^{1,2}. Historically, patients with ENS were noted to have wide nasal corridors following surgery despite a paradoxical sensation of nasal obstruction^{1,2}. Other symptoms, including nasal crusting, dryness, nasal discharge, and nasal pain often accompany, or replace nasal obstruction³. This syndrome can have a devastating impact on patients' quality of life: constant feeling of suffocation, elevated anxiety, disrupted concentration, chronic hyperventilation, chronic fatigue, severe sleeping difficulty and psychological disorders⁴.

The precise pathogenesis of ENS is poorly understood. Altered nasal aerodynamics is often suspected as a major contributing factor. The application of computational fluid dynamics (CFD) can achieve detailed examination of nasal aerodynamics, and have the potential to improve our understanding of ENS. Yet, there is a void in the literature. Most prior CFD studies are based on virtual turbinectomies simulated on healthy noses^{5,6}. 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 ENS, while some patients undergoing contemporary, mucosal sparing procedures develop those symptoms historically associated with ENS⁷. Thus, it is important to focus on the small subset of patients who unfortunately develop ENS in order to accurately investigate the pathogenesis.

The loss of sensory nerve fibers or compromised wound healing may be another crucial factor contributing to ENS. Previous studies have shown that the perception of nasal airflow clearly involves activation of nasal trigeminal cool afferents when the cool ambient air is inspired^{8,9}. Supporting evidence also comes from menthol administration, which when topical applied will produce the illusion of decongestion and improved nasal airflow without actually altering nasal morphology¹⁰. We now know that menthol activates a trigeminal cool sensitivity receptor, TRPM8, and thus enhances the perceived coolness during breathing^{11,12}. These data posited the damaged cool sensitive TRPM8 trigeminal pathway as a factor to the lack of sensation of nasal airflow in ENS patients^{13,14}. Yet, there exists limited data regarding this.

In this study, we attempt to examine and quantify both the nasal airflow and the nasal trigeminal sensory function changes among ENS patients and compare to healthy controls. A small group of ENS patients that we enrolled also have both pre- and post-surgery CT scans available, allowing us to examine for the first time the nasal aerodynamics changes pre vs. post turbinate/sinus surgery that may lead to ENS symptoms. These data, when complemented with nasal trigeminal cool afferent evaluation, gives insight into this important and debilitating disorder.

MATERIALS AND METHODS

Study Population

Six ENS patients were enrolled. Their age ranged from 27–57 with a mean of 45.2. Their symptoms were confirmed through a combination of SNOT-22, ENS6Q, NOSE, acoustic

rhinometry and rhinomanometry (Table 1). Previous published normative data on 22 healthy subjects were used for comparison with ENS patients^{14,15}. The data set includes acoustic rhinometry, rhinomanometry measurements, as well as CT-based CFD modeling of normative nasal airflow. Fourteen additional healthy controls were also recruited specifically to establish normative data of Menthol LTD that were not available in the literature. All protocols were approved by The Ohio State University, Institutional Review Board.

Questionnaire

All participants were asked to fill out questionnaires documenting their medical history, SNOT-22, NOSE score and ENS6Q. All patients indicated bilateral symptoms during their evaluation. The Sino-nasal Outcome Test (SNOT-22)¹⁶ and Nasal Obstruction Symptom Evaluation (NOSE)¹⁷ are two commonly used validated outcome questionnaires for nasal sinus patients. ENS patients had significantly elevated SNOT-22 (54.5 ± 15.6) and NOSE scores (78.3 ± 19.1). ENS6Q is a recently validated specific, 6-item questionnaire as an adjunct to the standard SNOT-22 questionnaire to discriminate patients with suspicion of ENS¹⁸. A score of ENS6Q >11 is indicative of ENS. All patients fit this criterion, except patient #4 who did not fill out the ENS6Q. His disease status was confirmed based on the fact that he underwent inferior turbinate reduction and middle turbinectomy, with open nasal airway, yet he complains of severe nasal obstruction (NOSE =90).

Rhinometry

The minimum (narrowest) cross-sectional area (MCA) in the anterior 5 cm of the nasal airway was collected unilaterally using an acoustic rhinometry (SRE21000, RhinoMetrics A/S, Denmark) for each subject. Unilateral nasal resistance during normal breathing was measured by anterior rhinomanometry (SRE21000, RhinoMetrics A/S) and expressed as flow rate at the reference pressure drop of 75 Pa (ml/s@75 Pa). So, the higher the flow rate, the less the nasal resistance.

CT Scan and CFD Model

Following the questionnaire and rhinometry measurements, ENS patients immediately received a research CT scan using a cone beam in-office CT scanner (3D Accuitomo 170, J. Morita USA, Inc.). Three patients also brought in their pre-surgery CT scans. These CT scans enabled the construction of CFD nasal airway models for each subject at various time points using methods described previously^{19,20}. In brief, the scans were imported into the commercial software AMIRA (Visualization Sciences Group, USA) to extract nasal cavity geometry. After necessary segmentation, smoothing, and correction for artifacts, a three-dimensional surface geometry of the nasal airway was generated. Then the commercial grid generator ICEM CFD (Ansys, Inc., USA) was applied to generate a computational mesh. A four-layer prism mesh was adopted at the boundary with a total height of 0.2 mm near the mucosal surface to more accurately model the rapidly changing near-wall air velocity. Then the initial meshes were refined by gradient adaptation and boundary adaptation until grid independence of the solutions was achieved. After the grid adaptation, the final nasal cavity mesh ranged from 2.9 million to 4.3 million hybrid finite elements.

Next, inspiratory quasi-steady laminar nasal airflow is simulated (Fluent®, Fluent Inc, USA) by applying a physiologically realistic pressure drop of 15 Pa between the nostrils and the nasal pharynx²¹. This pressure drop of 15 Pa was chosen to simulate restfully breathing, a state that is most relevant to patients' symptoms during routine daily life^{14,15,19,20}. Along the nasal walls, the usual no-slip velocity condition was applied, and the wall is assumed to be rigid. The numerical solutions of the continuity, momentum equations were determined using the finite-volume method. A second-order upwind scheme was used for discretization. The SIMPLEC algorithm was used to link pressure and velocity. The discretized equations were then solved sequentially using a segregated solver. Convergence was obtained when the scaled residuals of continuity and momentum quantities were less than 10^{-5} .

Menthol Lateralization Detection Thresholds (LDT)

Measurement of lateralization thresholds is a common assessment of nasal trigeminal sensitivity²². As with other trigeminal stimulants, menthol elicits both an odor (via olfaction) and a cooling sensation (via the TRPM8 trigeminal pathway). The concept of this test is based on the fact that nonirritating odorants cannot be lateralized, and thus the lateralization threshold is a measure of nasal trigeminal sensitivity to volatile compounds that is independent of the chemical's effect on the olfactory system²². Our procedure was adapted from the literature^{8,23}. In brief, menthol is diluted into mineral oil in clear glass bottles in a 20-step binary dilution series, starting at a concentration of 0.125 g/ml (5g/40mL), the next dilution half of that, and next a quarter of that, so on. The final dilution step (#20) would have a dilution of $1/2^{19}$ times of the starting concentration, or 2.38×10^{-7} g/ml. All material 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 sniffs from a pair of bottles, one in each nostril - one with Menthol and the other blank with only mineral oil. The subject is forced to identify which side contains the Menthol (which is termed: lateralization). The trials were conducted based on a force-choice ascending method of limits²⁴. Each stimulus concentration is presented at most once, in ascending concentration. Testing ends when the subject: (1) has responded correctly in four consecutive trials and (2) are certain that the last response was correct (equal or above 7 on a scale of 0–10 in confidence rating). The latter criterion represents an attempt to reduce the chances of false positive, as four consecutive “lucky guesses” are not a rare event (6.25%). The threshold is determined as the first of the four consecutive correct trials and reported in dilution step or bottle number. The dilution bottles will be numbered 1–20 accordingly. One important modification implemented to the above scheme included the ability to obtain unilateral thresholds. The consecutive correctness left and right side were tracked separately, while the presentation order to either side remained random. For example, the consecutive correct trials on the left side only depended on the previous correct or incorrect identification trials when the Menthol was presented to the left side.

Data Analysis

To determine the nasal airflow and nasal trigeminal sensory functions changes due to the surgery and ENS disease processes, we compare: 1. Nasal airflow changes pre- vs. post-turbinate surgery leading to the ENS symptoms (n=3); 2. Nasal airflow features between ENS patients (n=6) and healthy controls (n=22); 3. Trigeminal sensory measurement

between ENS patients (n=5) and healthy controls (n=14). One patient (#6) did not come in for Menthol LTD and Rhinometry measurement, thus the sample size is reduced in the last analysis. Two-tailed paired T-tests were used for within group comparison (e.g. between pre and post-surgery), and Two-tailed independent-sample T-tests without assuming equal variance were used for cross-group comparison (e.g. between ENS and healthy controls).

RESULTS

Nasal Morphology and Nasal Resistance

Figure 1 demonstrates the nasal morphology between pre-, post-surgery ENS patients and healthy controls. To account for different overall lengths of different noses, each nasal cavity was sectioned into uniformly spaced coronal planes. The averaged cross-sectional nasal airway area (excluding sinuses) for each coronal plane was plotted as a function of normalized distance from nostrils to pharynx. This was performed for pre- and post-surgical ENS patients as well as the healthy controls. As expected, the cross-sectional areas in the turbinate region were significantly larger in the post-surgical when compared to the pre-surgical area ($p<0.05$). It is worth noting that this finding is in line with recent CT based measurements of ENS patients²⁵. However, pre-surgical cross-sectional areas were similar to those of the healthy control group than the post-surgical ones.

Table 2 tabulated the MCA measured by Acoustic Rhinometry and the nasal resistance, obtained through either Rhinomanometry or CFD simulation, for ENS patients and the healthy controls. Corroborating findings in Figure 1, the average post-surgery MCA of ENS patients were higher than that of healthy controls, and post-surgical reductions in nasal resistance were observed and were significantly lower than that of healthy controls ($t=4.23$, $p<0.005$), which confirms the paradoxical nature of the sensation of nasal obstruction in these patients². Similar to Figure 1, pre-surgery nasal resistances were comparable to healthy controls. Among all, patient #2 had most severe nasal obstruction on the right side pre-op, which can also be seen in the pre-op CT scan in Figure 2.

Flow patterns, distribution and wall shear stress

Figure 2, 3 and 4a) showed the CFD simulated nasal airflow patterns pre- vs. post-surgery for three ENS patients with pre-surgery CT. Figure 4b,c,d) showed the simulated nasal airflow patterns of the other three patients with only the post-surgery CT scan. The coronal velocity contour plots (2nd row) revealed that even though the pre-surgery airways were much narrower, the nasal airflow patterns were more evenly distributed throughout the inferior and lateral regions of the nasal airway, resembling normal airflow patterns (see Figure S1). However, post-surgery, the flow is directed toward the middle meatus region, leaving the inferolateral region of the nasal cavity with no airflow (0 air velocity). All ENS patients had some form of inferior turbinate reduction. Paradoxically, the inferior turbinate reduction did not draw more airflow to the airway surrounding inferior turbinate, rather there was a reduction of airflow intensity surrounding inferior turbinate for all ENS patients.

We calculated wall shear stress (WSS) as an indicator for airflow-mucosa interactions. WSS represents the shear force of airflow exerted onto a unit area of nasal mucosa. The WSS was

much lower surrounding the inferior turbinate post-surgery as compared to that of pre-surgery (3rd row). The overlapping of airflow streamline plot and the WSS plots on the lateral turbinate wall with septum removed from the view (4th row) demonstrated that the reduction of inferior turbinate WSS was the result of more congregated airflow towards the middle turbinate region. The airflow stream formed a very abnormal narrow jet, especially in patient (#3, 5), which was never seen among the healthy controls.

We further quantified the airflow distribution in the nasal airway in three regions: inferior, middle and superior on one coronal plane (see example in Figure 2 top middle graph). Figure 2 and 3 (bottom middle) then quantitatively confirmed that the averaged WSS in the inferior regions was significantly reduced as compared to that of pre-surgery for patient 2 and 3. Figure 5 demonstrates regional a) cross-sectional area, b) flow rate percentage, and c) WSS of all ENS patients and compared to healthy controls. The results demonstrated that the increased inferior region airway cross-sectional area post-surgery (Figure 5a, $p < 0.05$) paradoxically resulted in flow rate percentage reduction inferiorly (Figure 5b, $p < 0.05$). As a consequence, a significant increment of flow rate percentage occurred in the mid region (Figure 5b, from pre-surgery $56.2\% \pm 14.7\%$ to post-surgery $75.6\% \pm 14.6\%$, $p < 0.05$). Significantly decreased WSS in the inferior region post-surgery was also observed ($p < 0.05$, Figure 5c). Surprisingly, the airflow rate and WSS exist no statistical significant between ENS patients pre-surgery and healthy controls.

Menthol Lateralization Detection Thresholds

In Table 2 and Figure 5d), ENS patients had statistically significantly lower Menthol LDT (9.2 ± 4.6) as compared to healthy controls (14.8 ± 1.6 , $t = 3.78$, $p < 0.005$). If impairment of Menthol LDT was defined as 2 standard deviations below normal value ($< 5\%$), all ENS patients except Patient 3 had impaired Menthol LDT on one side or both sides (< 11.6).

DISCUSSION

The etiology of ENS, a rare but debilitating disease, remains poorly understood. The underlying pathogenesis has been attributed to possible radical surgery (especially historically when mucosal and bone resection was more common), poor mucosal wound healing, altered nasal aerodynamics, and impaired nasal sensory function. In this study, we have the opportunity to examine multiple factors within a small cohort of ENS patients and compare them to a healthy control group. Interestingly, our data demonstrate that symptoms related to ENS did not necessarily result from most radical resection of turbinate tissue. The majority of this ENS patient cohort had much of their turbinate tissue preserved, except for patient 4 (middle turbinectomy) and 6 (inferior turbinectomy). However, patients 3 and 5 (relatively persevered turbinate tissue) were among the worst in distorted nasal aerodynamics. The one common nasal aerodynamic distortion among all ENS patients post-surgery was the congregated nasal airflow forming into a narrow band in the middle meatus region, leaving the airway surrounding the inferior turbinate with little or no airflow.

Why did this distorted nasal aerodynamic profile occur?

The distortion in aerodynamics among ENS patients seems paradoxical, as inferior turbinate reduction should open up the airway surrounding the inferior turbinate, thus facilitating more flow through that region. On the contrary, among ENS patients, the flow rate and intensity surrounding the inferior turbinate after reduction surgery significantly decreased, defeating this common assumption concerning the therapeutic mechanism of IT reduction. The cause could be related to multiple factors. First, among a healthy population, the peak airflow would occur equally at all three nasal meatuses (see Figure S1). However, the nasal airflow of pre-surgery ENS patients were all peaked at the middle meatus (Figure 2,3,4 and S1(b2)) with a moderate predominant airflow in the middle meatus ($56.2\% \pm 14.7\%$ of total flow). This may represent a pre-disposing condition increasing the possibility of airflow distortion after IT reduction. Second, among all ENS patients, the inferior turbinate surgery was not isolated, but accompanied by Septoplasty or FESS that potentially opens up the middle nasal airway as well. We know that airflow is driven not only by the path of least resistance, but also by its momentum. The post-surgery ENS patient may be akin to a large room in which a jet stream of air is passed. Resistance is low in all directions and so the airstream maintains its original path. Similarly, in patients with pre-surgical flow that trend toward the middle meatus, decreasing resistance in the lower nasal airway may not overcome the tendency, as the resistance in that region remains low. Septoplasty or FESS may contribute to this phenomenon as well.

We further hypothesized that IT reduction may be more effective or more safe in patients whose pre-surgery airflow peak were near the nasal floor or inferior meatus. With the pre-existing inferior flow tendency, the expanded inferior airway may be more effective to increase and distribute the airflow around the inferior turbinate, with potentially better outcome. Obviously, this hypothesis needs to be further studied.

Functional Consequences of the Distorted Aerodynamics

Along with the rest of the nasal anatomy, healthy nasal turbinates may serve to partition the nasal airflow uniformly throughout the nasal cavity to better facilitate normal nasal physiology. Among healthy controls, the nasal airflow is widely distributed (Figure S1). Although regions of higher or lower flow may exist, it is very rare to find regions with zero velocity (dark blue) as in the post-surgery ENS cases. A uniformly distributed nasal airflow theoretically improves efficiency, resulting in a better capability to warm, humidify and filter the inspired airflow, while preventing unwanted desiccation of the mucosa. Many ENS patients complain of excessive nasal dryness or crusting, potentially due to their over-congregated nasal airflow that over stresses a small patch of the nasal mucosa.

The more widely distributed airflow could also improve the capacity of the nasal mucosal to detect airflow. It has been reported mucosal detection sensitivity among a normal population has significant regionally variability^{26,27}, and potentially more so among ENS patients. Theoretically, assuming normal sensitivity of at least some portion of nasal mucosa, a widely-distributed nasal airflow pattern would lead to the perception of normal airflow via receptors in that region. Thus, patients with a normal / wide pattern of airflow may have better “opportunity” to sense available flow. Conversely, patients in whom the airflow

pattern is directed to a small subsite of the nasal cavity, or in whom a significant portion of the nasal mucosa is either removed or insensate (due to scar, poor healing or desiccation), have potentially less “opportunity” to sense airflow, even in the absence of significant nasal resistance. The paradoxical sensation of nasal obstruction in ENS patients may be related to a combination of loss of neural sensitivity and reduction in the surface area stimulated by mucosal cooling^{6,8,14}. Some ENS patients respond well to “cotton test” when a saline-soaked cotton is placed inside the nose at various locations. The cotton may potentially redistribute the nasal airflow to mucosa regions that still have the normal sensory function, and thus enable the patient to regain their sensation to nasal airflow.

Nasal Neurosensory Losses

Another key finding in this study is the confirmation of nasal neurosensory impairment among ENS patients. We found that ENS patients had significant lower Menthol LDT (9.2 ± 4.6) as compared to healthy controls (14.8 ± 1.6 , Table 2). Converting dilution steps to concentration, healthy controls can detect the nasal cooling by Menthol at ~50 times ($2^{5.6}$) lower in concentration than ENS patients. There is sufficient evidence that the perception of nasal airflow involves activation of nasal trigeminal cool afferents when of cool ambient air is inspired^{8,28}. Menthol activates TRPM8 trigeminal cool receptors¹¹, thus impaired Menthol LDT may be indicative of patients’ lack of sensation of airflow. The consistency and low variability in Menthol LDTs among healthy control is a demonstration of the validity of this test. Patient 3 is the only patient that had normal bilateral Menthol LDT, but also is the one with most distorted airflow patterns among all.

The exact causes of the sensory loss remain unknown. We did not find any correlation between Menthol LDT and unilateral nasal resistance among healthy controls. In other words, more or less overall nasal airflow within the normal range does not result in better or worse LDT. But the distorted aerodynamics in ENS patients may have an impact on mucosal sensory recovery, with either too little stimulation or too high stresses. There is evidence that nasal trigeminal senses do undergo adaptive processes during acute or prolonged exposure and disease processes^{29–32}. How to promote mucosal neurosensory recovery could be a future area of research to find treatment options for ENS.

Measurement of Menthol LDT does have one pitfall that it cannot probe regional mucosal sensitivity, as the whole nasal cavity was exposed to the inhaled Menthol. Mapping of mucosal sensitivity to menthol^{33,34} or to temperature probes might find mucosal regions still with good neurosensory functions among ENS patients. Future treatment can then direct nasal airflow targeted to these regions to restore patient’s sensation to airflow.

Limitation

The sample size in this study is relative small, mainly because ENS is a rare patient population and difficult to recruit. But comparing to the current literature with only a single case report on the nasal aerodynamics of one atrophic rhinitis³⁵, we feel that our study as a case-series with control group, would readily advance the current field of knowledge. Despite the small sample size, we have already found statistical significance in both the distorted nasal aerodynamics and the impaired trigeminal functions as compared to healthy

controls. The ENS cohort in this study is also highly heterogeneous with many undergone multiple surgeries, including middle turbinate resection and endoscopic sinus surgery. However, this heterogeneity is unavoidable when studying ENS because 1) the sample size is never large enough to divide into sub-groups; 2) ENS patients often have a complex treatment history. We believe the best approach is to embrace the heterogeneity in the analysis and extract the common features among all ENS patients. In this study, we focused on the aerodynamics distortions and trigeminal cool sensitivity impairment based on our previously developed hypothesis^{8,14}, and with results preliminarily supporting it.

CONCLUSION

This study integrates CFD simulations and trigeminal sensory examinations to explore the etiology of ENS. The results suggest that the development of ENS is likely related to multiple factors, when aligned, result in this devastating disease. Such factors include: surgical impact, pre-existing airflow patterns, distorted nasal aerodynamics, as well as the overlapping neurosensory losses. In the future, CFD simulations combined with sensory testing could be used to further investigate the surgical impact on nasal aerodynamics and neurosensory functions, and hopefully the collective knowledge would then lead to optimized surgical outcome, and ultimately to preventing ENS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Average and standard deviation of cross-sectional area (excluding sinuses) as a function of normalized distance to the nostril, for ENS patients pre-, post-surgery and the healthy controls groups. To account for different overall lengths of different noses, each nasal cavity was sectioned into uniformly spaced coronal planes. The normal values were more comparable to the pre-surgery cases than to post-surgery ones. The post-surgery cross-sectional areas were significantly higher than that of pre-surgery in the nasal turbinate region (* $p < 0.05$).

Figure 2.

Patient 2, age 27, had turbinate reduction and septoplasty in 2015, and immediately complained of a lack of sense of nasal airflow, along with upper lip paralyzed for a few weeks. Pre-surgery CT scan showed inferior turbinate hypertrophy pre-surgery, especially on the right side. Post-surgery CT showed a bilateral turbinate reduction, especially aggressive on right turbinate head. CFD analysis showed post-surgical reductions in nasal resistance, especially on the right side (see Table 2). However, the post-surgery nasal airflow (2nd row) congregates towards the middle meatus and leaving some inferior and lateral airway region with no airflow (blue color = 0 air velocity). In the 3rd row, wall shear stress (WSS), the shear force of airflow exerted onto the nasal mucosa, was much lower surrounding the inferior turbinate post-surgery (blue color = 0 WSS) as compared to that of pre-surgery and was the direct result of congregated airflow streamline towards the middle meatus post-surgery (4th rows, the overlapping of airflow streamline and the WSS plots on the left lateral turbinate wall as an example). WSS can be viewed as an indicator for airflow-mucosa interactions. The regions of inferior, middle and superior airway were defined in the top middle graph. Bottom middle bar graph showed a significant reduction in WSS in the inferior region.

Figure 3.

Patient 3, age 38, had the turbinate reduction, septoplasty, and FESS in 2002, and continue to complain of nasal obstruction. CT scan showed left to right septal deviation pre-surgery. Post-surgery CT showed bilateral turbinate reduction and maxillary antrostomy. This patient is the only patient that had normal bilateral Menthol LDT, but had the most distorted airflow patterns among all. The streamline jet towards the middle meatus and leaving most of the inferior and lateral airway region with no airflow. Wall shear stress (WSS) was much lower surrounding the inferior turbinate post-surgery as compared to that of pre-surgery.

Figure 4.

CT, plots of velocity contour, wall shear stress, and streamline patterns for the remaining four ENS patients.

Figure 5.

Regional a) cross-sectional area, b) flow rate percentage, and c) WSS of ENS patients pre- and post-surgery and compared to healthy controls (* $p < 0.05$). The regions of inferior, middle and superior airway were defined (in Figure 2 and 3 top middle graphs). The results showed a) significant increased airway cross-sectional area post-surgery, especially in the inferior region ($p < 0.05$), which paradoxically resulted in significant flow rate reduction inferiorly (b), but a significant increase in flow rate percentage in the mid region (b). Significantly decreased WSS in the inferior region post-surgery was also observed (c). Surprisingly, the airflow rate and WSS exist no statistical significant between ENS patients pre-surgery and healthy controls. d) Boxplot of Menthol LDT of ENS patients ($n=10$ sides) and healthy controls ($n=28$ sides). ENS patients have significantly lower (poorer) Menthol LDT ($p < 0.005$).

Table 1

Patient information.

Patient ID	Age	Gender	Pre-CT	SNOT22 (0–110)	ENS6Q (0–30)	NOSE (0–100)	Prior Nasal Sinus surgeries
1	47	M	Yes	29	19	65	2009- Septoplasty & RF turbinate reduction 2009- Submucosa turbinate reduction 2011- RF turbinate reduction (*ENS) 2011- Concha bullosa (*Worsen)
2	27	M	Yes	75	30	100	2015- Turbinate reduction and septoplasty (*ENS)
3	47	F	Yes	71	16	95	2002- Turbinate reduction, Septoplasty and FESS (*ENS)
4	57	M	n/a	50	n/a	90	2009- septoplasty, Turbinate reduction (*ENS) 2010- FESS
5	51	M	n/a	45	12	45	2003- Cryo-turbinate reduction (*ENS) 2006- IT submucosa resection 2009- Septoplasty
6	42	M	n/a	57	29	75	2006- Partial turbinectomy and septoplasty (*ENS) 2007- Turbinate reduction and septoplasty

(*ENS) indicates the time point in which each patient indicated that their ENS become most prominent for them.

Table 2

Minimum cross-sectional area (MCA) measured by Acoustic Rhinometry, the nasal resistance obtained through either Rhinomanometry or CFD simulation, and measured Menthol LDT for ENS patients and the healthy controls.

Patient ID	Rhinomanometry (ml/s@75 Pa)		Minimum Cross area (cm ²)		Menthol LDT (dilution #)		Pre-op flowrate CFD (ml/s@15Pa)		Post-op flowrate CFD (ml/s@15Pa)	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
1	220.6	247.3	0.47	0.48	15	11 [*]	185.0	195.4	179.7	180.0
2	176.8	73.2	0.62	0.44	9 [*]	6 [*]	149.0	18.1 [*]	182.8	169.3
3	169.5	94.5	0.45	0.45	14	15	124.0	170.0	127.6	180.0
4	200.7	203.1	1.62 [*]	0.88 [*]	3 [*]	3 [*]	--	--	245.5	216.0
5	69.8	183.3	0.7	0.72	6 [*]	10 [*]	--	--	76.6	176.5
6	--	--	--	--	--	--	--	--	164.4	179.1
Patient Average (SD)	163.9 (62.8)		0.68 (0.36)		9.2 (4.6) ^{**}		140.3 (65.1)		173.1 (41.4) ^{**}	
Healthy Controls	120.9 (67.5)		0.51 (0.18)		14.8 (1.6)				116.0 (41.7)	

* Values that beyond two standard deviation of normative values.

** Two tailed T-test against healthy group. p<0.05

- All nasal resistance was expressed as flow rate at the reference pressure drop (ml/s@Pa). So, higher the flow rate, the less the nasal resistance.

- Menthol LDT results were reported in dilution steps.